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Contents

Protocols

A Positive Emotion–Focused Intervention to Increase Physical Activity After Bariatric Surgery: Protocol for a Pilot Randomized Controlled Trial (e39856)
Emily Feig, Lauren Harnedy, Anne Thorndike, Christina Psaros, Brian Healy, Jeff Huffman

Providing Accessible ReCreation Outdoors–User-Driven Research on Standards: Protocol for Mobile and Web-Based Interviews for Winter Assessments (e38715)
Mike Prescott, Stéphanie Gamache, W Mortenson, Krista Best, Marie Grandisson, Mir Mostafavi, Delphine Labbé, Ernesto Morales, Atiya Mahmood, Jaimie Borisoff, Bonita Sawatzky, Laura Bulk, Julie Robillard

A Multilevel Integrated Intervention to Reduce the Impact of HIV Stigma on HIV Treatment Outcomes Among Adolescents Living With HIV in Uganda: Protocol for a Randomized Controlled Trial (e40101)
Massy Mutumba, Fred Ssewamala, Rashida Namirembe, Ozge Sensoy Bahar, Proscovia Nabunya, Torsten Neilands, Yesim Tozan, Flavia Namuwo, Jennifer Nattabi, Penina Acayo Laker, Barbara Mukasa, Abel Mwebembezi

Feasibility of Monitoring Patients Who Have Cancer With a Smart T-shirt: Protocol for the OncoSmartShirt Study (e37626)
Emma Steen-Olsen, Helle Pappot, Allan Green, Henning Langberg, Cecilie Holländer-Mieritz

A Living Database of HIV Implementation Research (LIVE Project): Protocol for Rapid Living Reviews (e37070)
Ingrid Eshun-Wilson, Nathan Ford, Noelle Le Tourneau, Stefan Baral, Sheree Schwartz, Christopher Kemp, Elvin Geng

The Use of Segmental and Suprasegmental Sequencing Skills to Differentiate Children With and Without Childhood Apraxia of Speech: Protocol for a Comparative Accuracy Study (e40465)
Min Wong, Eddy Wong, Shelley Velleman

Developing an Immersive Virtual Reality Training System for Novel Pediatric Power Wheelchair Users: Protocol for a Feasibility Study (e39140)
Sara Drisdelle, Liam Power, Scott Thieu, Jordan Sheriko

Understanding Racial Disparities in COVID-19–Related Complications: Protocol for a Mixed Methods Study (e38914)
Jessica Harding, Shivani Patel, Teaniese Davis, Rachel Patzer, Bennett McDonald, Doraina Walker-Williams, Ram Jagannathan, Larissa Teunis, Jennifer Gander

Biomarkers of Exposure and Potential Harm in Exclusive Users of Nicotine Pouches and Current, Former, and Never Smokers: Protocol for a Cross-sectional Clinical Study (e39785)
David Azzopardi, Linsey Haswell, Justin Frosina, Michael McEwan, Nathan Gale, Jesse Thissen, Filimon Meichanetzidis, George Hardie
Soil-Transmitted Helminth Infection in Malaysia: Protocol for a Scoping Review (e36077)
Muhammad Mohd Hisham, Fazila Ahmad, Hasmah Mohamed Haris, Noor Lodz, Norzawati Yoep, Eida Muhammad, Rafidah Ali, Nor Muhamad.
A Positive Emotion–Focused Intervention to Increase Physical Activity After Bariatric Surgery: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Physical activity levels after bariatric surgery are usually low, despite the significant protective health benefits of physical activity in this population. Positive psychological well-being is associated with improved adherence to health behaviors, but bariatric surgery patients often have negative associations with physical activity that prevent sustained engagement.

Objective: The Gaining Optimism After weight Loss Surgery (GOALS) pilot randomized controlled trial is aimed at testing a novel intervention to increase physical activity after bariatric surgery, which incorporates positive psychological skill-building with motivational interviewing and goal-setting.

Methods: The GOALS trial is a 2-arm, 24-week pilot randomized controlled trial that aims to enroll 58 adults who report less than 200 minutes per week of moderate to vigorous physical activity and a desire to become more active 6-12 months after bariatric surgery. GOALS is testing the feasibility, acceptability, and preliminary efficacy of a positive psychology–motivational interviewing telephone intervention targeting to increase physical activity and associated positive affect. Intervention components include positive psychology, goal-setting, self-monitoring via provided Fitbits, and motivational interviewing to overcome barriers and increase motivation. The intervention is compared to a physical activity education control that includes mailings with psychoeducation around physical activity and provision of a Fitbit. The primary outcomes of the pilot trial are feasibility and acceptability, measured as session completion rates and participant ratings of ease and helpfulness of each session. The main secondary outcome is change in accelerometer-measured moderate to vigorous physical activity post intervention and at 24-week follow-up. Additional outcomes include changes in attitudes related to physical activity, psychological well-being, and physical health measures.

Results: This multiphase project was funded in 2020 and institutional review board approval was obtained for the proposed trial in 2021. Recruitment for the randomized controlled trial began in July 2022. Upon completion of the pilot trial, we will examine the feasibility, acceptability, and preliminary efficacy of the intervention.

Conclusions: Although bariatric surgery is the most effective treatment available for severe obesity, weight regain occurs, often in the context of low psychological well-being. Many individuals would benefit from learning strategies to increase positive psychological well-being after bariatric surgery, which could help them maintain lifestyle changes. Positive psychology is a novel approach to improve adherence by increasing positive associations with health behaviors including physical activity. The GOALS pilot trial will determine whether this type of intervention is feasible and acceptable to this population and will provide a foundation for a future full-scale randomized controlled efficacy trial.
Introduction

Bariatric surgery is the most effective treatment available for severe obesity, often resulting in cost-effective, sustained weight loss [1-3]. However, approximately 25% of surgical patients do not achieve long-term weight loss maintenance [2-4]. Weight loss is associated with remission of weight-related comorbidities (eg, type 2 diabetes, hypertension, and hypercholesterolemia), and weight loss maintenance is vital for preserving these improvements in health [3]. Physical activity is critical for weight loss maintenance and improved health after bariatric surgery, particularly given the increased risk of cardiometabolic disease in this population [5-7].

After bariatric surgery, experts recommend individuals to engage in at least 150 minutes per week of moderate to vigorous physical activity (MVPA), and even higher levels may be needed to control weight [8-10]. Unfortunately, a large majority of people who have bariatric surgery do not meet this recommendation [11-13]. Increasing physical activity, even without weight change, can improve insulin sensitivity, cardiopulmonary fitness, blood pressure, and blood lipid levels, all of which confer a lower risk for cardiac and metabolic disease in the general population [14-17]. Behavioral interventions to improve physical activity after bariatric surgery show promise, but the evidence is still limited by a lack of trials that do not include an in-person exercise program and are well-powered with long-term follow-up [18-20].

Emotional factors play a role in physical activity engagement and health outcomes. Psychological distress predicts lower physical activity levels and less weight loss after bariatric surgery [21], and these individuals are more likely to experience depressive symptoms than the general population [22,23]. Conversely, positive psychological constructs such as optimism and positive affect are associated with improved health independent of depression but have not been examined thoroughly in people who have bariatric surgery [24-26]. Further, positive affect during physical activity has been shown to predict future physical activity, supporting the “upward spiral” theory of lifestyle change [27,28]. This theory posits that by experiencing positive affect when performing a health behavior, nonconscious motives increase one’s likelihood of repeating that behavior. Over time, health behaviors become reinforcing rather than burdensome. However, most people experience a decrease in positive affect during exercise [29], and sedentary women with obesity have been found to experience even lower pleasure during physical activity than those with a BMI in the normal or overweight category [30]. People undergoing bariatric surgery may be missing out on this “upward spiral” owing to emotional barriers to physical activity, such as anxiety about getting injured, shame about appearance, and experiences of weight stigma, as well as physical barriers such as increased shortness of breath and discomfort [31-33]. This group would benefit from new skills to increase positive affect during physical activity as well increased psychological well-being in general.

Physical activity interventions that include positive psychology may be particularly effective after bariatric surgery. In addition to improving overall well-being, positive psychology interventions could improve physical activity by targeting positive affect during physical activity engagement [34,35]. Positive psychological interventions may be more effective in combination with an adherence-based program such as motivational interviewing, a technique that focuses on clarifying motivation, addressing ambivalence, and setting achievable goals [36]. Indeed, a combined, remotely delivered positive psychology—motivational interviewing (PP-MI) intervention has shown preliminary efficacy in improving health behaviors in patients with type 2 diabetes and those with heart disease [37-39]. However, this intervention does not address the unique barriers that are common after bariatric surgery (eg, history of negative experiences with exercise due to injuries or weight stigma, adapting to a drastically changing body, and managing excess skin after weight loss) and does not directly address affect during physical activity.

The Gaining Optimism After weight Loss Surgery (GOALS) pilot randomized controlled trial (RCT) is testing an adapted PP-MI intervention promoting physical activity in individuals who have undergone bariatric surgery in the past 6-12 months. This paper describes the design and development of the intervention.

Methods

Overview

The GOALS trial is a 2-arm, 24-week pilot RCT that tests the feasibility, acceptability, and preliminary efficacy of a PP-MI telephone intervention, in comparison to a control arm, on physical activity and psychological, behavioral, and physical health outcomes immediately post intervention and at 24-week follow-up. The primary outcome of the trial is feasibility and acceptability of the intervention as measured by session completion rates and participant ease and utility ratings. The secondary outcomes are change at postintervention 10-14 weeks and 24-week follow-up in MVPA measured using an accelerometer. Additional outcomes include changes in light physical activity and steps per day, attitudes related to physical activity (enjoyment, self-efficacy, perceived barriers, and exercise identity), psychological well-being (symptoms of...
depression and anxiety, optimism, positive affect, internalized weight bias, and general self-efficacy), and health measures (exercise capacity, BMI, bariatric surgery behavioral adherence, and general health status) post intervention and at 24-week follow-up.

Ethics Approval
The institutional review board of the Mass General Brigham initially approved the multiphase study in 2020 (2021P001006).

Study Development
The GOALS intervention and study protocol were developed and refined in accordance with the Obesity-Related Behavioral Intervention Trials (ORBIT) model [40]. The ORBIT model focuses specifically on early, pre-efficacy phases of intervention development and emphasizes a flexible, iterative approach to moving between phases. The GOALS intervention is based on a PP-MI intervention that was initially developed for people with heart disease [37]. To adapt the intervention for the unique experiences of those who have bariatric surgery, a qualitative study was performed to understand the emotional experiences of people with a recent history of bariatric surgery regarding physical activity (ORBIT phase 1a and 1b; design: define and refine) [33]. Results from this study informed adaptation from the original PP-MI intervention to develop the GOALS intervention. Next, a proof-of-concept trial of the newly developed intervention was completed in 12 participants with exit interviews to refine study procedures and intervention content (ORBIT phase 11a; preliminary testing: proof of concept). Results from this study phase led to further adjustments in the intervention that is now being tested in the described pilot RCT (ORBIT phase 11b; preliminary testing: pilots). These include content changes to address additional common barriers to physical activity (eg, history of injuries), adjusting the positive psychology content to include some general exercises in addition to those focused on physical activity, and some small changes to session order and organization.

Population
The GOALS trial is enrolling adults (age 18+ years) with a history of bariatric surgery in the prior 6-12 months. They also must self-report less than 200 minutes per week of MVPA and a desire to increase physical activity. While the physical activity recommendation is 150 minutes per week of MVPA, we chose a higher cutoff owing to a high likelihood of overestimation in self-reported physical activity [12], along with additional benefits of higher activity levels for weight loss promotion and maintenance [9,10]. Participants must have telephone access for study sessions and be able to read and speak English. Individuals are excluded from the study if they have cognitive deficits that preclude participation or informed consent assessed using a 6-item assessment tool designed to assess suitability for research participation [41], illness likely to lead to death in the next 6 months per chart review, inability to be physically active (eg, severe arthritis), severe psychopathology that may limit the ability to participate in the study per chart review, or current participation in another program targeting physical activity besides the standard care they receive at their surgery center.

Participant Recruitment
Our goal is to randomize 58 participants. We identify patients with surgery dates in the relevant time frame using the hospital system’s Research Patient Data Registry, which allows for searching of electronic medical records to extract lists of patients who meet certain criteria. We send opt-out letters to patients from this list by mail and through the patient portal. Letters briefly describe the study and provide contact information if patients want to decline further contact. Letters are followed by a recruitment phone call 2 weeks later for those who do not opt out. We also can advertise for the study using a flyer to be distributed during postoperative groups and visits within the bariatric surgery clinic. These recruitment methods have been used successfully in prior studies [33].

Participant Screening
Interested participants complete a screening phone call that includes a version of the International Physical Activity Questionnaire–Short Form modified to include brisk walking as a form of moderate activity [42], a 6-item cognitive deficit assessment [41], and questions about interest and ability to increase physical activity and participation in any other physical activity program. If eligible, their baseline visit is scheduled at this time.

Assessment Visits
Participants attend assessment visits at baseline, end of treatment (10-14 weeks), and follow-up (24 weeks) at the hospital’s translational clinical research center. Assessment visit timing is designed to assess both the immediate and sustained intervention impact. Informed consent is obtained at the baseline visit. At each assessment, participants provide demographic and medical information (eg, medical comorbidities and weight history) and complete self-report measures via REDCap. Physiological measures are obtained by a trained translational clinical research center staff member, and 5-mL samples of blood are drawn. Staff also perform a 6-minute walk test to assess functional exercise capacity [43]. Participants are asked to wear an ActiGraph GT3X-BT accelerometer [44] for 7 days (minimum acceptable use is 4 days with 10 hours of recorded data) at each assessment. Participants are paid US $100 for completing each assessment visit.

Randomization Visit
After wearing the accelerometer for 7 days following the baseline visit, participants return the accelerometer and are randomized 1:1 with a random number generator to a study condition (PP-MI or control) after sufficient wear time is confirmed. Only participants who complete accelerometer and return for this visit are randomized. At this time, study staff provide the participant a Fitbit to aid with self-monitoring physical activity and helps them set it up with a study-created account. If they are randomized to PP-MI, they are given the study manual and meet with a study interventionist for approximately 45 minutes for an in-person discussion of the introduction and first session of the program, including setting a long-term physical activity goal to reach by the end of the program. If they are randomized to the control group, they are provided an educational handout about physical activity.

https://www.researchprotocols.org/2022/10/e39856
Intervention Components

The GOALS intervention was adapted and refined on the basis of results from the formative qualitative study and from interventionist experience and participant feedback from a proof-of-concept trial of the intervention [33]. It is delivered over 10 weeks via weekly 30–45–minute phone calls supported by a written participant manual. A window of 14 weeks for intervention completion allows for flexibility in the timing of weekly sessions. Each week includes a topic related to increasing physical activity and a positive psychology skill that is focused on increasing positive emotions in general and during physical activity (see Table 1). Participants are assigned pages in the manual to read and worksheets to complete each week. The physical activity portion of the call includes a review of the prior week’s physical activity topic and of their activity levels from the prior week, including whether they met their goal based on Fitbit data or other methods of self-monitoring, and noting positive emotions experienced during physical activity that week. Furthermore, a new topic is assigned to be completed over the subsequent week and a new physical activity goal is collaboratively set for the upcoming week on the basis of their activity level in the prior week. This goal is customized to each participant’s current activity level and interest, and is primarily self-determined with input from the interventionist as needed. The positive psychology portion includes a review of written assignments from the prior week and associated positive thoughts and feelings identified, followed by introduction to the next week’s topic and assignment. Reviewing, reflecting, and planning for the future sessions encourage integration of positive psychology skills learned into daily life by developing a specific plan to build a habit. All content is delivered using a motivational interviewing approach. The specific weekly topics are described in Table 1. Participants are also sent psychoeducation about physical activity via mail or email as in the control condition (see the Control Content section for details).

Table 1. Weekly intervention topics.

<table>
<thead>
<tr>
<th>Week</th>
<th>Physical activity topic</th>
<th>Positive psychology topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Getting started with increasing activity: benefits of physical activity, important</td>
<td>Identifying positive feelings during exercise: pay attention to and write down specific</td>
</tr>
<tr>
<td></td>
<td>and confidence in making a change, and setting an overall program goal</td>
<td>positive emotions during and after physical activity</td>
</tr>
<tr>
<td>2</td>
<td>Pros and cons of change/SMARTb goals: consider pros and cons of making a behavior</td>
<td>Gratitude for positive events: identify 3 good things that happen this week, one related</td>
</tr>
<tr>
<td></td>
<td>change and of staying the same, setting goals that are specific, measurable, attainable,</td>
<td>to exercise and two broadly, write about them and associated positive thoughts and feelings</td>
</tr>
<tr>
<td></td>
<td>relevant, and time-based</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Barriers and problem-solving: identify barriers to physical activity and brainstorm ways</td>
<td>Positive reappraisal – general: learn about positive reappraisal as a way of seeing the</td>
</tr>
<tr>
<td></td>
<td>to overcome them</td>
<td>silver lining in a negative situation, use it in response to a situation this week</td>
</tr>
<tr>
<td>4</td>
<td>Strength training and equipment resources: set a strength-training goal in addition to</td>
<td>Positive reappraisal for physical activity: consider common negative experiences with</td>
</tr>
<tr>
<td></td>
<td>general physical activity goal; identify and use exercise equipment</td>
<td>physical activity and how to positively reappraise; use positive reappraisal for one</td>
</tr>
<tr>
<td></td>
<td></td>
<td>situation related to physical activity this week</td>
</tr>
<tr>
<td>5</td>
<td>Neighborhood, online, and social resources: brainstorm resources for increasing</td>
<td>Using perseverance: review benefits of perseverance, pick physical activity-related goal</td>
</tr>
<tr>
<td></td>
<td>activity and use a new one this week</td>
<td>to achieve using perseverance this week</td>
</tr>
<tr>
<td>6</td>
<td>Reviewing and reflecting: review progress so far, adjust long-term goals if needed,</td>
<td>Reviewing and reflecting: review skills learned so far, make a plan to integrate one</td>
</tr>
<tr>
<td></td>
<td>and reassess importance and confidence</td>
<td>into daily life this week to build a habit</td>
</tr>
<tr>
<td>7</td>
<td>Reducing sedentary time: assess most sedentary activities and make a plan to incorporate</td>
<td>Focusing on meaning during physical activity: identify nonweight reasons for physical</td>
</tr>
<tr>
<td></td>
<td>standing breaks and small increases in movement throughout the day</td>
<td>activity and practice thinking of these motivators when making the decision to be active</td>
</tr>
<tr>
<td>8</td>
<td>Managing slips: normalize slips, plan how to avoid long-term decreases after slips</td>
<td>and during activity this week</td>
</tr>
<tr>
<td>9</td>
<td>Finding new routes: assess walking environment while trying a new local walking route</td>
<td>Remembering past successes: write about a time in the past when you were successful with</td>
</tr>
<tr>
<td>10</td>
<td>Planning for the future: review progress, set goals for future increase or maintenance</td>
<td>exercise, and about the qualities that were helpful in succeeding</td>
</tr>
<tr>
<td></td>
<td>of physical activity</td>
<td></td>
</tr>
</tbody>
</table>

aParticipants are asked to identify positive emotions during exercise every week throughout the intervention.
bSMART: specific, measurable, attainable, relevant, and time-based.

Intervention Delivery and Fidelity

Interventionists are doctoral level psychologists or psychology doctoral students. All sessions are audio-recorded, and at least 25% of calls are reviewed for fidelity by the principal investigator using a fidelity scale developed for the trial to ensure consistency in intervention delivery. The scale measures mention of session-specific topics and procedures (eg, review of the prior week’s physical activity), use of motivational interviewing techniques, and that other psychological techniques are not used. Cases are reviewed and discussed in weekly supervision.
Control Content

Participants randomized to the control condition receive a Fitbit and instructions for its use at their randomization visit. They are also provided with educational information about physical activity and its benefits at 4 time points throughout the intervention period (in person at randomization visit, mailed or emailed at weeks 3, 6, and 9). The study research assistant calls control participants at the midpoint of the intervention period to ensure they are receiving educational materials. These include publicly available infographics from the Centers for Disease Control and Prevention and psychoeducation material used in primary care offices affiliated with this hospital discussing overcoming barriers to physical activity and giving instruction for simple strength exercises to be completed at home. Specific physical activity goals are not provided for control participants. Fitbits are provided to all participants to ensure that group differences are not simply due to Fitbit use.

Outcome Assessments

The primary outcomes of this study are feasibility and acceptability. Feasibility of the intervention is measured as the number of sessions attended by each participant. The intervention will be considered feasible if at least 7 of the 10 sessions are completed, on average. Intervention acceptability is measured using participant ratings on ease and utility of each intervention topic on a scale from 0 to 10 (0=“not at all easy/helpful”; 10=“very easy/helpful”). The intervention will be considered acceptable if average ratings are ≥7 out of 10.

Physical activity is assessed using accelerometers (ActiGraph GT3X-BT). At least 4 days of at least 600 minutes of wear time are required for data to be considered valid, according to established recommendations [45,46]. We will calculate average MVPA in terms of minutes per day (1952 counts per minute) and light physical activity (100-1951 counts per minute) and the daily step count. Raw data are analyzed using ActiLife (version 6.13.14; ActiGraph) in 60-second epochs. The International Physical Activity Questionnaire–Short Form is used to assess self-reported physical activity [42]. Self-efficacy for exercise is measured with the Self-Efficacy for Exercise Scale [47], exercise identity is measured with the Exercise Identity Scale [48], exercise enjoyment is measured with the Physical Activity Enjoyment Scale [49], and barriers to being active are measured with the Barriers to Being Active Quiz [50].

Psychological outcomes include positive affect measured using the Positive and Negative Affect Scale [51], optimism with the Life Orientation Test–Revised [52], symptoms of depression and anxiety with the Hospital Anxiety and Depression Scale [53], internalized weight bias with the Weight Bias Internalization Scale–Modified [54], and general self-efficacy with the General Self-Efficacy Scale [55].

Health-related outcomes include BMI, waist circumference (broadest hip and midpoint between last rib and iliac crest), percent body fat assessed with the RJL Systems Quantum IV Bioelectrical Impedance Analyzer, exercise capacity assessed using the 6-minute walk test [43], adherence to the MBS diet and vitamin regimen assessed with the Bariatric Surgery Self-Management Questionnaire [56], and general health status measured with the Short Form–12 [57]. All self-report measures have been validated in large samples.

Several physiological markers of cardiometabolic health are also measured at assessment points to test procedural feasibility in preparation for a future fully powered trial. These include blood pressure measured in mm Hg, blood lipids (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, and triglycerides), HbA1c, and high-sensitivity c-reactive protein. We do not anticipate meaningful changes in these measures in this pilot trial; hence, we have not included them as formal outcomes. Table 2 summarizes the timing of the assessments.
Table 2. Timing of assessments [56].

<table>
<thead>
<tr>
<th>Measure</th>
<th>Screening</th>
<th>Visit 1 (week 0)</th>
<th>Visit 2 (week 2)</th>
<th>10 weekly intervention calls</th>
<th>Visit 3 (week 14)</th>
<th>Visit 4 (week 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feasibility</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Completion rate</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Acceptability</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Weekly ratings</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Secondary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objective moderate to vigorous physical activity</td>
<td>N/A</td>
<td>Actigraph given</td>
<td>Actigraph returned</td>
<td>N/A</td>
<td>Actigraph mailed 1 week prior</td>
<td></td>
</tr>
<tr>
<td><strong>Additional outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objective light physical activity</td>
<td>N/A</td>
<td>Actigraph given</td>
<td>Actigraph returned</td>
<td>N/A</td>
<td>Actigraph mailed 1 week prior</td>
<td></td>
</tr>
<tr>
<td>Objective steps per day</td>
<td>N/A</td>
<td>Actigraph given</td>
<td>Actigraph returned</td>
<td>N/A</td>
<td>Actigraph mailed 1 week prior</td>
<td></td>
</tr>
<tr>
<td>Self-reported physical activity</td>
<td>χ²</td>
<td>X</td>
<td>N/A</td>
<td>Reported weekly from Fitbits and self-monitoring</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Self-efficacy for exercise</td>
<td>N/A</td>
<td>X</td>
<td>N/A</td>
<td>N/A</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Exercise identity</td>
<td>N/A</td>
<td>X</td>
<td>N/A</td>
<td>N/A</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical activity enjoyment</td>
<td>N/A</td>
<td>X</td>
<td>N/A</td>
<td>N/A</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Barriers to being active</td>
<td>N/A</td>
<td>X</td>
<td>N/A</td>
<td>N/A</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Positive affect</td>
<td>N/A</td>
<td>X</td>
<td>N/A</td>
<td>N/A</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Optimism</td>
<td>N/A</td>
<td>X</td>
<td>N/A</td>
<td>N/A</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Depression</td>
<td>N/A</td>
<td>X</td>
<td>N/A</td>
<td>N/A</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Anxiety</td>
<td>N/A</td>
<td>X</td>
<td>N/A</td>
<td>N/A</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Internalized weight bias</td>
<td>N/A</td>
<td>X</td>
<td>N/A</td>
<td>N/A</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>MBS diet and vitamin adherence</td>
<td>N/A</td>
<td>X</td>
<td>N/A</td>
<td>N/A</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>BMI</td>
<td>N/A</td>
<td>X</td>
<td>N/A</td>
<td>N/A</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>N/A</td>
<td>X</td>
<td>N/A</td>
<td>N/A</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Body fat percentage</td>
<td>N/A</td>
<td>X</td>
<td>N/A</td>
<td>N/A</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Exercise capacity</td>
<td>N/A</td>
<td>X</td>
<td>N/A</td>
<td>N/A</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>General health status</td>
<td>N/A</td>
<td>X</td>
<td>N/A</td>
<td>N/A</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

aN/A: not applicable.
bχ²: measure assessed at this timepoint.

**Analytical Approach**

**Power and Sample Size**

This feasibility study is not designed to detect significant between-group differences in physical activity and other outcomes; rather, its primary aim is to estimate feasibility and acceptability of the intervention. With 29 subjects receiving the intervention, we will be able to estimate the proportion who complete the intervention (feasibility) with a CI width of approximately ±0.2. We will examine the effect sizes of the intervention outcomes in addition to P values owing to low power.

**Statistical Analysis Plan**

We will calculate the average proportion of sessions completed to measure feasibility. The study will be considered feasible if at least 7 of 10 sessions are completed on average. Acceptability will be measured with means and SDs of participants’ ratings of session ease and utility, compared to our hypothesized target of ≥7 out of 10 for each rating. For physical activity and other psychological, behavioral, and physiological outcomes, we will model changes in each outcome using a repeated measures regression model with a fixed effect of treatment condition, a categorical effect of time, and a time by treatment interaction. The interaction will estimate the difference in the change with time comparing the treatment groups. To account for the repeated measures on each participant, we will use an
unstructured covariance matrix. In addition to tests of statistical significance, which will be exploratory, given the sample size, we will calculate effect sizes to estimate the magnitude of effect of the intervention. The effect size will be estimated as the difference in the mean change with time between the groups from the interaction term divided by the estimated SD of the change with time from the unstructured covariance matrix. All tests will be considered significant based on a 2-tailed α level of .05.

Results

Funding for this multiphase project was awarded in July 2020. The first 2 years of the award were developmental. Approval from the institutional review board for the proof-of-concept trial and RCT was attained in May 2021. The proof-of-concept trial was conducted from July 2021 through June 2022. Recruitment for the RCT began in July 2022, and study completion is anticipated by July 2024. The trial is registered at ClinicalTrials.gov [NCT04868032].

Discussion

We hypothesize that the GOALS intervention will be feasible and acceptable and will improve physical activity and psychological well-being. After bariatric surgery, patients typically do not meet physical activity recommendations, and they receive little guidance and support to help them succeed [13]. The GOALS trial addresses this need by testing a PP-MI intervention for physical activity, which is specifically customized to the needs of this population.

While health behavior change interventions are common, the PP-MI approach is novel in its additional focus on addressing the lack of positive reinforcement that may be restraining many from developing and maintaining a consistent physical activity routine and enhancing positive psychological well-being more broadly [33]. By incorporating positive psychological skill development with motivational interviewing, self-monitoring, and goal-setting for physical activity, we hope to build participants’ self-efficacy for being active while also teaching them how to make exercise a more enjoyable experience that they will want to continue doing. Results from other versions of PP-MI interventions in other medical populations suggest that this approach is generally accepted and leads to greater well-being and MVPA, even compared to active controls [37-39]. The GOALS intervention aims to further integrate the positive psychology approach with physical activity engagement by focusing specifically on the identification and building of positive affect during physical activity and by addressing psychological barriers to being active consistently.

Another strength of the GOALS intervention is its remote delivery. In-person postoperative interventions have struggled with attendance, with common barriers including living long distances from the clinic and lack of time off from work [58-61]. By using a written manual along with weekly phone calls, participants are able to complete GOALS assignments flexibly and can more easily fit in weekly sessions from work or home. They also learn how to build physical activity into their routines in a sustainable way by finding resources in their own environments to facilitate activity rather than attending a prescribed exercise training program that has an end date.

We chose to focus the GOALS intervention on physical activity exclusively rather than also including a diet component. This was in part because patients typically receive more guidance about the postoperative diet from their surgical center than they do about physical activity. Further, we decided to focus more on the direct mental and physical health benefits of physical activity instead of encouraging exercise as a tool to lose more weight. While dietary changes are more strongly associated with weight loss than with increasing physical activity [62], patients can achieve significant health benefits from increasing physical activity independent of their weight [14-17]. By focusing on these nonweight motivators, physical activity may be more likely to improve body image [63]. When considering that long-term maintenance of physical activity after weight loss from surgery is complete, building motivators separate from weight loss is critical.

We chose the time window of 6-12 months post bariatric surgery for study enrollment based on careful consideration of several factors. By 6 months, most patients have completed standard postoperative group sessions and other care, so they may have time and interest in additional support at that time. This also allows us to target patients who have not been able to sufficiently increase physical activity on their own, as by 6 months, their physical recovery from surgery should be complete, as should their adaptation to the new diet. We limited the maximum time since surgery to 12 months to identify people who still have high motivation to make weight-related behavioral changes following their surgery.

Strengths of the study include an iteratively developed intervention incorporating patient preferences and feedback, remote delivery, randomized design, and objective measurement of physical activity and biometric outcomes. Study limitations include a small sample size with insufficient power to detect significant effects at this pilot stage and single-site delivery, which may reduce the generalizability of our results.

If the GOALS pilot RCT is feasible, acceptable to patients, and leads to improvements in physical activity and psychological outcomes, the next step will be to test the efficacy of GOALS on physical activity in a full-scale trial. Ultimately, a program such as GOALS could be integrated into clinical postoperative care as a remotely delivered, longer-term approach to promote physical activity and psychological well-being after bariatric surgery.
Data Availability
The data sets generated during and analyzed in this study will be available from the corresponding author on reasonable request at study completion.

Conflicts of Interest
None declared.

References


Abbreviations

GOALS: Gaining Optimism After weight Loss Surgery
MVPA: moderate to vigorous physical activity
ORBIT: Obesity-Related Behavioral Intervention Trials
PP-MI: positive psychology–motivational interviewing
RCT: randomized controlled trial

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Protocol

Providing Accessible ReCreation Outdoors–User-Driven Research on Standards: Protocol for Mobile and Web-Based Interviews for Winter Assessments

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Abstract

Background: Although there have been recent efforts to improve access to Canadian national parks, many remain not fully accessible to people with disabilities. Winter conditions, in particular, present challenges that limit their participation in outdoor activities.

Objective: This study aimed to develop a novel method to assess park access during winter, which will inform recommendations for national park standards to meet the needs of all park visitors (regardless of ability) during winter conditions.

Methods: A larger participatory mixed methods research project exploring park access was adapted. A 3-phase approach has already been proposed to achieve the study objectives. In the first phase, a scoping review of the existing accessibility standards will be conducted. In the second phase, objective audits of trails and features in 6 parks, 3 in western Canada and 3 in eastern Canada, will be conducted, as well as mobile interviews with 24 various participants in each region regarding their experiences of and recommendations for improving the park’s accessibility. In the final phase, a Delphi participatory consensus development process will be used, based on the data gathered in the first 2 phases, to prioritize recommendations for standards. This paper will focus on the second phase of the study, specifically on whether the in-person winter mobile interviews (ie, walking and wheeling interviews) with people who have a wide range of disabilities while visiting 3 parks in 2 provinces were modified. Changes were made to accommodate the extreme winter weather conditions in Quebec while using safe and informative data collection methods.
Results: In Quebec, one park, where winter conditions are safer, has been assessed in person (n=4). Web-based interviews were used to facilitate the assessment of other winter and summer conditions in two other parks (n=8). Winter and web-based interviews were completed in April 2022. Data are currently being collected and analyzed, and results will be completed by December 2022.

Conclusions: We expect that adapting the protocol to gather further information on winter conditions and access to parks will provide high-quality and rich data to better inform park access standards. This participatory mixed methods research will inform the development of park standards that consider the accessibility needs of all people.

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KEYWORDS
parks; accessibility; standards; user-oriented research; winter; disability; access; participatory; national parks; barriers; participation; Canada; national park; participation; outdoor; activity; standard; interview; safe; virtual; summer; data; mix-method; development

Introduction

Background
The purpose of this study is to inform accessibility standards in Canadian national parks. Such technical standards do not exist. The protocol, which was previously published [1], reported a participatory approach that will be used with people with disabilities in British Columbia (BC) and Quebec, Canada. A 3-phase approach has already been proposed to achieve the study objectives. In the first phase, a scoping review of the existing accessibility standards will be conducted. In the second phase, objective audits of trails and features in 6 parks, 3 in western Canada and 3 in eastern Canada, will be conducted, as well as mobile interviews with 24 various participants in each region regarding their experiences of and recommendations for improving the park’s accessibility. In the final phase, a Delphi participatory consensus development process will be used, based on the data gathered in the first 2 phases, to prioritize recommendations for standards.

This paper describes the modifications made to address specific challenges related to extreme winter conditions that were experienced at the beginning of the study and, thus, the second phase of the study.

Winter conditions can present serious obstacles for individuals living with a wide range of disabilities (snow and ice made walking dangerous, tires and casters becoming stuck in the snow, difficulty ascending inclines or ramps, and cold hands while using controls or pushing rims, frozen batteries, seat cushions or backrests, or electronics) [2-6]. Having initiated our research activities, we have identified some challenges in carrying out interviews with certain disability groups during winter weather conditions. For example, in discussions with walker and cane users, we learned that the distances and unsafe trail conditions during winter were key barriers to completing the in-person mobile interviews as originally proposed. Thus, our data collection will be incomplete if we rely solely on in-person interviews at the park. We found that even moderate to easy park conditions can be too challenging for some participants, in all weather conditions. As a result, the distances participants can travel limits the number of features they are able to assess and provide feedback on. This is intensified in cold winter conditions where the health risks to participants and the reduction in distances they are able to travel will significantly reduce the breadth and depth of data we are able to collect.

Objectives
The overall goals of the main study remain the following: (1) to identify park accessibility standards that exist internationally, (2) to identify the accessibility challenges that people with disabilities face in park environments, and (3) to prioritize and recommend accessibility standards for national parks.

The specific objective of this paper is to describe the modified protocol that will be used to inform park standards in summer and winter conditions in Quebec. These protocol modifications will only be made in Quebec, where winter conditions pose more difficult or dangerous experimental conditions, including the transportation risks owing to driving to the mountain parks at this time of the year.

Advisory committees were created in both provinces (Quebec and BC), including individuals with a variety of disabilities (one in each province) to ensure the consideration of inputs or concerns of these individuals in the research project through a participatory research approach. These committees include individuals with mobility, visual, and hearing disabilities; intellectual disabilities; autism spectrum disorder; dementia; and Alzheimer disease. Quebec’s committee was specifically solicited to validate the proposed modifications to the protocol described in this paper.

Methods

Overview
Modifications have been made to the second phase of the project that involves in-person mobile interviews. The proposed mobile interview protocol was previously published [1]. Interviews will take place in the park assigned to the participants. The interviews will be administered by trained researchers. The mobile interview will take approximately 2 hours along 3 predetermined routes of 500-1300-m length during both summer and winter.

In Quebec, 2 of 3 parks will be evaluated through web-based interviews in winter (n=8 participants). One park, located in an urban location with nearby amenities, will be evaluated using the initial in-person mobile interview protocol format (n=4 participants), as participant safety can be assured.

https://www.researchprotocols.org/2022/10/e38715
Web-based interviews facilitate the collection of feedback on features that were planned and, beyond this, by including footage of park elements that are not in the parks, which we selected to be assessed in person. This approach will allow us to collect data when we otherwise might not be able to because most mobility-aid users will be unable to get to or use the trails in winter.

Web-based interviews will also be used to explore access issues in summer conditions with participants who will take part in web-based interviews to allow for comparison. This will ensure comparable results, help inform national standards more effectively, retain methodological consistency, and enable us to gather data from people who would not be able to participate in our original protocol. These adaptations are an example of the participatory nature of the study where the concerns of participants were considered to refine the mechanisms for data collection.

**Mobile Versus Web-Based Interviews**

In Fall 2021, the weather became very cold with snow accumulation in Quebec. Four in-person mobile interviews were conducted as originally planned, at which time we observed that participants provided fewer details when answering questions during the in-person winter mobile interviews because they felt uncomfortable (eg, too cold). To address this challenge, we attempted to reduce burden on participants by focusing on questions about features that were altered owing to weather.

The data collection plan retains the preinterview survey from the original protocol and adapts the in-person mobile interview to take into consideration participant burden [1]. Participants who take part in the in-person winter mobile interviews will also complete a summer in-person mobile interview. This strategy will allow us to collect rich data in both winter and summer conditions, while ensuring the comfort and safety of the participants. Table 1 presents a summary of each step.

In addition to the in-person mobile interviews, we will perform web-based interviews. Videos and pictures of trails and features that are similar to those found in national parks were collected from parks in the Quebec City region (eg, Parc Jacques Cartier, Forêt Montmorency, and Plaines of Abraham) both in summer and winter as well as web-based images from national parks to depict the breadth of potential activities available in parks across seasons and the potential for accessibility barriers. Web-based summer interviews will be conducted at the same time for methodological consistency by using the same approach as the web-based winter interviews.

The web-based interviews will not be mobile interviews. The aim is not to comment on a trail as we view it in its entirety but rather to show participants various park features in different contexts to obtain as much feedback as possible on them. The videos and pictures will elicit impressions and opinions to complete a semistructured interview. The web-based interviews will be conducted in the participants’ home or at the research center depending on participant preference. Participants will review videos and pictures of features and trails on a computer monitor or electronic device. Blind and low-vision individuals will not take part in web-based interviews; the in-person mobile interviews allow them to better experience the environment, which could only be described at great lengths to provide sufficient details to truly inform them. A similar set of questions as those in the in-person interviews will be used in the web-based interviews. This will include items from the Stakeholders’ Walkability/Wheelability Audit in Nature (SWAN-PARKS) instrument and open-ended questions to assess trail and feature accessibility and conditions and explore the positive and negative impressions of the experience. Participants will also be asked to provide recommendations for improving the interview experience.

However, way-finding exercises as described in the original protocol, such as estimating distance and slope, pointing to the origin of the route, and sketching maps of the route, which are part of the in-person mobile interviews, will not be conducted during the web-based interviews [1].
Table 1. Summary of steps of in-person mobile interviews from the original protocol and modifications for web-based interviews.

<table>
<thead>
<tr>
<th>Step and summary</th>
<th>Status of modification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Preinterview survey</strong></td>
<td>Unchanged, will be done for web-based interviews in the same manner as the in-person mobile interviews</td>
</tr>
<tr>
<td>Web-based questionnaire (Qualtrics) about sociodemographic characteristics (eg, age and sex), disability and mobility status (eg, diagnoses and assistive aids used), subjective wayfinding skills, preferences for park settings and activities, and transport mode to parks</td>
<td></td>
</tr>
<tr>
<td><strong>2. Mobile interviews</strong></td>
<td>Unchanged for in-person summer and winter mobile in-person interviews</td>
</tr>
<tr>
<td>Interviews in the park assigned to the participant [7-9] (administered by trained researchers) along 3 predetermined routes of 500-1300–m length (recorded audio and film)</td>
<td>In-person summer and winter mobile interviews</td>
</tr>
<tr>
<td>Map of the intended route of exercise to ask for expectations</td>
<td></td>
</tr>
<tr>
<td>Structured questions (presence or absence of features or characteristics): Stakeholders’ Walkability/Wheelability Audit in Nature (SWAN-PARKS) tool</td>
<td>Only for in-person summer mobile interviews</td>
</tr>
<tr>
<td>Semistructured questions (about their experiences related to way-finding and wayfaring)</td>
<td></td>
</tr>
<tr>
<td><strong>3. Postroute interview questions (for each of the 3 routes)</strong></td>
<td>Only for in-person summer mobile interviews</td>
</tr>
<tr>
<td>Objective spatial skills test: orientation and estimation skills. Participants will be positioned at a predefined location and asked to point a compass in the direction of the origin of the route. They will also be asked to estimate the distance and slope to a predefined landmark in the distance [10,11]</td>
<td>In-person summer and winter mobile interviews</td>
</tr>
<tr>
<td>Rate the route on a 7-point Likert scale: perceived physical demand, mental demand, safety, enjoyment, and confidence to find their way independently</td>
<td></td>
</tr>
<tr>
<td>Recall the route verbally or by drawing the route and all its features onto a route map [12]</td>
<td>Only for in-person summer mobile interviews</td>
</tr>
<tr>
<td>Describe the wayfaring and wayfinding experiences overall and provide additional feedback and recommendations</td>
<td>In-person summer and winter mobile interviews. For winter, changes due to seasonality will be noted</td>
</tr>
</tbody>
</table>

**Types of Interviews**
Participants of the web-based interviews will complete the data evaluations for both summer and winter conditions using the methods described above. As for the in-person mobile interviews, including those conducted during winter, there are no changes to the protocol followed in BC (the second site), and all interviews will be conducted on site. In Quebec, 4 in-person winter mobile interviews will be conducted at Plains of Abraham (the participants are already recruited), where conditions can be mitigated more easily. The remaining 8 will be web-based interviews.

**Sample Distribution**
The number of people to be interviewed and the distribution of participants by disability or mobility type will remain unchanged; that is, a purposive sample of 48 people (24 at each site) with a broad range of disabilities, who use a variety of mobility devices, will be recruited. To be included, participants will need to be at least 18 years of age, able to travel approximately 3 km with rests over a 2-3–hour period, and able to communicate directly with researchers (verbally) or indirectly through an assistant or attendant. Participants will be recruited through partners and participants from previous studies and selective advertising if necessary.

We intend to recruit 24 participants for summer (3 manual wheelchair users, 3 power wheelchair users, 3 scooter users, 3 people who use walkers, 3 people who use canes or crutches, 2 people who are D/deaf and hard of hearing, 3 people who are blind, and 4 people with cognitive impairments) and 12 for winter interviews at each site.

**Participants**
Table 2 presents an overview of the participants’ distribution in Quebec. Overall, 24 participants will be recruited in Quebec (8 for Plains of Abraham—4 of whom will participate in both the in-person summer and the winter mobile interviews and 4 will participate in only the summer interviews; 4 in-person summer mobile interviews each for Jacques-Cartier National Park and Forêt Montmorency; and 8 web-based interviews that include both summer and winter conditions).
Table 2. Sample distribution (Quebec) according to participants characteristics.

<table>
<thead>
<tr>
<th>Category</th>
<th>In-person mobile interview at Plains of Abraham during summer</th>
<th>In-person mobile interview at Plains of Abraham during winter</th>
<th>In-person mobile interview at Jacques-Cartier National Park during summer</th>
<th>In-person mobile interview at Forêt Montmorency during summer</th>
<th>Web-based interview</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheelchair mobility</td>
<td>1 with a scooter, 1 with a power wheelchair (PWC), and 1 with a manual wheelchair (MWC)</td>
<td>1 with a PWC and 1 with an MWC</td>
<td>1 with a scooter and 1 with a PWC</td>
<td>1 with a PWC</td>
<td>1 with a scooter and 2 with MWCs</td>
</tr>
<tr>
<td>Walkers, canes, or crutches</td>
<td>1 with a walker and 1 with a cane</td>
<td>None</td>
<td>None</td>
<td>1 with a cane</td>
<td>2 with walkers and 1 with a cane</td>
</tr>
<tr>
<td>Visual disability</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>Hearing disability</td>
<td>1</td>
<td>None</td>
<td>None</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>Cognitive disability</td>
<td>1</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>4 of the 8</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Total during summer (n=24)</td>
<td>8</td>
<td>None</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Total during winter (n=12)</td>
<td>None</td>
<td>4</td>
<td>None</td>
<td>None</td>
<td>8</td>
</tr>
</tbody>
</table>

Data Analysis: Descriptive Analysis

Transcripts generated from the in-person mobile and web-based interviews will document what was being said or observed and by whom. Pertinent quotes will be coded to reflect the feature or experience being explained (way-finding or wayfaring) by the participant and any observation made by the researchers [1].

For in-person mobile interviews, the quotes and their codes will be digitized in the geographical information system (GIS) at the location that it occurred. This will be linked to the participant survey responses through their ID as a separate file in the GIS (delimited file without spatial information) [1].

For the web-based interviews, as for the in-person mobile interviews, a mixed methods coding process will be used. We identified a list of codes in accordance with the content of the web-based interview guides, and we will adjust the codes in accordance with the emerging data [13]. According to Linneberg and Korsgaard [14], "As the research process develops, so does the type of coding, which also allows the researcher to move from basic descriptive codes toward answering the research question posed." Web-based interviews will not be analyzed using the spatial transcript method as described in the original protocol because the activity will not occur in the parks; therefore, there will be no geospatial contextual information available.

Ethical Considerations

The study was approved by Behaviour Research Ethics Boards at the Centre intégré universitaire de santé et de services sociaux de la Capitale-Nationale (Project #2021-2120) and the Research Ethics Board at the University of British Columbia (H20-04036). Approval was also obtained from the regional health authorities at each site. All study participants will provide informed consent. Evaluation in parks started in August 2021, and web-based interviews started in March 2022.

Results

Funding for this study was obtained from Accessibility Standards Canada. Using the web-based interviews along with the already proposed in-person mobile interviews allows us to examine features that participants would not be able to comment on because of topography or weather conditions. The results support the development of a spatial transcript and thematic analysis that helps decipher patterns of park experiences between participants across diverse variables such as gender, mobility device use, way-finding abilities, and season. A grounded visualization approach will be used to examine the qualitative and quantitative data derived from the in-person and web-based methods. This involves an iterative analysis of the results, including topographical data derived from open data and the environmental audit such as slope, cross slope, and trail surface conditions to gain a better understanding of the park experience [15,16]. This approach provides a thick, spatially contextualized description of the interactions and perceptions that people with disabilities have with the natural environment and provides the funding agency with more information for the identification of accessibility standards in a park context. Data collection, analysis, and results will be completed by the end of 2022.

Discussion

Principal Findings

The purpose of the original protocol previously published [1] was to describe the methodology for informing park accessibility standards. The modified approach proposed in this paper will facilitate data collection on park access for people with diverse disabilities during winter months, as well as the rest of the year, while reducing discomfort and risk. Not everyone has the ability or the capacity to use park installations as they are currently built, regardless of weather conditions. Additionally, cold temperatures, snow accumulation, and icy roads and trails make
it difficult to move around parks. As a result, the area that can be assessed in the park would be reduced, and this would limit our ability to collect data. This will also allow us to obtain feedback about features and activities that people with disabilities have never been able to participate in because of accessibility issues. This would assist with site planning (placement of features), which is a significant concern of the Accessibility Standards Canada’s Outdoors Accessibility Committee that is currently developing standards (which author MP is a member).

In addition to allowing us to obtain feedback about more features in the park, web-based interviews may make recruitment more successful. Many of the challenges that limit mobility also affect decisions regarding study participation. Conducting interviews in participants’ homes or at the laboratory will reduce travel demands on participants and mitigate the impact of being outdoors for several hours during the in-person mobile interview.

To our knowledge, this is the first study to leverage a web-based interface for collecting data about outdoor environments with people with disabilities. The potential impacts generated by the modification of the original protocol include the possibility of exploring more barriers and access issues in a wider range of parks and conditions. Most people with disabilities avoid going out in the winter but would still like to be active [4,17]. They might not be aware of the potential opportunities that exist. Using the web-based method allows us to explore these features and better inform accessibility standards. Without the web-based method, this exploration would not be possible.

Limitations
This project targets national parks. It is hoped that the obtained finding could also be useful in the design of community parks, but these kinds of parks were not specifically targeted in this project. The limitations of this approach are a modest reduction of insights on the real-world experiences of people with disabilities travelling along winter trails and limited feedback about wayfinding requirements. However, these changes are proposed to maximize participant safety, while no adapted equipment is available on site. These limitations are mitigated by the fact that we will complete these activities in the winter in 1 park in Quebec and all 3 parks in BC.

Conclusions
People with disabilities' valuable insights on winter conditions and parks will inform accessibility standards to be used in national parks and beyond. Accessibility in winter conditions can be very difficult to attain and very difficult to assess in real-life situations for certain groups. This also applies to certain individuals in summer conditions. By gathering individuals with disabilities’ opinions using a variety of methods that allow individuals to participate in the discussion regarding park access during all seasons while respecting their capacities can provide a solid basis on which to better plan park design to overcome obstacles during all seasons.

Acknowledgments
The authors would like to thank Accessibility Standards Canada for their generous funding and our partners and committee members for assisting in designing and recruiting participants for the study. FR is supported by a Quebec Health Research Funds Senior Salary Grant. KLB is supported by a Quebec Health Research Funds Junior 1 Salary Award. WBM was supported by a New Investigator Award from the Canadian Institutes of Health Research.

Conflicts of Interest
None declared.

References

https://www.researchprotocols.org/2022/10/e38715
Protocol

A Multilevel Integrated Intervention to Reduce the Impact of HIV Stigma on HIV Treatment Outcomes Among Adolescents Living With HIV in Uganda: Protocol for a Randomized Controlled Trial

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Abstract

Background: HIV stigma remains a formidable barrier to HIV treatment adherence among school-attending adolescents living with HIV, owing to high levels of HIV stigma within schools, rigid school structures and routines, lack of adherence support, and food insecurity. Thus, this protocol paper presents an evidence-informed multilevel intervention that will simultaneously address family- and school-related barriers to HIV treatment adherence and care engagement among adolescents living with HIV attending boarding schools in Uganda.

Objective: The proposed intervention—Multilevel Suubi (MSuubi)—has the following objectives: examine the impact of M-Suubi on HIV viral suppression (primary outcome) and adherence to HIV treatment, including keeping appointments, pharmacy refills, pill counts, and retention in care; examine the effect of M-Suubi on HIV stigma (internalized, anticipated, and enacted), with secondary analyses to explore hypothesized mechanisms of change (eg, depression) and intervention mediation; assess the cost and cost-effectiveness of each intervention condition; and qualitatively examine participants’ experiences with HIV stigma, HIV treatment adherence, and intervention and educators’ attitudes toward adolescents living with HIV and experiences with group-based HIV stigma reduction for educators, and program or policy implementation after training.

Methods: MSuubi is a 5-year multilevel mixed methods randomized controlled trial targeting adolescents living with HIV aged 10 to 17 years enrolled in a primary or secondary school with a boarding section. This longitudinal study will use a 3-arm cluster randomized design across 42 HIV clinics in southwestern Uganda. Participants will be randomized at the clinic level to 1 of the 3 study conditions (n=14 schools; n=280 students per study arm). These include the bolstered usual care (consisting of the literature on antiretroviral therapy adherence promotion and stigma reduction), multiple family groups for HIV stigma reduction plus family economic empowerment (MFG-HIVSR plus FEE), and Group-based HIV stigma reduction for educators (GED-HIVSR). Adolescents randomized to the GED-HIVSR treatment arm will also receive the MFG-HIVSR plus FEE treatment. MSuubi will be provided for 20 months, with assessments at baseline and 12, 24, and 36 months.
Results: This study was funded in September 2021. Participant screening and recruitment began in April 2022, with 158 dyads enrolled as of May 2022. Dissemination of the main study findings is anticipated in 2025.

Conclusions: MSuubi will assess the effects of a combined intervention (family-based economic empowerment, financial literacy education, and school-based HIV stigma) on HIV stigma among adolescents living with HIV in Uganda. The results will expand our understanding of effective intervention strategies for reducing stigma among HIV-infected and noninfected populations in Uganda and improving HIV treatment outcomes among adolescents living with HIV in sub-Saharan Africa.

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KEYWORDS
HIV/AIDS; stigma; adolescents; school

Introduction

Background

HIV/AIDS among adolescents remains a public health concern worldwide. Over 1.7 million children aged <15 years live with HIV [1], and almost half of all new HIV infections worldwide occurs in youth aged 15 to 24 years [2]. Sub-Saharan Africa (SSA) bears the brunt of the HIV epidemic in children and adolescents, accounting for more than 88% of the global population of adolescents living with HIV and 80% of the 460,000 new infections worldwide among adolescents [1]. Uganda is home to more than 170,000 adolescents living with HIV. This figure is expected to increase as adolescents remain highly vulnerable to HIV infection [3], perinatal transmission of HIV continues to occur [4], and expanded access to antiretroviral therapy (ART) increases the longevity of persons infected with HIV [5-7]. However, similar to other countries [8-11], adolescents living with HIV in Uganda have lower levels of ART adherence (<50%) [12,13], low rates of viral suppression [14], and high attrition from HIV care than children and adults living with HIV [15-18]. Nonadherence to HIV care potentiates secondary transmission of drug-resistant HIV among nonvirally suppressed adolescents living with HIV engaging in unprotected sex [19-21], and undermines global efforts to eradicate AIDS [22]. Without improvements in HIV prevention, testing, and treatment, a staggering 360,000 adolescents may die of AIDS-related diseases by 2030 [4].

Adolescents living with HIV in boarding schools are more disadvantaged and have lower levels of HIV treatment adherence. HIV stigma [23-25], poverty (including food insecurity) [26,27], and poor mental health [13,28-31] are increasingly being listed as the most potent barriers to ART adherence in Uganda and SSA. The school social context is very disadvantageous for adolescents living with HIV. First, adolescents living with HIV lack the family support that typically facilitates treatment adherence [13,32]. Second, the lack of privacy (given the living arrangements) coupled with high levels of HIV stigma (internalized, anticipated, and enacted) heightens adolescents living with HIV’s concerns about unintentional disclosure of HIV status. In our preliminary studies, adolescents living with HIV reported shaming, peer rejection, and exclusion from school activities after disclosure of their HIV status, resulting in suicidal thoughts and thoughts of school dropout [33,34]. Third, poverty-related food insecurity, manifesting as lack of food to accompany medications, is another barrier [35-38]. Adolescents living with HIV are often advised to take their drugs at bedtime to reduce medication side effects (eg, drowsiness or nausea) that may interfere with school activities. However, taking drugs on an empty stomach usually amplifies side effects. Poor parents are often unable to supplement their children’s school meals to support treatment adherence. The aim of this study is to examine the effects of an evidence-informed multilevel intervention—Multilevel Suubi (M-Suubi)—that seeks to simultaneously address multiple barriers to HIV treatment adherence and care engagement among school-attending adolescents living with HIV in Uganda.

High levels of HIV stigma persist in SSA, including Uganda [39,40], creating a formidable barrier to HIV treatment adherence among adolescents living with HIV [23-25]. Stigma is a societal process that manifests at multiple socioeconomic levels [41,42]. HIV stigma can manifest internally (ie, internalized and anticipated stigma) based on the perceived negative public attitude and encompassing feelings of one as reprehensible, damaged, and ineffective. These feelings may lead to mental health problems such as depression, posttraumatic stress disorder, suicidal ideation [33,43-45], feelings of loneliness and social isolation [23,46,47], diminished physical health [48-51], sexual risk behavior [52,53] and poor treatment adherence [20,25,54-57]. Adolescents living with HIV experience internal and external HIV stigma (ie, anticipated and enacted stigma, respectively) within homes and schools [58]—the most important adolescent development contexts. Many adolescents living with HIV live in extended family settings (owing to orphanhood), where enacted stigma is perpetuated through rejection, verbal insults, and ostracism [23,59-63]. Family members are often condemned and stigmatized in similar ways because of their association with adolescents living with HIV (ie, associative stigma) [64], which can negatively affect family functioning. Within schools, HIV stigma is rampant among peers and educators (eg, teachers, administrators, and nurses), manifesting as gossip, rejection, harassment, social isolation, and loss of friendship and social support [23,58,60,65]. Educators are often indiscernent, ignorant about HIV/AIDS, and uncaring and unresponsive to enacted stigma within schools [65]. These experiences can diminish adolescents living with HIV’s ability to develop a positive self-concept and form strong bonds with family members and
peers and increase their risk of mental health problems. HIV stigma and social exclusion lead to, or exacerbate mental health symptoms (eg, depression and suicidal ideation) and contribute to school dropout [23,33,34,58,60,66]. HIV stigma also undermines HIV treatment adherence and impedes adolescents living with HIV’s access to social support in school settings [65,67]. These adverse effects of HIV underscore the urgent need for interventions to reduce HIV stigma within schools and families.

HIV stigma exists at the intersection between HIV and poverty and perpetuates disparities among people living with HIV by concentrating the adverse impacts of HIV stigma on the poor [68,69]. Poverty is rampant among HIV-affected households [70-72] and is a significant risk factor for HIV acquisition [73] and poor HIV treatment outcomes [26,27]. People living with HIV from poverty-stricken households face greater challenges in accessing and sustaining HIV treatment owing to economic challenges, such as lack of transport to clinics [74,75] and inadequate meals to support medication adherence [36,38,76]. Numerous studies conducted in SSA [35-38], have identified food insecurity as a formidable barrier to ART adherence. Within boarding schools, inadequate nutrition or lack of foods or snacks may dissuade adolescents living with HIV from taking their medications because of concerns that taking drugs on an empty stomach can intensify side effects. Poverty can adversely affect the quality of family relationships, including parent-child communication, involvement [77-79] and parenting skills [80,81], which increases adolescents’ susceptibility to poor outcomes such as emotional and behavioral adjustment [78,82-86].

In SSA, where HIV has disrupted the social function of the family, schools are potential substitutes for providing supportive developmental contexts that can mitigate the risks for poor outcomes in vulnerable children, including adolescents living with HIV [87,88]. For adolescents living with HIV, the typical developmental challenges of adolescence are compounded by HIV-related challenges such as managing complex drug regimens, coping with multiple bereavements, comorbidities, and social challenges (eg, HIV disclosure) [89-91]. As such, adolescents living with HIV need additional support to successfully negotiate adolescence. However, poverty and food insecurity undermine their ability to fully participate in school, and HIV stigma in schools undermines their potential to support adolescents living with HIV. School-attending adolescents spend a large part of the day away from home, and for adolescents living with HIV, this means that they must take their daily medication while at school. Treatment is even more challenging for more than 60% of adolescents living with HIV who spend 9 to 10 months a year away from home in boarding sections—a form of parental opt-in institutional care with limited family visitation (typically monthly). Adolescents living with HIV in boarding schools are vulnerable to HIV stigma, abuse, poor nutrition, mental and physical difficulties, and poverty [23,58-60,67] and have significantly lower levels of ART adherence compared with adolescents living with HIV in day schools [92]. The lack of attention to addressing the school-related needs of the large population of in-school adolescents living with HIV in Uganda and other high HIV burden countries in SSA has adverse consequences for ongoing efforts to end the AIDS epidemic [22]. Targeting HIV stigma within schools is necessary to enhance HIV treatment outcomes and the educational achievement for adolescents living with HIV in SSA.

Recent systematic reviews indicate that interventions to reduce HIV stigma among adolescents living with HIV in resource-limited settings are almost nonexistent [93-98]. For example, of the 48 stigma reduction interventions [97], only 3 studies were aimed at people living with HIV in SSA, and none of these interventions targeted adolescents living with HIV or assessed the impact of stigma reduction on HIV treatment outcomes among adolescents living with HIV. Moreover, these interventions tend to be single-level focused (eg, focus exclusively on family) and use a limited range of intervention strategies [97]. Although several interventions have shown promise in improving HIV treatment adherence among adolescents living with HIV [99-102], they mostly focus on adolescents living with HIV commuting daily from home. However, the majority (>60%) of school-going children in Uganda (and in many sub-Saharan African countries heavily impacted by HIV) spend their time in boarding sections. The lack of attention to this group undermines the efforts to achieve the 95-95-95 targets in SSA. Building on our experience using multiple family groups (MFGs) and family economic empowerment (FEE) interventions to improve health outcomes among adolescents recruited from schools and clinics [26,78,103-106] and supported by the literature on the impact of HIV stigma within families and schools [23,33,34,58,60,65-67] and the impact of FEE on HIV treatment outcomes [107-111], we propose testing a culturally acceptable asset-based multilevel intervention (M-Suubi) that targets HIV stigma within schools and families to improve HIV treatment outcomes among adolescents living with HIV.

**Objectives**

Although several interventions have shown promise in improving HIV treatment adherence among adolescents living with HIV [99-102], they mostly focus on adolescents living with HIV commuting daily from home. However, most school-going children in Uganda and many sub-Saharan African countries heavily impacted by HIV spend their time in boarding sections. The lack of attention to this group undermines the efforts to achieve the 95-95-95 targets in SSA. Our research finds that MFG and FEE [27,100] can improve HIV care outcomes among adolescents living with HIV. Moreover, consistent with the existing literature in SSA [33], our recent combination intervention study, Bridges, situated within Ugandan schools, points to the importance of building supportive familial and school environments for adolescents affected by HIV/AIDS, including adolescents living with HIV [112-115]. Building on prior experience and evidence of effective HIV stigma reduction strategies [40,95,98,116], we propose to examine an evidence-informed multilevel intervention called M-Suubi (the word suubi means hope) intervention that seeks to simultaneously address multiple barriers to HIV treatment adherence and care engagement among adolescents living with HIV attending boarding schools in Uganda. M-Suubi comprises of three study conditions: (1)...
Bolstered usual care consisting of literature on ART adherence promotion and stigma reduction, (2) MFG for HIV stigma reduction plus FEE (MFG-HIVSR plus FEE), and (3) group-based HIV stigma reduction for educators (GED-HIVSR). The study is guided by the HIV stigma framework [64], asset theory [117,118], and family system theory [119,120] and has the following goals:

- **Aim 1:** examine the impact of M-Suubi on HIV viral suppression (primary outcome) and adherence to HIV treatment, including keeping appointments, pharmacy refills, pill counts, and retention in care.
- **Aim 2:** examine the effect of M-Suubi on HIV stigma (internalized, anticipated, and enacted), with secondary analyses to explore hypothesized mechanisms of change (eg, depression) and intervention mediation.
- **Aim 3:** assess the cost and cost-effectiveness of each intervention condition.
- **Aim 4:** qualitatively examine participants’ experiences with HIV stigma, HIV treatment adherence, and intervention.

Figure 1. Study conditions and assessments. BSOC: bolstered standard of care; FEE: family economic empowerment; GED-HIVSR: group-based HIV stigma reduction for educators; MFG-HIVSR: multiple family groups HIV stigma reduction for educators.

**Theoretical Framework**

This proposal is guided by the HIV stigma framework [64], asset theory [117,118], and family systems theory [119,120]. The HIV stigma framework [64] suggests that HIV stigma affects people living with HIV via three distinct mechanisms: stereotyping (cognitive), prejudice (affective), and discrimination (behavioral). M-Suubi focuses on all forms of HIV stigma (internalized, anticipated, and enacted) and uses a range of strategies (eg, education, skill building, empowerment, and empathy) to address HIV stigma at the individual, interpersonal, and institutional levels [95-98]. Consistent with a multilevel approach to HIV stigma reduction, M-Suubi targets following three ecological levels: (1) school using GED-HIVSR, (2) family using MFG-HIVSR plus FEE, and (3) individual (adolescents living with HIV) using locally adapted Suubi-MAKA [105,121,122] and Suubi+Adherence [26,123,124] curricula. All intervention arms use a variety of strategies (eg, education, cognitive restructuring, empowerment, and skill building) to address HIV stigma.

Our rationale for pairing MFG-HIVSR with FEE comes from mounting evidence that cognitive and behavioral changes in adolescents are influenced by economic stability, whereas family support and protective processes are needed to reinforce and maintain engagement in protective health behaviors. MFG-HIVSR will provide a safe setting for parents and their children to address HIV stigma, foster family communication, facilitate optimism and morale by normalizing shared experiences with other families, and enhance interpersonal and coping skills. FEE will alleviate the impact of family economic insecurity; hence, mitigating the potential impact of food insecurity on ART adherence and caregiver engagement among the study participants. More specifically, financial security will enable parents to support their children in schools through visitations and supplemental nutrition. For adolescents living with HIV, internalized stigma is targeted in the MFG-HIVSR using the locally adapted Suubi+Adherence curriculum [123] that discusses several adherence barriers including HIV stigma. These strategies will impact a range of psychological, behavioral, and health outcomes among adolescents living with HIV, caregivers, and educators. Guided by the HIV stigma framework, the GED-HIVSR targets educators (ie, teachers, school nurses, matrons, and administrators) to build HIV knowledge, foster empathy, and build support for adolescents living with HIV in boarding schools, whereas the MFG-HIVSR targets HIV stigma within families. Asset-based and family systems theory guides the MFG-HIVSR and FEE to alleviate poverty within families. Asset theory also guides our approach to GED-HIVSR, where we draw on skills and values of...
educators, emphasize the identification of resources within schools and the local community, and encourage educators to develop their own plans to support the needs of adolescents living with HIV, potentially promoting the ownership of intervention activities.

### Setting and Study Population

The target populations for this study are adolescents living with HIV, their caregivers, and educators within the Greater Masaka region in southwestern Uganda, a region heavily affected by HIV [125]. We plan to recruit 840 adolescents living with HIV and their caregivers from 42 community health centers (with HIV clinics) and their primary and secondary schools. We will work with clinics affiliated with Reach The Youth, our local implementing partner. For adolescents living with HIV randomized to treatment arm 2 (ie, MFG-HIVSR plus FEE and GED-HIVSR), we will include all the schools in the GED-HIVSR component, irrespective of the number of participants attending the school. From each of the selected schools, we will recruit up to five educators, including school nurses, head administrators, and teachers.

### Inclusion and Exclusion Criteria

The following are the inclusion criteria for participants: (1) the individual is HIV positive, defined as an adolescent who has tested positive with confirmation by medical report and has been disclosed to; (2) the individual is prescribed ART; (3) the individual is living within a family (defined broadly, not necessarily with biological parents); and (4) the individual is aged 10 to 17 years and enrolled in a primary or secondary school with a boarding section within the Greater Masaka region. At the clinic level, all eligible adolescents living with HIV from a particular household will be enrolled in the study and assigned to the same study condition.

The family inclusion criterion is that the participants must be caregivers of adolescents living with HIV who agree to participate in the study.

The educator inclusion criterion is that the participants must be teachers, school nurses, and administrators in the target schools who agree to participate in the study. For adolescents living with HIV randomized to treatment arm 2 (ie, MFG-HIVSR plus FEE and GED-HIVSR), we will include all the schools in the GED-HIVSR component, irrespective of the number of participants attending the school. All educators will be required to consent to participate in the study individually.

The following are the exclusion criteria: (1) significant cognitive impairment that interferes with the participants’ understanding of the informed consent process or (2) inability/unwillingness to commit to completing the study.

### Enrollment

After identifying potential study participants, we will compile a list of secondary schools attended, including the number of potential participants in each school, associated school features (ie, location and size), and willingness of these schools to participate in the study. Clinics will be randomized to 1 of 3 study arms, and all adolescents living with HIV and their caregivers will be enrolled in the study arm associated with their clinic. Only adolescents and their caregivers who meet inclusion criteria will be recruited. To characterize any potential bias in enrollment, we will collect information about the clinics (eg, location, clinic size, and reasons for nonparticipation) and use HIV clinic information (eg, sociodemographics and viral suppression rates) to characterize the potential bias from adolescents living with HIV and clinics that decline to participate in the study. For participants randomized to the GED-HIVSR intervention arm, we will collect information on the school location, type (eg, private or government-supported), size, and reasons for nonparticipation.

### Intervention Conditions

#### Control Arm: Bolstered Usual Care

All participants (in the control and treatment arms) will receive medical and psychosocial support as part of the bolstered usual care. All public clinics, including our study sites, follow procedures for pediatric ART initiation and monitoring as outlined in the National Guidelines for pediatric HIV care in Uganda [126]. As part of medical care, ART is prescribed by physicians and dispensed monthly by a pharmacist at the clinic. Specifically, immediately after initiation, or if clinically unstable, adolescents living with HIV are seen more frequently (weekly to monthly). Laboratory data—viral load (VL) and CD4 counts—are collected every 6 months until the patient is stabilized and then checked annually. For M-Suubi, data regarding HIV viral load, pharmacy refills, and pill counts will be collected from the charts. Psychosocial care is primarily provided by lay counselors trained in standardized ART adherence counseling. Typically, each patient receives 2 to 4 sessions of adherence counseling at initiation and when nonadherence is identified. Lay counselors also assist families with other psychosocial needs that may arise. However, adherence to counseling can vary substantially. Therefore, the usual care will be bolstered with enhanced adherence sessions to ensure more standardized and sufficient adherence counseling. All study participants will undergo 6 sessions to review HIV, ART, and ART adherence. We will bolster family communication around these topics using materials adapted from the cartoon-based curriculum used in the Suubi+Adherence study with adolescents living with HIV and their families [127]. This curriculum describes the lead characters (Mabebeere and Kamperempe), testing interactions with a nurse in which she describes the working of the HIV, ART, and adherence (including potential barriers such as HIV stigma). These materials will be discussed with the participating adolescents living with HIV to identify questions and barriers. Lay counselors in clinics have been trained to use these materials, and HIV clinics have incorporated this curriculum into their practice. Previous studies have shown that the Suubi+Adherence curriculum promotes adherence among adolescents living with HIV [127-130].

#### Treatment Arm 1: MFG-HIVSR Plus FEE

In addition to the bolstered usual care described earlier, adolescents living with HIV and their caregivers will participate in a family strengthening intervention delivered via MFG along with an FEE component. MFG is a family-centered, group-delivered, evidence-informed, strength-based 10-session
(weekly) intervention for children whose families struggle with poverty and associated stressors. It integrates components of existing evidence-based practices that successfully improve parental management, mental health–promoting family processes, and family strengthening [77,104,105,121,131-134]. For the purpose of M-Suubi, MFG-HIVSR has 6 additional sessions to cover HIV stigma–related issues. The specific MFG-HIVSR session content will be based on our previous interventions [79,103-105,121,132,133,135-145]. Sessions will focus on the core MFG components, also known as 4 Rs and 2 Ss (rules, responsibility, relationships, respectful communication, stress, and social support). Sessions focused on HIV stigma will be adapted from the existing Suubi curriculum and resources from the Ministry of Health. Each session provides opportunities to contextualize the content to the realities of family life and emergent cultural and values perspectives and tailor messages to the child’s age. These will include group activities, role-plays, sharing experiences, and family take-home activities. Families (adolescents living with HIV and their caregivers) will be combined into groups of up to 10 families to promote communication and support within and among families. MFG-HIVSR sessions will last approximately 1 hour and will be delivered twice weekly during school holidays when adolescents living with HIV are more readily available. Parent peer and community health workers already trained in MFG delivery will be recruited and will receive refresher training on M-Suubi’s content on HIV stigma. During MFG-HIVSR implementation, facilitators will receive 2 hours of monthly group supervision across sites. Given the significant and protective role families play in the health and well-being of adolescents living with HIV, we expect that strengthening family functioning and dialogue by involving caregivers through MFG-HIVSR will lead to better child outcomes, including reduced HIV stigma. These services will be bolstered with an FEE component provided via a youth development account described next.

In the FEE component, adolescents living with HIV will receive a youth development account with a 1:1 matched savings program at a financial institution accredited by the Bank of Uganda. Each youth development account will be opened in the adolescent’s name, with their primary caregiver as a cosigner, until the adolescent turns 18 years, at which time a cosigner will no longer be required. This is consistent with Ugandan banking law, which prohibits children aged <18 years from independently entering into a binding contract/operating a bank account. Family members and friends of adolescents living with HIV will be allowed and encouraged to contribute to this youth development account. It will be matched at a rate of 1:1 using money from the program. The match cap (maximum amount of youth contribution to be matched by the program) will be equivalent to US $20 per month or US $480 for the 24-month intervention period. During the intervention, adolescents will have direct access to both their personal savings deposited in the youth development account and the match provided by the study to pay for food, transportation to health clinics, and other necessities that may affect adherence. Matching will not be conditioned on the usual expenditure and/or savings goals dictated by programs [133,137,146]. The unconditional design recognizes that adolescents living with HIV and attending schools face competing demands (school fees, food for medication adherence, transport to clinics, etc) and that a conditional transfer may prohibit these vital expenditures, which may have implications for antiretroviral treatment adherence. In collaboration with participating financial institutions, the youth development account will be augmented with 4 sessions of financial literacy training, covering the basic principles of financial management, saving, and asset building.

**Treatment Arm 2: MFG-HIVSR Plus FEE Plus GED-HIVSR**

In addition to the bolstered usual care and MFG plus FEE described earlier, adolescents living with HIV in this arm will receive school-level HIV stigma reduction interventions targeting teachers, school nurses, matrons, and administrators (head teachers and director of studies) in their schools. The GED-HIVSR seeks to empower educators to reduce enacted HIV stigma and build supportive structures for adolescents living with HIV within their schools. Our rationale for adding this component to our intervention package is to test the added benefit of addressing school-level HIV stigma–related challenges on HIV treatment outcomes among adolescents living with HIV. Guided by an asset-based approach and drawing on evidence-based strategies for reducing HIV stigma in non–HIV-infected populations [63,97,98,147,148] and building support for adolescents living with HIV in school settings [149-151], GED-HIVSR seeks to impart educators in the intervention schools with HIV-related knowledge, provide a safe space for educators to explore their personal values and biases that may promote or hinder their role of supportive individuals and systems for adolescents living with HIV, and empower them with knowledge and skills to act as change agents within their schools.

The GED-HIVSR will be delivered as a 2-day workshop with a booster session in years 3 to 4. The details of each topic along with the targeted domain and delivery strategies are presented in Table 1. From each intervention school, we will recruit up to five educators including the school head teacher, director of studies, and school nurse. To standardize training and provide opportunities for peer-to-peer learning through group discussions, all educators will be convened at a central location for training. Workshop content will be delivered using a range of strategies including didactic lectures, role-play, testimonials from adolescents living with HIV, digital media (ie, documentaries), and discussions/brainstorming to promote participant engagement and active learning. Workshops will establish foundational knowledge on HIV transmission and treatment and cover content on HIV stigma and its impact on adolescents living with HIV and their families. Along with testimonials from adolescents living with HIV, we will use educational documentaries that portray the marginalization of people living with HIV to highlight the perpetuation of HIV stigma and its impact on these people, including adolescents living with HIV.
Table 1. Topics, delivery strategies, and targeted domains of group-based HIV stigma reduction for educators.

<table>
<thead>
<tr>
<th>Intervention topic</th>
<th>Intervention strategy</th>
<th>Targeted domain</th>
<th>Conceptual framework</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV transmission, treatment, and prevention; misconceptions and misbeliefs about people living with HIV</td>
<td>Didactic lectures; role-play; discussions</td>
<td>HIV knowledge; feelings toward people living with HIV</td>
<td>Cognitive factors: knowledge and beliefs</td>
</tr>
<tr>
<td>HIV and AIDS stigma: understanding and defining manifestations of stigma; intersecting stigmas; consequences for adolescents living with HIV, their families and communities; awareness of HIV stigma in schools and communities; strategies for combating stigma</td>
<td>Educational; documentary; testimony from adolescents living with HIV</td>
<td>Stigma manifestations; intersecting stigma (eg, stigma and poverty); gender</td>
<td>Cognitive factors: knowledge and beliefs</td>
</tr>
<tr>
<td>Educators’ understanding of the needs and challenges of adolescents living with HIV in school settings, including barriers to HIV treatment adherence; mapping barriers to addressing HIV stigma within schools</td>
<td>Contact with adolescents living with HIV (presentations and testimonials from adolescents living with HIV)</td>
<td>Drivers and facilitators of stigma</td>
<td>Cognitive empathy; parasocial learning; skill building</td>
</tr>
<tr>
<td>Evaluating options for action planning for change; task analysis and developing an action plan; identification of stakeholders and resources to support initiatives to reduce stigma and support adolescents living with HIV in schools</td>
<td>Participatory learning through breakout sessions to brainstorm and develop actions plans for their schools</td>
<td>Future actions to support adolescents living with HIV; sustainable programs and policies to support adolescents living with HIV</td>
<td>Social learning theory: modeling; efficacy; empowerment through skill building</td>
</tr>
</tbody>
</table>

Previous studies have shown that direct or indirect contact (eg, digital film presentations) with stigmatized groups results in broader and more enduring reductions in stigma [152-154]. Thus, we will use expert testimonials from adolescents living with HIV as direct contact opportunities for the educators to hear their personal experiences in dealing with stigma and to normalize adolescents living with HIV as human beings; hence, fostering acceptance and empathy for adolescents living with HIV. Open discussions will provide a safe place for educators to express their views and opinions of adolescents living with HIV, as well as explore strategies, resources, and barriers to support adolescents living with HIV within schools. This strategy of actively engaging educators in examining their biases and developing supportive strategies for adolescents living with HIV within their settings is consistent with the principles of empowerment that build a sense of ownership. Participants will then act as change agents within their schools by implementing activities that address the needs of adolescents living with HIV. To facilitate context-specific discussions, we will conduct quarterly visits (at least one visit per academic term) to individual intervention schools in between the workshops to establish how educators are supporting adolescents living with HIV within their schools and offer additional services (eg, training) based on the requests from the schools.

**Ethics Approval and Consent**

The research staff will obtain written informed consent and assent from the adult caregivers and children, respectively, before study enrollment. The consenting process for adults and children will be performed separately to avoid coercion. During face-to-face meetings, the adolescent’s primary caregiver will read and sign a standard consent form. In doing so, caregivers will be consenting to participation for themselves and assenting to the participation of their adolescents. Adolescents will sign an assent form that will be read aloud verbatim. If either the adolescent or caregiver refuses to participate, they will not be enrolled. According to the Uganda Law, emancipated minors, defined as persons aged ≤18 years who are pregnant, married, have a child, or are self-sufficient, will be allowed to consent on their own. Both consent and assent forms will be translated into Luganda (the most widely spoken local language in the study region) and back translated to English to ensure consistency. Both the assent and consent processes will be conducted verbally in Luganda, given that some caregivers and adolescents were illiterate. The study team will receive training on Good Clinical Practices so that sensitive research activities can be handled appropriately. In addition, all interviewees have completed the Collaborative Institutional Training Initiative certificate and National Institutes of Health certificate to safeguard the research participants.

We have obtained approval for the study procedures from the institutional review boards (IRBs) at the University of Washington in St. Louis, Missouri (IRB ID 202201128) and University of Michigan (HUM00211945) and from the in-country local IRBs in Uganda: Uganda Virus Research Institute (GC/127/867) and Uganda National Council of Science and Technology (SS1166ES).

The study has been registered with ClinicalTrials.gov (NCT05307250), as of April 1, 2022. The dissemination of the main study findings is targeted for 2025.

**Measures**

As shown in Figure 1, assessment will be conducted at baseline and at 12-, 24-, and 36-month follow-ups. All assessments, each lasting approximately 60 minutes, will take place at the clinic during school breaks. Although all the adolescents living with HIV will be attending school and expect to be English-speaking (the instructional language in all Ugandan schools), assessments will be conducted in English or Luganda (the local language).
depending on the English proficiency of the participants. All the interviewers will be fluent in English and Luganda. The questions will be translated from English to Luganda and back translated by a certified translator from a local university (Department of Languages) following standard procedures. The research team members who are fluent in Luganda and English will crosscheck all translated assessments. All the interviewers will receive highly structured and intensive training. Assessments will be conducted using standardized measures adapted from previous studies conducted in Uganda [104,133,141]. Any measures that have not been used will be pretested and made culturally appropriate to the Ugandan context. For questions measuring sensitive behaviors (eg, adherence), we will use audio computer-assisted self-interviews, where the participant takes the survey herself on a mini laptop. Nonsensitive questions will be administered by the interviewer. For the biological assay, blood specimens for HIV VL testing will be collected at baseline and 12, 24, and 36 months after the intervention. In accordance with the Abbott platform, VL will be dichotomized into undetectable (<40 copies/ml) and detectable (≥40 copies/ml) levels.

**Qualitative Component**

Semistructured in-depth interviews will be conducted at baseline and at 12-, 24-, and 36-month follow-ups with adolescents living with HIV and their caregivers (n=40 dyads) in the 2 intervention arms. Baseline interviews will focus on the following aspects: (1) participants’ experience of decision-making (eg, costs, benefits, barriers, and facilitators) associated with HIV treatment adherence and (2) HIV stigma and its perceived impact on their lives. Follow-up interviews will unpack the longer-term impact, including experiences of stigma and key multilevel factors affecting HIV treatment–related behaviors of the participants after the intervention. Specifically, in addition to the baseline interview topics, 12-month interviews will examine the following: (1) experiences of the participants with their respective intervention components (ie, MFG-HIVSR, FEE, and GED-HIVSR), including perceived benefits and key multilevel (individual, family, school, contextual, and programmatic) influences that affect their participation and (2) intervention sustainability. In addition to topics explored at baseline (HIV stigma and decision-making on HIV treatment), the follow-up interviews will explore the sustained impact of the intervention to examine changes over time in HIV stigma and decision-making associated with treatment adherence and the sustained impact of the intervention over time.

In addition, educators (n=20) will be interviewed at baseline and at follow-up (12, 24, and 36 months). Baseline interviews will focus on their attitudes toward adolescents living with HIV and how HIV stigma manifests within their school context. Follow-up interviews, in addition to topics covered during baseline, will explore educators’ experiences with the training and resulting programs implemented within their school, facilitators and barriers to program implementation, recommendations, and sustainability. A purposive criterion sampling strategy [155] will be used to select adolescents living with HIV and their caregivers. Adolescents living with HIV who score in the highest and lowest quartiles of internalized stigma at baseline (to be identified using the HIV stigma mechanism scale), and 20 participants (10 from each quartile) and their caregivers from each treatment condition will be randomly selected (n=40 dyads; these numbers will be sufficient for theoretical saturation) [156-158] and interviewed. This sampling method will ensure that participants with varying experiences are represented and will allow us to identify common patterns and variations across participants’ experiences. In addition, 20 educators across the 2 treatment arms will be randomly selected for interviews. Interviews will be conducted in English or Luganda, based on the participants’ preferences. The questions will be translated (English to Luganda) and back translated by researchers assistants, and then reviewed by 2 proficient team members (MM and PN). Each interview will last approximately 60 minutes and will be audiotaped. The same participants will be interviewed at each time point.

### Data Analysis

**Primary Analyses for Aim 1**

To examine the effect of M-Suubi on HIV viral suppression, we hypothesize the following:

- **H1a**: MFG-HIVSR plus FEE will have higher odds of viral suppression than control participants (bolstered usual care).
- **H1b**: MFG-HIVSR plus FEE plus GED-HIVSR will have higher odds of viral suppression than control participants.
- **H1c**: MFG-HIVSR plus FEE plus GED-HIVSR will have higher odds of viral suppression than MFG-HIVSR plus FEE.

To test these 3 hypotheses, we will fit a 3-level generalized linear mixed model (LMM) with fixed effects for the study arm, time, and their interaction. Our analysis will follow an intent-to-treat approach, such that all participants are included in the analyses, irrespective of whether they have complete or incomplete outcome data. Maximum likelihood (ML) and multiple imputation (MI) procedures will be used to address missing data with sensitivity analyses. Sensitivity analyses will be performed using pattern-based MI to examine the robustness of the results under different missing data assumptions. We will use random intercepts for school/clinic ID to account for clustering of persons within schools and their affiliated clinics and include random intercepts, random slopes, and their covariance for person ID to account for clustering of repeated measurements within persons. Reflecting the binary HIV viral suppression outcome, a binomial distribution and log link will be used to fit a log-binomial model to estimate the relative risks. If the log-binomial model does not converge, we will substitute a Poisson model with robust SEs [159,160]. To maximize rigor, quasi-likelihood methods will not be used. Instead, maximum likelihood estimation via adaptive Gaussian quadrature with 15 integration points will be used to ensure stable solutions [161]. To test hypotheses H1a to H1c, we will perform 3 time-averaged comparisons of repeatedly measured observations across study arms to examine the intervention effects over the duration of the study period. As all possible comparisons among the 3 study arms will be evaluated, the α will be set at .05/3=.017 for each of these 3 planned comparisons. Any additional post hoc comparisons (eg, paired comparisons of groups at each time point) will maintain a nominal α of .05 using simulation-based step-down multiple comparison methods [114]. Our team has
considerable experience fitting 3-level generalized LMMs to analyze data from our cluster randomized asset-based intervention trials [113,162].

**Primary Analyses for Aim 2**
To examine the effect of M-Suubi on HIV stigma, we hypothesize the following:

1. H2a: MFG-HIVSR plus FEE will have lower mean HIV stigma than control participants (bolstered usual care).
2. H2b: MFG-HIVSR plus FEE plus GED-HIVSR will have lower mean HIV stigma than control participants.
3. H2c: MFG-HIVSR plus FEE plus GED-HIVSR will have lower mean HIV stigma than MFG-HIVSR plus FEE.

To test these hypotheses, we will fit LMMs using the same fixed effects (study arm, time, and study arm-by-time) and random effects for the school/clinic (random intercepts) and person levels (random intercepts, random slopes, and their covariance) as proposed in the H1 analyses described earlier. To test hypotheses H2a to H2c, we will perform 3 time-averaged comparisons of repeatedly measured observations of stigma across study arms to examine the intervention effects over the duration of the study. To maintain a nominal type I error rate of 5% across tests of H2a to H2c, α will be set at .05/3=.017 for each planned time-averaged comparison. Our analyses will follow an intent-to-treat approach, and ML and MI approaches will be used to address missing data (as described in aim 1 earlier). To maximize rigor, the assumptions of normality and constant variance of residuals for these continuous outcomes in LMMs will be evaluated by examining histograms of the residuals and scatter plots of predicted values-by-Cholesky-scaled residuals, respectively. Transformations of outcomes will be used as needed to improve data conformance with model assumptions. Inferences for models whose residual statistics still do not fully meet assumptions following transformations will be generated via robust heteroskedastic-consistent Huber-White “sandwich” variance estimators [163]. All analyses will include outlier and influential case screening via the computation of Cook values, and likelihood displacement statistics. If outliers are found, the results will be reported with and without outliers included [164,165].

**Randomization, Sample Size, and Power Analysis**
We used NCSS Statistical Software Program PASS [166] to compute the minimum detectable effect size estimates for hypotheses H1a to H1c and H2a to H2c proposed to fulfill specific aims 1 and 2, respectively. For all power analyses, we assume power=0.80, α=.05/3=.017, and 4 repeated assessments from 714 participants conservatively assuming 15% attrition. Standardized minimum detectable effect sizes range from .26 to .35. Therefore, our study will have the power to detect small to medium effects for the proposed hypotheses.

**Aim 3: Evaluate the Cost-effectiveness of Each Intervention Condition**
Following the standard practice of measuring the cost-effectiveness of interventions, we will measure costs on a per-person basis. The intervention costs will include all program costs incurred for running the GED-HIVSR and MFG-HIVSR plus FEE programs and not just the savings match of the youth development account. The research costs will not be included in this study. Data on the savings match costs will be readily available from the management information system. Data on the costs of other program elements will be drawn from the project administrative records collected throughout the intervention period. In the analyses, the costs from multiple years will be adjusted for inflation, depreciation, and discounting. The outcome analyses described earlier will be used to estimate the extent to which the *Combined Intervention (MFG-HIVSR plus FEE plus GED-HIVSR)* versus *MFG-HIVSR plus FEE alone* increased particular outcomes (eg, viral suppression). The per-person costs of *MFG-HIVSR plus FEE and GED-HIVSR* and *MFG-HIVSR plus FEE alone* will then be divided by the relevant effect sizes to produce estimates of cost-effectiveness. We will calculate CIs for point estimates using two methods: Monte Carlo [167] and bootstrap [168].

**Aim 4: Qualitative Component Analysis**
The interviews will be transcribed and uploaded to NVivo (version 12; QSR International) [169]. Data will be analyzed using a recurrent cross-sectional approach. Each wave of data will first be analyzed independently to understand experiences at each time point of data collection [170]. Analytic induction techniques [171] will be used for coding. Initially, 10 interview transcripts randomly selected across the 2 study groups will be read multiple times and independently coded by the team using sensitizing concepts to identify emergent themes (open coding) [172]. Broader themes will be divided into smaller, more specific units until no further subcategories are necessary. Analytic memos will be written to further develop categories, themes, and subthemes, and to integrate the ideas that emerge from the data [172,173]. Codes and the inclusion/exclusion criteria for assigning codes [174] will be discussed as a team to create the final codebook in NVivo. Each transcript will then be independently coded by 2 investigators using the codebook. Intercoder reliability will be established. A level of agreement ranging from 66% to 97% based on the level of coding indicates good reliability [155]. Disagreements will be resolved through team discussions. The secondary analysis will compare/contrast themes and categories within and across groups to identify similarities, differences, and relationships among the findings. Member checking, peer debriefing, and audit trails will be used to ensure rigor [158]. The data will be analyzed using both recurrent cross-sectional and trajectory approaches. After this initial analysis is completed, a second analysis will focus on the differences and similarities between the time points. Central themes from each wave of data collection will be compared using these 3 subsets of questions. The coded data will be organized into matrices with major themes (along the y-axis) and time points (along the x-axis) to explore how the data, in the existing thematic groupings, changed or did not change over time (eg, new concerns and change in priorities), as well as new major themes that emerge from one time point to another.
Results

The M-Suubi study was initiated in September 2021. The first 6 months of this 5-year study were a preparation period for obtaining IRB approval, mobilizing financial institutions, and recruiting clinics and adolescents. Data collection commenced in April 2022, with screening and recruitment of study participants, as well as completion of baseline assessments. Implementation of the MFG-HIVSR, GED-HIVSR, and FEE components will follow after randomization of the study participants, and the intervention will be delivered over a period of 20 months. Follow-up assessments will be conducted at 12, 24, and 36 months after completion of the baseline assessments.

Discussion

Overview

To the best of our knowledge, this is the first study to evaluate a culturally acceptable multilevel intervention to reduce HIV stigma within homes and schools and to improve HIV treatment adherence among in-school adolescents living with HIV in Uganda. HIV stigma reduction interventions targeting adolescents living with HIV in boarding school sections are nonexistent, and multilevel interventions addressing intrapersonal, interpersonal, and institutional stigma are scarce. The MFG approach is culturally consistent with SSA’s collective approach of families raising children “together,” which strengthens its appeal to communities and its likelihood of success. The asset-savings–led approach has demonstrated efficacy in reducing HIV-risk behaviors among HIV-affected adolescents [78,104,105,131,175,176] and has improved ART adherence among adolescents living with HIV [26]. The focus on schools is consistent with the United Nations Educational, Scientific and Cultural Organization’s Good Policy and Practice on HIV in Schools report [176], which established a road map for supporting schools as caring contexts for children affected by HIV/AIDS. M-Suubi makes use of existing community institutions to deliver the intervention and builds local capacity, which will ensure an eventual scale-up. M-Suubi will provide much-needed evidence on effective strategies for reducing HIV stigma among school-attending adolescents living with HIV in Uganda. More importantly, this study will provide evidence on the effects of a multilevel intervention comprising of family-based economic empowerment and financial literacy combined with a school-based HIV stigma reduction intervention for educators. In so doing, it will enable an ecological assessment of the cascading effects of multilevel HIV stigma reduction strategies. In addition, the inclusion of educators as a target population will provide a unique opportunity to generate data on the prevalence and impact of HIV stigma among educators and effective intervention strategies to reduce HIV stigma within schools. To date, these data are nonexistent.

Limitations

This study has some limitations. First, it targets adolescents living with HIV in southwestern Uganda, so the study findings may not be generalizable to adolescents living with HIV in Uganda or other high HIV burden countries in SSA. Second, the study focuses on adolescents living with HIV attending primary or secondary school. Adolescents living with HIV in vocational schools and other nontraditional school settings are not included in the study, which may bias the generalization of the study findings. Nonetheless, this study uses a sound methodological approach, which will enhance the quality of data generated in this study. The study findings, if successful, would advance knowledge to bridge the existing gap in evidence-based scalable HIV stigma interventions for adolescents living with HIV in resource-limited settings such as Uganda.

Acknowledgments

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Data Availability

Data sets from this study will be available to researchers through the National Institutes of Health Central Data Repository.

Conflicts of Interest

None declared.

Multimedia Appendix 1


[PDF File (Adobe PDF File), 122 KB - resprot_v11i10e40101_app1.pdf ]
References


74. Mutumba et al. JMIR RESEARCH PROTOCOLS


Abbreviations

**ART:** antiretroviral therapy  
**FEE:** family economic empowerment  
**GED-HIVSR:** group-based HIV stigma reduction for educators  
**IRB:** institutional review board  
**LMM:** linear mixed model  
**MFG:** multiple family group  
**MFG-HIVSR:** MFG HIV stigma reduction for educators  
**MI:** maximum imputation  
**ML:** maximum likelihood  
**SSA:** sub-Saharan Africa  
**VL:** viral load
Feasibility of Monitoring Patients Who Have Cancer With a Smart T-shirt: Protocol for the OncoSmartShirt Study

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Abstract

Background: Studies have shown that there may be dissimilar perceptions on symptoms or side effects between patients with cancer and health care professionals. This may lead to symptomatic patients notifying the clinic irregularly or not telling the clinic at all. Wearables could help identify symptoms earlier. Patients with low socioeconomic status and less self-awareness of their health may benefit from this. A new design of wearables is a smart t-shirt that, with embedded sensors, provides measurement flows such as electrocardiogram, thoracic and abdominal respiration, and temperature.

Objective: This study evaluates the feasibility of using a smart t-shirt for home monitoring of biometric sensor data in adolescent and young adult and elderly patients during cancer treatment.

Methods: The OncoSmartShirt study is an explorative study investigating the feasibility of using the Chronolife smart t-shirt during cancer treatment. This smart t-shirt is designed with multiple fully embedded sensors and electrodes that engender 6 different measurement flows continuously. A total of 20 Danish patients with cancer ≥18 years old in antineoplastic treatment at Department of Oncology Rigshospitalet Denmark will be recruited from all cancer wards, whether patients are in curative or palliative care. Of these 20 patients, 10 (50%) will be <39 years old, defined as adolescent and young adult, and 10 (50%) will be patients >65 years old, defined as elderly. Consenting patients will be asked to wear a smart t-shirt daily for 2 weeks during their treatment course.

Results: The primary outcome is to determine if it is feasible to wear a smart t-shirt throughout the day (preferably 8 hours per day) for 2 weeks. Inclusion of patients started in March 2022.

Conclusions: The study will assess the feasibility of using the Chronolife smart t-shirt for home monitoring of vital parameters in patients with cancer during their treatment and bring new insights into how wearables and biometric data can be used as part of symptom or side-effect recognition in patients with cancer during treatment, with the aim to increase patients’ quality of life.

Trial Registration: ClinicalTrials.gov NCT05235594; https://beta.clinicaltrials.gov/study/NCT05235594

International Registered Report Identifier (IRRID): PRR1-10.2196/37626

(KEYWORDS
biometric sensor technology; cancer; home monitoring; patient-generated health data; sensor; smart t-shirt; remote monitoring; adolescent; protocol; patient; youth; health care professional; cancer treatment

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Introduction

Collecting biometric sensor data by wearables is an example of real-time patient-generated health data that can provide vital and detailed objective information about patients. Although previous results from our research group have shown that the literature on wearables is very heterogeneous and lacks consensus [1], studies show that wearables may have the potential to improve quality of oncological treatment and increase patients’ quality of life [2-5].

During oncological treatment, most patients are primarily seen in outpatient clinics where the number of visits is determined by type of treatment and the expected side effects [6]. The symptoms and side effects, experienced by patients with cancer, depend on the type of cancer, the treatment modality, and the preexisting comorbidity [7-9]. Patients are informed to notify the clinic if they experience side effects or increased symptoms. In worst case scenarios, patients may need acute hospital treatment, while in other cases, side effects are more related to poorer treatment compliance and reduced quality of life [2].

A wearable is a noninvasive and wireless sensor device that can monitor and collect health parameters on various biometric data points such as skin temperature, respiration rate, heart rate, and physical activity. The device normally transmits the health data to an app (eg, on a smartphone), which registers the readings. The devices can be worn in different ways, depending on the design of the device (eg, a smartwatch around the wrist) [10,11]. Thus, wearables offer the opportunity of monitoring patients passively in their own environment while they are outside the hospital. This allows the patients to carry on with their daily life and thus minimize the burden from the decrease in their quality of life [12].

Studies have shown that there may be dissimilar assessments and perceptions on symptoms between patients and health care professionals [13,14], which is reflected by the fact that health care professionals often underestimate patients’ symptoms [15]. This may cause patients with symptoms or side effects to notify the clinic irregularly or not to notify the clinic at all, which could lead to unnecessary discomfort for patients and suboptimal treatment. In such cases, wearables could help identify symptoms or side effects earlier. In particular, patients with low socioeconomic status and less self-awareness of their health are assumed to benefit from using wearables [3].

A new design of a wearable is the smart t-shirt. A smart t-shirt is designed with sensors embedded into the fabric, which allows for the 24/7 monitoring of electrocardiogram (ECG), thoracic and abdominal respiration, and so on. Originally, smart t-shirts were designed to support athletes in their performance analysis and improving health care as a wearable medical device [16]. Compared to other wearables, the smart t-shirt enables health professionals to monitor an increased number of health parameters on various biometric data points. Furthermore, data collection is predicted to be exact and completely comparable to conventional medical measuring devices [17,18]. Studies have shown that smart t-shirts can monitor 12-lead ECG acquisition with the same quality of standard Holter recording [17-19].

These new technologies allow health professionals to track patients’ health more extensively. At the same time, the new tools provide precise information without recall and reporting bias, which can lead to a better and more accurate cancer treatment [3,20-22]. However, knowledge in using wearables in an oncological setting is limited [12,20,23,24], and it has been highlighted that there is very little consensus and awareness of adherence to wearables. This is an essential part of being able to use and compare collected biometric sensor data [1], and it could be questioned whether oncological patients are able to adhere to the use of a smart t-shirt during their treatment.

In this paper, the study design of the OncoSmartShirt feasibility study is described. The purpose of this study is to evaluate the feasibility of using a smart t-shirt for remote monitoring of biometric sensor data in adolescent and young adult (AYA) and elderly patients during cancer treatment.

Methods

Study Design

The OncoSmartShirt study is an explorative study investigating the feasibility of using the Chronolife Smart t-shirt during cancer treatment. This smart t-shirt is designed with multiple sensors and electrodes fully embedded, which engender 6 different measurement flows continuously [25]. This trial is an investigator-driven partnership between Department of Oncology Rigshospitalet and Chronolife and is registered at ClinicalTrials.gov (NCT05235594). The study is conformed to the guidelines of General Data Protection Regulation and is registered at the Capital Region of Denmark (P-2021-357). The trial is approved by the local division for IT and Medico Technology in the Capital Region of Denmark and is a collaboration between Department of Oncology Rigshospitalet, Department of Innovation Rigshospitalet, and Telemedico Knowledge Center Capital Region of Denmark. Approval from the National Committee on Health Research Ethics is not required for this trial in the Danish context.

The acceptance and comfort of wearing the Chronolife smart t-shirt throughout the day (preferably 8 hours per day) for 2 weeks is investigated in all 20 enrolled patients. The intervention period will elapse at any time in the patient’s antineoplastic treatment course.

Secondly, qualitative telephone interviews will be carried out, and patients will be asked to fill in a questionnaire concerning their experience with wearing the shirt. Topics included in the interviews are, among others, the material and design of the smart t-shirt, feeling social stigma, and surveillance. The interview guide and patient questionnaire are available in Multimedia Appendices 1 and 2, respectively. The study will be performed in a public health care system, and the smart t-shirt will be given to the patients by the hospital. Only the patient included in the trial will be allowed to wear the t-shirt during the study period. Patients will be responsible for charging and washing the shirt and are required to return the shirt at study...
termination. No biometric data of vital parameters collected by the wearable will be published or monitored by health care professionals during the study. All other interventions, such as oncological care and treatment, will be kept to their normal routine. Participation in the study will not result in any payment or reward for the included patients.

**Patients and Recruitment**

A total of 20 Danish patients ≥18 years old who have cancer and are in antineoplastic treatment will be recruited continuously. Of these 20 patients with cancer, 10 (50%) will be <39 years old, defined as AYA, and 10 (50%) >65 years old, defined as elderly, will be included. These 2 age groups were included, as we expected that these would differ the most from each other in terms of acceptance of the smart t-shirt. There will be no requirements regarding specific cancer diagnosis, and both patients in curative and palliative care will be included meaning that all types of patients with cancer can be included. These broad inclusion criteria are designed to make inclusion in the study as simple as possible. Therefore, recruitment of patients with cancer in the study will take place consecutively in all cancer departments at the Department of Oncology Rigshospitalet, Denmark. Patients will be eligible if they read and speak Danish and have the capacity to provide written informed consent to participate in the study. Patients can withdraw their consent at any time. Patients with serious cognitive deficits and who cannot reliably provide informed consent will be excluded. Inclusion in the study will have no interference with the planned oncological treatment.

**Hardware**

The study device in the trial consists of four units; a washable smart t-shirt fitted with multiple sensors and electrodes from Chronolife, a companion smartphone or tablet app, an accredited secure data hosting server, and a web interface [25]. The Chronolife smart t-shirt is commercialized and “CE marked” for the consumer market. The smart t-shirt is designed for every-day use. The electrical sensors embedded in the shirt allows detection of 6 physiological parameters: ECG (beat per minute), thoracic and abdominal respiration (respiration per minute), thoracic impedance (kOhm), physical activity (steps), and skin temperature (°C) [25]. The sensors are powered by a nonremovable rechargeable battery. Additionally, the t-shirt is equipped with a memory card that stores data and a Bluetooth interface that transmits data. These are fully integrated into the t-shirt and have been sealed in water-resistant coatings.

**Software**

The smart t-shirt connects to the smartphone app via a QR code located on the shirt. The health data collected by the sensors in the shirt are transmitted by Bluetooth Low Energy to the connected smartphone app designed for storage (Figure 1). Furthermore, the smartphone app provides further data transmission through 3G or 4G Wi-Fi to an accredited data-hosting server that will store data and provide data for a web interface for analysis and algorithm training [25]. Figure 1 illustrates the four components and the flow of data.

**Statistical Analysis**

**Endpoints**

The primary endpoint is to assess the feasibility of using the Chronolife smart t-shirt based on completion rate, which in this trial is defined as the number of included patients using the smart t-shirt at least 8 hours per day during the 2 weeks study period.

Secondary endpoints are to assess technical feasibility in a Danish health care system, including data acquisition rate and
data completeness. Qualitative interviews with the patients regarding the use of the smart t-shirt will be performed. Patients will be asked to fill in a questionnaire concerning their experience with wearing the t-shirt. As explorative endpoint changes in heart rate, skin temperature, physical activity, and respirations frequency will be presented descriptively.

Descriptive data will be collected and analyzed in the statistical software SPSS Statistics (IMB Corp).

**Power**

A power calculation is not required for this type of study because it is a feasibility study with no control group and no formal statistical hypothesis testing, and thus, the sample size is not driven by formal power calculations. This sample size corresponds to studies of the same nature in the literature [26-28].

**Ethical Considerations**

The inclusion of patients will not begin until the Data Protection Agency has granted their relevant approval for the study. Patients will receive verbal and written information and must provide written informed consent. Moreover, they can withdraw at any time during the study. The Scientific Ethics Committees for the Capital Region of Copenhagen has been informed; however, approval is not required for this type of study according to Danish law.

**Results**

Inclusion of patients started in March 2022. Data collection is expected to be completed in autumn 2022. Processing of data is expected to begin in autumn 2022 as well.

**Discussion**

The study will assess the feasibility of using the Chronolife smart t-shirt for remote home monitoring of vital parameters in AYA and elderly patients during their treatment course. This study will bring new insights into how wearables and biometric data potentially can be used as a part of symptom recognition in patients with cancer during the treatment course in the quest of increasing their quality of life, given that the use of smart t-shirts is feasible. Data from this study can be used in designing future prospective studies using the smart t-shirt as intervention, along with the recommendation from the Clinical Trials Transformation Initiative on Developing Novel Endpoints Generated by Mobile Technologies for Use in Clinical Trials 2017. In future studies, it would be relevant to examine the relationship between biometric data collected from wearables and the perception of symptoms and side effects from patients and clinicians.

**Acknowledgments**

The Chronolife smart t-shirts have been donated to the trials by Chronolife. The donation does not entail any financial obligations to the manufacturer. In addition to donating t-shirts, the manufacturer has contributed with education in the use of smart t-shirts and helped with technical support for included patients and clinicians.

**Data Availability**

Data from this study are not yet available. Data will not be publicly available due to institutional restrictions.

**Conflicts of Interest**

None declared.

Multimedia Appendix 1

Interview guide.

[PDF File (Adobe PDF File), 71 KB - resprot_v11i10e37626_app1.pdf ]

Multimedia Appendix 2

Patient questionnaire.

[PDF File (Adobe PDF File), 154 KB - resprot_v11i10e37626_app2.pdf ]

**References**


Abbreviations

AYA: adolescent and young adult
ECG: electrocardiogram
A Living Database of HIV Implementation Research (LIVE Project): Protocol for Rapid Living Reviews

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Abstract

Background: HIV implementation research evolves rapidly and is often complex and poorly characterized, which makes the synthesis of data on HIV implementation strategies inherently difficult. This is further compromised by prolonged data abstraction processes due to variable interventions, outcomes, and context, and delays in the publication of review findings; this can all result in outdated and irrelevant systematic reviews.

Objective: The LIVE project (A Living Database of HIV Implementation Research) aims to overcome these challenges by applying an implementation science lens to the conduct of rapid living systematic reviews and meta-analyses to inform HIV service delivery priorities and guideline development.

Methods: The LIVE project will generate a series of living systematic reviews exploring implementation strategies for improving HIV cascade outcomes (HIV infection, HIV diagnosis, linkage and retention in HIV care, viral suppression, and mortality). We will search Embase and MEDLINE as well databases specific to review questions for studies conducted after 2004 using predefined search terms to identify studies conducted in any age group or setting, and using implementation strategies that target policy makers, society, health organizations, health workers, and beneficiaries of care and their families. Both randomized controlled trials and observational studies will be included to ensure reviews include pragmatic data. In addition to assessments of methodological quality, features of the implementation strategies, relevance for implementation, and evidence quality will be determined using recognized frameworks. After initial publication, knowledge gaps will be identified, and review questions and search strategies revised to address ongoing critical areas of inquiry. Updated searches will be conducted every 6 months, with subsequent ongoing screening, data abstraction, and revision of meta-analyses.

Results: As of July 2022, five reviews are at various stages of development within the LIVE project. Three systematic reviews are underway and living review processes are in development for two reviews with estimated completion over the next 12 months.

Conclusions: This project and resulting systematic reviews will provide critical insights for HIV service delivery to inform international guideline development.

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KEYWORDS
living review; HIV; systematic review; rapid review; implementation; HIV infection
Introduction

Systematic reviews addressing HIV implementation research questions are challenged by difficulties in synthesizing heterogenous pragmatic research and can become outdated rapidly. As HIV prevention strategies, testing methods, and treatments become increasingly effective, current primary HIV research and evidence synthesis questions are refocong on how best to implement effective interventions to ensure long-term sustained engagement in HIV care [1,2]. This continuous emergence of new implementation research means that traditional methods for generating “static” systematic reviews that may take months or years to produce can quickly become obsolete [3,4]. With each new guideline development cycle, new review teams, searches, protocols, and reviews are undertaken, resulting in substantial duplication of efforts, delays in the generation of synthesized evidence and inability for guideline developers to quickly update recommendations.

Living and rapid review methods have been developed in recent years (now catalyzed by the COVID-19 pandemic) to address these inefficiencies and increase the utility of review evidence; these methods have however been infrequently applied to HIV implementation research [5]. The field of HIV implementation science is a rapidly evolving field, with frequent changes to HIV service delivery approaches (eg, multi-month prescribing), drug delivery systems for HIV treatment (eg, long-acting antiretrovirals), and HIV prevention (eg, vaginal rings) and testing modalities (eg, HIV self-testing). Living methods offer an approach for systematic review updating, where new evidence is incorporated into a review as it emerges, generating a continual updating process that maintains the relevance of synthesized findings and builds on previous work. Living reviews require an explicitly stated commitment to a predetermined frequency of searches and review updating [6]. Rapid reviews aim to accelerate the review process through the elimination or attenuation of some systematic review requirements, including searches in fewer databases, applying language or publication year restrictions, limiting gray literature searches, applying data mining processes, and altering duplicate screening, data extraction, and quality appraisal processes [7,8]. Rapid reviews are being conducted with increased frequency to respond to policy-making needs [9,10]. Rapid and living processes are ideal for incorporation into “living guidelines”—a dynamic guideline development process that, instead of conducting mechanistic guideline updates with a predetermined frequency, uses the results of continuous literature surveillance, rapid updating of prioritized reviews, and frequent virtual consultations with guideline panels to create a continuous guideline development and revision process; this helps to ensure that policy makers and health workers can make up-to-date, evidence-based public health decisions [11-14]. Accelerating the pace of evidence synthesis and dissemination can facilitate the early and effective adoption of new strategies for improving health and reduce the evidence-practice gap [15,16].

Heterogeneity, a frequent and desirable property of implementation research, further complicates evidence synthesis for HIV service delivery. The application of systematic review and meta-analytic methods—originally designed for homogenous efficacy data—to complex implementation research questions can result in systematic review findings that are of limited relevance to policy makers [17-19]. Establishing the effectiveness of strategies to increase HIV testing or antiretroviral therapy uptake and adherence requires detailed characterization of strategy features (eg, where, how, and who delivered the intervention) as well as incorporation of pragmatic data that establishes effectiveness under real-world conditions. Tools are available for characterization of implementation strategies, assessment of real-world relevance of primary research, and reporting of implementation research methods and results, but to date such tools have had limited application in HIV implementation research evidence synthesis [20-23]. Heterogeneity does not preclude evidence synthesis; it is important to develop approaches to accommodate varied study designs and implementation strategies and still draw conclusions from the evidence.

The Living Database of HIV Implementation Research (LIVE) project aims to generate a series of methodologically robust rapid and living reviews characterizing and evaluating the effects of HIV implementation strategies on HIV cascade outcomes through an ongoing process of data abstraction and frequent review updates to produce valid and relevant synthesized evidence that contributes to a rapid public health response to HIV. In addition, this work will identify evidence gaps and put forward new approaches for reviewing and meta-analyzing complex implementation research specific to HIV but with relevance to evidence synthesis in the implementation science field more broadly.

Methods

This project protocol was designed according to PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines, living review guidelines, and World Health Organization (WHO) and Cochrane rapid review guidelines [6,8,10,24].

Identification of Review Questions

Relevant HIV implementation science questions will be developed in consultation with HIV guideline development groups. This will include questions regarding effectiveness of HIV implementation strategies. Individual review protocols will be published on PROSPERO, the international prospective register of systematic reviews.

Eligibility Criteria

Studies eligible for inclusion in living rapid reviews include those conducted in any population group or age category from any setting. Randomized controlled trials (RCTs), cohort studies (with or without a comparison arm), cross-sectional studies, and natural experiments are eligible for inclusion. Incorporation of a broad range of study designs including both randomized controlled trials and observational studies will facilitate exploration of the broad spectrum of implementation research assessing the performance of implementation strategies under trial and real-world conditions.

Studies must evaluate the implementation of evidence-based HIV interventions (strategies aimed at implementing a change...
to the way HIV testing, antiretroviral treatment [ART], or prevention is delivered to modify patient behavior and improve outcomes) and report on at least one HIV cascade outcome (HIV incidence, HIV testing uptake, ART initiation, ART adherence, viral suppression, retention in care) (Table 1). Eligible studies will be restricted to English language publications.

Table 1. Eligibility criteria for inclusion in LIVE rapid living reviews.

<table>
<thead>
<tr>
<th>Eligibility criteria</th>
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<tbody>
<tr>
<td>Population</td>
</tr>
<tr>
<td>All settings, all ages</td>
</tr>
<tr>
<td>Implementation strategy</td>
</tr>
<tr>
<td>Implementation strategy aimed at (1) implementing a change to the way HIV care and prevention strategies are delivered or (2) modifying patient behavior</td>
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<tr>
<td>Comparison</td>
</tr>
<tr>
<td>Other intervention, standard of care, or no comparison</td>
</tr>
<tr>
<td>Outcome</td>
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<tr>
<td>HIV incidence, HIV testing uptake, antiretroviral therapy initiation, antiretroviral therapy adherence, viral suppression, retention in care</td>
</tr>
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</table>

Database Searches
An information specialist will conduct searches of a minimum of two databases—MEDLINE and Embase—and will include CINAHL and other databases depending on the considered added value for the specified review question as determined in consultation with an information specialist. Search outputs will be refined through an iterative process of cross-checking against known studies in the field. Once finalized, automated searches running at a predetermined frequency (initially every 6 months) will generate updated lists of studies for screening and eligibility assessment and abstraction. Searches will include studies published between 2004 to the day of the search, but may be restricted to more recent studies depending on the specified review question.

Gray Literature Searches
At minimum, conference abstracts of the International AIDS Society and the Conference on Retroviruses and Opportunistic Infections will be searched for the previous two years. Additional conference searches will depend on their relevance to review questions. Clinical trial registries including ClinicalTrials.gov and WHO International Clinical Trials Registry Platform registries will be searched routinely; depending on the specific review, further trial registries may be considered.

Screening
Several team members may be involved in screening processes. Abstract and full-text screening will be conducted using Covidence software [25]. For abstract screening, 2 team members will screen the first 20% of abstracts with conflict resolution; once approaches to screening are calibrated and consistency developed, ongoing abstract screening will be conducted by one team member. Full-text screening will be conducted by one team member and excluded full texts will be screened by a second. Conference and clinical trial registry searches will be conducted by one team member with confirmation of eligibility of included abstracts by a second.

Data Abstraction
Study data will be abstracted into the LIVE database hosted on the Airtable platform (a relational database designed to be easily modified by end users and widely used commercially [26]. Extracted study outcomes will include numerators and denominators as well as adjusted and unadjusted effect estimates. Data abstraction and methodological quality assessments will be conducted by one team member and reviewed by a second team member. Descriptive information will be extracted from each study (including details on publication, study design, setting, context, and demographic characteristics) and additional data regarding the critical characteristics and components of implementation strategies will be recorded using existing frameworks for evaluating characteristics of implementation strategies, reporting of implementation outcomes, assessments of real-world relevance of primary research, and implementation characteristics of trial design (Table 2). By applying these implementation science tools and frameworks, the LIVE project will employ evidence synthesis methods that accommodate complexity, recognizing that heterogeneity is an inherent feature of the current HIV response and is essential [1].

Table 2. Tools used to assess study quality and characterize intervention strategies for living rapid reviews.

<table>
<thead>
<tr>
<th>Assessment tool</th>
<th>Purpose</th>
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<tbody>
<tr>
<td>Cochrane risk of bias tools [27,28]</td>
<td>Assess the methodological quality of randomized controlled trials</td>
</tr>
<tr>
<td>Newcastle Ottawa scale [29]</td>
<td>Assess the methodological quality of cohort and cross-sectional studies</td>
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<tr>
<td>Proctor implementation strategy framework [20]</td>
<td>Characterize implementation strategies</td>
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<tr>
<td>Proctor implementation outcome classification system [21]</td>
<td>Characterize and assess reporting implementation outcomes</td>
</tr>
<tr>
<td>Pragmatic explanatory continuum indicator summary (PRE-CIS)-2 tool [22]</td>
<td>Evaluate explanatory vs pragmatic approaches of studies</td>
</tr>
<tr>
<td>Curran effectiveness-implementation hybrid trial designs [30]</td>
<td>Characterize trial types based on focus: clinical effectiveness versus implementation</td>
</tr>
</tbody>
</table>
Analyses

We will characterize individual study populations, implementation interventions, comparisons, and HIV cascade outcomes and other outcomes relevant to the review questions including harms and unintended consequences. We will use funnel plots to explore publication bias. If there is sufficient quantitative data, these data will be meta-analyzed in R, Stata, or SAS programs, depending on the type of data available for analysis (e.g., continuous, binary, incidence, adjusted effect estimates, single means, or proportions). Pooled results and forest plots for random effects will be generated using Mantel-Hansel, Peto, generalized linear models, or generic inverse variance [31]. Inconsistency will be reviewed qualitatively to detect clinical diversity (population, context, implementation strategy) or methodological diversity (risk of bias, study design), and quantitatively using $I^2$, Kendall $\tau$ statistics, and subgroup analysis. Decisions regarding the appropriateness of pooling data, subgrouping, and sensitivity analyses will be conducted by study teams and will follow guidelines as set out by the Cochrane Handbook. Given the inherently heterogenous nature of HIV implementation research, we anticipate substantial explained and unexplained heterogeneity; as a result, pooled estimates may in many cases not reflect one true population effect estimate relevant to all contexts but rather a broader assessment of overall benefit or harm across various contexts [32]. Where sufficient data are available, we will use meta-regression to explore heterogeneity.

In addition, where multiple strategies are presented, network meta-analyses (NMA) may be conducted and will follow guidelines for conduct and reporting of NMA. The frequentist or Bayesian NMA approaches will be used to generate networks, evaluate inconsistency, and rank interventions. Although the inherent nature of implementation strategies may in some cases violate the assumption of transitivity due to variability in context and strategy heterogeneity—in terms of design and fidelity to intervention delivery—this analytic technique allows for the comparison of multiple interventions that have not been compared directly due to public health urgency and resource constraints [33].

Where data are insufficient for meta-analysis, we will summarize data narratively. The overall confidence in the review findings will be evaluated using recognized methodologies for rating evidence certainty such as the Grading of Recommendations Assessment, Development, and Evaluation system [34].

Living Processes

Once a review is completed and published, a continuous living process will be adopted to keep the review findings up to date as required [6,35]. First, the systematic review question will be examined in the light of the primary review findings and in consultation with key stakeholders (e.g., WHO guideline developers) to determine if the question remains relevant in its current format, whether the review question should be altered to address different population groups, and whether additional strategies or specific implementation or HIV cascade outcomes should be focused on. Search strategies will be examined and refined to ensure that all relevant new terms and databases are included in updated search strategies. A comprehensive systematic search will be conducted every 6 months. If no new studies are detected, review records will be updated with the most recent search date and specify that no new relevant studies have been identified. If new studies are identified but appear unlikely to change the review findings or are insufficient for new meta-analyses, study data will be extracted but no meta-analyses will be performed. If new findings are deemed critical for revised or updated guidelines, new meta-analyses of all studies identified to date will be conducted and published in a peer reviewed journal. With each 6-month cycle, considerations for retirement of reviews will be revised, as the importance of research questions will be expected to change over time [36]. Such reviews may contribute to living guidelines, an emerging methodological area where guidelines are continuously assessed to determine whether they are sufficiently up to date and whether new studies or information is available that may change the guideline, leading to cycles of refinement and revision or retirement [14].

Results

As of July 2022, five reviews are at various stages of development within the LIVE project. Data extraction is underway for 3 systematic reviews with the aim of completion by the end of December 2022; living review processes are under development for 2 reviews.

Discussion

The LIVE project seeks to enhance the use of implementation research to inform guideline development and ultimately policy making. The project proposes to produce “living” systematic reviews by applying an ongoing updating and data extraction process to support guideline developers, including but not limited to questions on HIV service delivery at the WHO. In this project protocol, we outline a plan to support ongoing guideline development processes in HIV testing and use of antiretrovirals, but also identify how through the maintenance of living reviews this work can contribute to the future conceptualization and development of “living guideline” processes.

The additional application of implementation research tools and taxonomies further position this work to contribute to guidelines that directly impact global implementation efforts, particularly for questions in HIV service delivery. By broadly exploring how, where, and for whom HIV implementation strategies are most effective, the LIVE project will advance the implementation science field by directly addressing inherent heterogeneity and intervention complexity in implementation science evidence synthesis and support future HIV service delivery guideline development.

This work may be limited by difficulties in maintaining reviewers over the long term and ensuring continuous updates; the project will work to overcome this by involving a broad review team to ensure the ongoing longevity of individual systematic reviews. A further challenge may be decisions regarding when to publish an updated version of a review, retire a review, or alter review questions. To address this, decisions
regarding review updates will be determined in close collaboration with experts and policy makers to ensure ongoing relevance.

Synthesizing implementation research evidence is complex. This protocol and review portfolio propose new directions for implementation science evidence synthesis that also have relevance for other implementation questions beyond HIV service delivery.

Acknowledgments
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We would like to acknowledge the work of Jeanna Wallenta, Chris Kemp, and Siyu Wang in developing the Living Database of HIV Implementation Research (LIVE) platform for systematic review data abstraction.

Conflicts of Interest
None declared.

References


29. Covidence. URL: https://www.covidence.org/ [accessed 2022-08-22]


**Abbreviations**

- **ART**: antiretroviral therapy
- **LIVE**: Living Database of HIV Implementation Research
- **NMA**: network meta-analysis
- **PRISMA-P**: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
The Use of Segmental and Suprasegmental Sequencing Skills to Differentiate Children With and Without Childhood Apraxia of Speech: Protocol for a Comparative Accuracy Study

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2Research Centre for Language, Cognition, and Neuroscience, The Hong Kong Polytechnic University, Hong Kong SAR, Hong Kong
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Abstract

Background: Childhood apraxia of speech (CAS) is a motor-based speech sound disorder (SSD) with a core impairment in the planning and programming of spatiotemporal parameters of speech movement sequences. CAS may cause deficits in both segmental and suprasegmental components of speech, and it can severely affect children’s ability to speak intelligibly and communicate effectively and impact their quality of life. Assessment tasks, such as the maximum performance tasks (MPT) and Syllable Repetition Task (SRT), examine children’s segmental sequencing skills to assist with the diagnosis of CAS. In Hong Kong, although the MPT and SRT have been used clinically to diagnose CAS in Cantonese-speaking children, their validity has not been reported. There is an urgent need for such investigations. Suprasegmentally, lexical stress errors have been reported as a consensual feature and to aid in the diagnosis of CAS. However, there are challenges in diagnosing CAS in children who speak tonal languages like Cantonese. A recent study has reported lexical tone errors in Cantonese-speaking children with CAS. Furthermore, deficits in pitch-variation skills were found in Cantonese-speaking children with CAS using a tone sequencing task (TST). It is hypothesized that there is a universal deficit in pitch-variation skills among tonal and nontonal language speakers with CAS. Further investigations of pitch-variation skills using the TST in Cantonese-speaking children with CAS may shed light on suprasegmental deficits in tonal languages and contribute to the development of a valid diagnostic tool for CAS in children who speak other tonal languages, such as Vietnamese, Thai, and Mandarin.

Objective: This study aims to examine the diagnostic potential of the MPT, SRT, and TST in diagnosing Cantonese-speaking children with CAS and to investigate pitch-variation skills in Cantonese-speaking children with and without CAS.

Methods: A total of 25 children with CAS and 3 groups of age- and gender-matched controls (non-CAS SSD only group, non-CAS SSD co-occurring with language impairment group, and typical development group) will be recruited. All participants will perform the MPT, SRT, and TST measures. Their performances on these tools will be perceptually judged and acoustically measured.

Results: Data collection will last from January 1, 2022, to October 30, 2023. As of August 2022, the project has recruited 4 children in the CAS group, 21 children in the non-CAS SSD group, 4 children in the speech and language impairment group, and 53 children in the typical development group.

Conclusions: It is anticipated that Cantonese-speaking children with CAS will have poorer pitch-variation skills than the control groups and that the MPT, SRT, and TST will be appropriate diagnostic tools for identifying CAS in Cantonese-speaking children. The project will benefit the field of speech-language pathology locally and internationally, with short- and long-term impacts.

International Registered Report Identifier (IRRID): DERR1-10.2196/40465
Introduction

Background

Childhood apraxia of speech (CAS) is a motor-based speech sound disorder (SSD) with a core impairment in planning and programming of spatiotemporal parameters of speech movement sequences. It can occur as an idiopathic neurogenic SSD or as a result of known neurological impairment [1]. It can severely affect children’s ability to speak intelligibly and communicate effectively. CAS onsets from childhood and may persist into adolescence and adulthood [2-4]. It left untreated, the quality of life of children with CAS will be affected because of the long-term consequences of CAS on articulation, speech intelligibility, expressive language [5], academic performance, and social functioning [2-4,6,7].

CAS in children is characterized by deficits in both segmental and suprasegmental components of speech. The American Speech-Language-Hearing Association [1] reported that there are three consensus features, including (1) inconsistent errors in sequential repetitions; (2) deficits in coarticulation or syllable segregation (ie, choppy speech); and (3) prosodic deficits, especially lexical stress errors. Lexical stress errors, as one of the consensual features of CAS, have been widely studied in English speakers because of their high value as a suprasegmental marker of CAS [8]. The errors reflect underlying deficits in speech motor planning and programming skills that control the intensity, frequency, and duration of suprasegmental parameters. Deficits in the temporal control of lexical stress production have been documented, but it has been difficult to separate other specific acoustic aspects of lexical stress, such as pitch [9].

CAS Diagnosis in English-Speaking Children

The gold standard for making a CAS diagnosis primarily relies on perceptual judgments of CAS experts. However, very recently, a pilot study reported only moderate agreement among 4 expert listeners [10]. Along with perceptual judgment, the maximum performance tasks (MPT) [11] and Syllable Repetition Task (SRT) [12] have been reported to provide valuable relevant information about segmental sequencing skills in children with CAS. Both MPT and SRT assess deficits in speech processing. The MPT aims to assess motor involvement in children with speech problems [11]. Specifically, the maximum repetition rate for trisyllabic stimuli (MRtri) and maximum fricative duration (MFD) in MPT assess underlying deficits in the motor planning and programming of speech [13], while the maximum repetition rate for monosyllabic stimuli and maximum phonation duration assess deficits in speech motor execution. The SRT targets encoding, memory, and transcoding processes, which refer to mapping, prearticulatory or phonological planning, and transformation of the phonological plan into a motor plan, respectively [14]. Although the terminology is not identical, both the MPT and SRT address the same underlying deficits of CAS, speech motor planning and programming skills. Research has shown that the MPT has high sensitivity and specificity (ranging from 89% to 100%) in making a CAS diagnosis [11], whereas a cutoff transcoding score of 80 on the SRT is able to differentiate children with CAS from children with concomitant speech delay and language impairment (LI) [15].

CAS Diagnosis in Cantonese-Speaking Children

There are challenges in diagnosing CAS in children who speak tonal languages like Cantonese. In Hong Kong, speech-language pathologists may apply English-based research findings to assess, diagnose, and treat children with CAS among the local Cantonese-speaking population. Although MPT and SRT have been used clinically to diagnose CAS in Cantonese-speaking children, the validity of applying these objective measures and diagnostic criteria from English-speaking populations to Cantonese-speaking populations is unknown. Owing to the segmental and suprasegmental differences between English and Cantonese, such as the fact that English has lexical stress patterns while Cantonese has lexical tones, English-based findings cannot be fully applied to Cantonese speakers with CAS, especially as prosodic deficits are one of the consensual clinical features of CAS. The current gold standard relies on expert perceptual judgment of clinical features reported in the English literature. Therefore, it is possible that misdiagnoses or underdiagnoses are occurring in the current clinical practice in Hong Kong. As higher frequency treatment is suggested for children with CAS [16] owing to the need for speech motor learning, inaccurate diagnoses may impact children, families, and society in terms of allocation of resources. Therefore, a valid diagnostic tool is urgently needed for Cantonese speakers with CAS to correctly identify and provide appropriate treatment to children with CAS.

Previous Pilot Studies

A recent study [14] identified a new clinical feature, namely tone production errors, which has not been reported in English speakers with CAS. The authors proposed that the same underlying deficit of speech motor planning and programming skills manifests differently in Cantonese and English [14]. Both English and Cantonese speakers with CAS may have similar control challenges with the correct production of segments; however, they control suprasegmentals differently because of linguistic differences. Suprasegmentals are overlaid differently for lexical stress in English versus lexical tone in Cantonese. English speakers apply 3 stress features—simultaneous pitch, loudness, and duration variations—to syllables to express a grammatical or pragmatic meaning. Cantonese speakers vary the pitch of segments to indicate different lexical meanings. Owing to these differences, further investigations of lexical tone errors are vital to increase the understanding of tone production skills in children with CAS.

In an effort to further explore tone production skills in Cantonese-speaking children with CAS, tone sequencing tasks (TSTs) have been used in 2 studies to examine the accuracy,
consistency, and duration of tone production in Cantonese-speaking children with CAS [17,18]. The TST is considered to be a potential assessment task that reflects impairment in speech motor planning and programming in Cantonese-speaking children with CAS [17,18]. It requires children to produce 5 repetitions of each item that is formed of 3 early-acquired Cantonese tones, that is, tone 1 (high-level), tone 2 (high-rising), and tone 4 (low-falling). Wong et al [18] administered the initial version of the TST to 2 Cantonese-speaking children with CAS and 2 Cantonese-speaking children with non-CAS SSDs. The results showed that children with CAS performed significantly more poorly than children without CAS in sequencing tones. The effect sizes (Cohen's $d$) for tone accuracy and consistency were 0.68 and 0.60, respectively. Both of them were considered to be medium-to-large effect sizes.

In a subsequent study, the research team examined the linguistic effects of syllable structure and lexical status on TSTs using the second version of the TST [18]. A total of 4 Cantonese-speaking children with CAS were matched with 3 children with non-CAS speech and LI (S&LI), 3 with LI alone, and 3 with typical development (TD). Tone accuracy was judged perceptually and calculated as the percentage of tones correct. The consistency strength procedure adopted from the study by Williams et al [19] was used to calculate consistency scores. In the study by Wong et al [20], the team added 2 acoustic measures (ie, fundamental frequency [$F_0$] values and acoustic duration) to further examine the data. The results showed both syllable structure and lexical status effects. Cantonese-speaking children with and without CAS showed significant between-group differences in $F_0$ values for both vowel and consonant-vowel structures, as well as tone accuracy, tone consistency, and acoustic duration of word stimuli. A small to medium effect size (Cohen's $d$ ranging from 0.22 to 0.61) was obtained for $F_0$ values, whereas large effect sizes were obtained for tone accuracy (Cohen's $d$ ranging from 1.37 to 1.98), tone consistency (Cohen's $d$ ranging from 1.36 to 1.85), and acoustic duration (Cohen's $d$ ranging from 0.9 to 1.45). The results suggest that syllable structure and lexical status play some roles in tone sequencing skills in children with CAS. In summary, these pilot studies suggest that children with CAS have difficulty with pitch-variation skills, specifically tone sequencing skills, and perform more poorly than control groups. The findings also support the diagnostic potential of TST as it provides a platform to investigate pitch variation in children with CAS and should be further developed as a linguistically appropriate assessment tool for Cantonese-speaking children. However, the generalizability of these findings is limited because of the extremely small sample sizes.

**Studying Pitch-Variation Skills Using the TST**

Pitch-variation skills refer to the skills of varying $F_0$ values within and between syllables in tonal languages. Pitch-variation skills present in English lexical stress patterns and Cantonese lexical tones. Although lexical stress errors have been empirically studied and it has been found that children with CAS have a deficit in the temporal control of lexical stress productions [9], the development and disorders of pitch-variation skills embedded in lexical stress errors remain unknown. Kopera and Grigos [9] attempted to examine the acoustic properties (ie, duration, peak $F_0$, and average $F_0$) of lexical stress errors using the pairwise variability index [21] between children with and without CAS. No significant between-group difference was found. The authors concluded that lexical stress errors in children with CAS can only be studied in a collective fashion, such as using the lexical stress ratio [8], which examines pitch, loudness, and duration simultaneously, instead of investigating acoustic parameters independently.

Nevertheless, new findings have shown significant between-group differences in both $F_0$ values and acoustic duration between children with CAS and control groups [20]. This preliminary result suggests that Cantonese-speaking children with CAS have difficulty in varying pitch and that pitch-variation skills in Cantonese speakers with CAS can be studied independently via the TST in the context of this tonal language. This provides the basis for further investigations of pitch-variation skills in children with CAS who speak other tonal languages (eg, Mandarin, Vietnamese, and Thai) as well as children with CAS who speak nontonal languages (eg, English). TST can be used in English to assess pitch-variation skills in children with CAS in an out-of-stress context. This application may elucidate the role of pitch control in out-of-stress contexts and shed light on pitch control across languages in speakers with CAS.

**The Goal of the Proposed Study**

This study aims the following:

1. To show that the MPT and SRT can contribute to the diagnosis of CAS in Cantonese-speaking children.
2. To document differences in pitch-variation skills in Cantonese-speaking children with versus without CAS.
3. To prove that TSTs are effective in diagnosing CAS in Cantonese-speaking children.

We hypothesized the following:

1. The MPT and SRT would differentiate Cantonese-speaking children with CAS from those without CAS.
2. Cantonese-speaking children with CAS would have significantly poorer pitch-variation skills than the control groups.
3. TSTs would differentiate Cantonese-speaking children with CAS from those without CAS.

**Methods**

**Protocol Version**

The original version of the protocol was submitted to the Research Grants Council of the Hong Kong Special Administrative Region Government on October 30, 2020. This protocol is version 2, in which the sample size was changed from 120 to 100 children. This change was approved by the Research Grants Council on May 17, 2022.

**Study Design**

This is a comparative accuracy study that will compare the diagnostic accuracy of the MPT, SRT, and TST in children with and without CAS.
**Participants**

A total of 25 children with CAS will be recruited for the study. The inclusion criteria are as follows: (1) age between 3 years and 6 years 11 months, (2) diagnosed with or suspected of having CAS by a qualified speech-language pathologist, (3) no hearing impairment or structural abnormality that affects speech production, and (4) Cantonese as the main language for daily communication. The same number of age- and gender-matched children will be recruited for each of the following 3 control groups: non-CAS SSDs only, non-CAS SSDs co-occurring with S&LI, and TD. The non-CAS SSD group will be recruited because it will allow a direct comparison between children with and without CAS. Research has shown that LI is usually present in children with CAS [5]; therefore, an S&LI group will be included to compare the performance of children with and without CAS, while controlling for language skills. A total of 100 participants will be recruited. Originally, a sample size of 172 participants (ie, 43 for each group) was estimated from the effect size of tone accuracy in a pilot study [20] via power analysis. An actual power of 0.954 could be achieved from 172 participants with an error probability of 0.05 ($F_{106}=2.658$). There should be sufficient children with CAS in this population. However, taking into consideration the time and effort needed to screen and find suitable participants with and without CAS, SSD, and S&LI, it will be very challenging to recruit 172 participants within 2 years (the proposed study period). In addition, many reported studies [22,23] have only recruited 20 to 30 children with CAS for the investigations of assessment and diagnostic accuracy. Therefore, the total sample size was reduced to 100 participants.

**Recruitment**

A recent study estimated the population-based prevalence of CAS in children aged 4 to 8 years to be 1 child per 1000 [24]. Given that there were about 303,000 children between the ages of 5 and 9 years in Hong Kong in the mid-2020 [25], there may be 303 children in this age range in Hong Kong who are currently impacted by this severe motor speech disorder. Children were recruited through local advertising and invitations. Recruitment posters were posted in the university campus and on the web via social media platforms. The digital version of the posters was posted on the official Facebook page of the university speech-language therapy clinic, the Facebook page and Instagram accounts of Cantonese CAS, and the personal Facebook and Instagram accounts of the members of the research team. For the CAS group, recruitment information was also delivered to speech-language pathologists who attended local continuing education seminars on Cantonese CAS. Personal invitations were sent to the parents of children with CAS who have connections with the research team. The non-CAS groups were recruited from the general public by forwarding the digital posters to the parents of preschool children on WhatsApp chat groups, inviting parents of the children who were receiving speech-language therapy services in the university clinic, and sending invitation emails to kindergartens located in the same district as the university.

**Procedure**

**Initial Assessment**

An expert speech-language pathologist will conduct initial assessments to diagnose each participant, if appropriate. The expert speech-language pathologist will have at least 10 years of clinical experience in assessing and treating Cantonese-speaking children with and without CAS. The assessment tasks include case history, speech sample collection, standardized language tests (ie, Hong Kong Test of Preschool Oral Language [Cantonese] [26] and Hong Kong Cantonese Receptive Vocabulary Test [27]), standardized articulation test (ie, Hong Kong Cantonese Articulation Test [28]), imitation of polysyllabic words, a standardized tone identification test (ie, Cantonese Tone Identification Test [29]), an oral and speech motor control assessment [30], and the documentation of prosodic characteristics. If a child is suspected to have autism spectrum disorder (ASD), the expert speech-language pathologist will conduct further assessments. According to Tierney et al [31], there is high comorbidity between CAS and ASD. The diagnosis of CAS and ASD may be delayed or inaccurate when both conditions are present in a child; children with CAS may be wrongly diagnosed with ASD and vice versa. Therefore, the Autism Diagnostic Observation Schedule, Second Edition [32], a standardized tool with high specificity and sensitivity for diagnosing ASD [33], will be administered to obtain information about the appropriateness of an ASD diagnosis. The assessment session will be audio- and video recorded so that another expert speech-language pathologist can review the assessments and diagnose independently. The CAS diagnosis will be confirmed if both speech-language pathologists reach a consensus on the presence of CAS features. The diagnosis of CAS will be confirmed based on international standards and the methods used in our previous pilot study [20]. A CAS diagnosis will be based on the presence of 3 consensual features [1] and 4 clinical features that have reported 91% diagnostic accuracy [22], with appropriate modifications for Cantonese-speaking children, and across different assessment tasks (eg, speech sample, imitation of polysyllabic words, standardized articulation test, and diadochokinetic tasks). Murray et al [22] suggest using (1) syllable segregation, (2) lexical stress matches, (3) percent phonemes correct from polysyllabic words, and (4) articulatory accuracy on repetitions of [p t k ] for the differential diagnosis of CAS. Modification of some of these features is necessary for Cantonese. The second feature will be changed to *lexical tone errors* owing to the prosodic differences between English and Cantonese. The third feature will be changed from both segmental and suprasegmental correctness to only segmental correctness because of the constant duration of Cantonese syllables [34]. This set of criteria was used in our previous pilot study [20].

**MPT and SRT**

Every child will perform the MPT, SRT, and TST. The order of administration will be randomized. The administrative procedures and interpretation of MPT and SRT are described in the studies by Rvachew et al [35] and Rvachew and Matthews [15], respectively. There are four tasks in the MPT, including (1) maximum phonation duration, (2) MFD, (3) maximum
repetition rate for monosyllabic stimuli, and (4) MRRtri. A total of 6 scores can be obtained from these tasks [11]. A dyspraxia score of 0, 1, or 2 is obtained from the performances of MFD and MRRtri. A dyspraxia score of 2 indicates the presence of CAS in children.

The SRT includes 18 items [12]. The items are formed of early developing phones (eg, [m], [d], [n], and [a]), which are easier for younger or severely impaired children to produce. The items included eight 2-syllable stimuli (eg, [bada]), six 3-syllable stimuli (eg, [bamana]), and four 4-syllable stimuli (eg, [bamadana]). The SRT gives 4 scores, including a competency score, an encoding score, a memory score, and a transcoding score. The interpretation of these 4 scores is based on z-scores from the means and SDs reported in the study by Lohmeier and Shriberg [36]. Table 1 presents a comparison of MPT and SRT.

### Table 1. Comparison of the maximum performance tasks (MPT) and Syllable Repetition Task (SRT).

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>Motor planning and programming of speech</td>
<td>Encoding process (mapping)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Memory process (praearticulatory or phonological planning)</td>
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<td></td>
<td></td>
<td>Transcoding process (transformation of the phonological plan into a motor plan)</td>
</tr>
<tr>
<td>Scores</td>
<td>MPD&lt;sup&gt;a&lt;/sup&gt;: mean duration of the longest prolongation of [a] and [mama]</td>
<td>Competency: PCC&lt;sup&gt;e&lt;/sup&gt; of 18 items</td>
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<tr>
<td></td>
<td>MFD&lt;sup&gt;b&lt;/sup&gt;: mean duration of the longest prolongation of [s], [t], and [z]</td>
<td>Encoding: percentage of consonants within-manner class substitution errors (excluding voicing errors)</td>
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<td></td>
<td>MRRmono&lt;sup&gt;c&lt;/sup&gt;: score: mean repetition rate for the fastest repetition of each [pa], [ta], and [ka]</td>
<td>Memory: ratio of PCC for 3-syllable items to PCC for 2-syllable items</td>
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<td></td>
<td>MRRtri&lt;sup&gt;d&lt;/sup&gt; score: number of syllables produced per second in the child’s fastest repetition of [p t k]</td>
<td>Transcoding: percentage of items that are produced with ≥1 additions</td>
</tr>
<tr>
<td></td>
<td>Sequence score: 1 for correct sequence and 0 for unsuccessful production</td>
<td>Interpretation of the scores is made based on the z-scores from the means and SDs reported in the study by Lohmeier and Shriberg [36]</td>
</tr>
<tr>
<td></td>
<td>Attempt score: number of attempts required to produce the correct sequence</td>
<td>Cutoff scores for CAS diagnosis [37]:</td>
</tr>
<tr>
<td>Criteria of CAS diagnosis</td>
<td>A dyspraxia score of 2 indicates the presence of CAS; it is obtained when</td>
<td>Competency score=65</td>
</tr>
<tr>
<td></td>
<td>MRRtri ≤3.4 or</td>
<td>Encoding score=46.9</td>
</tr>
<tr>
<td></td>
<td>Sequence=0 or</td>
<td>Memory score=67.5</td>
</tr>
<tr>
<td></td>
<td>Dyspraxia score is not 0 or 1</td>
<td>Transcoding score=80</td>
</tr>
</tbody>
</table>

<sup>a</sup>MPD: maximum phonation duration.  
<sup>b</sup>MFD: maximum fricative duration.  
<sup>c</sup>MRRmono: maximum repetition rate for monosyllabic stimuli.  
<sup>d</sup>MRRtri: maximum repetition rate for trisyllabic stimuli.  
<sup>e</sup>PCC: percentage of consonants correct.  
<sup>f</sup>CAS: childhood apraxia of speech.

### TST Procedure

The TST proposed in this study is a shorter version modified based on the findings in the study by Wong et al [18]. This new version of TST has 16 stimuli, derived from 2 vowel structures, 2 consonant-vowel structures with early acquired sounds, and 3 early acquired Cantonese tones. The details of the TST are listed in Table 2. There are twelve 1-syllable items and four 3-syllable items. Both word and nonword stimuli are included. The participants will repeat each item as fast as they can 5 times. Four outcome measures will be obtained from the TST:

Most of the stimuli used in the MPT and SRT are shared between English and Cantonese. For example, the vowel [a] and initial consonants [m], [f], and [s] in the MPT and SRT are shared in Cantonese. Although the voiced consonants [b] and [d] and voiceless consonants [p], [t], and [k] in English cannot be found in Cantonese, these sounds can be replaced by voiceless unaspirated [p] and [t] and voiceless aspirated [pʰ], [tʰ], and [kʰ] in Cantonese. This replacement is logical as, from a motor perspective, the contrastive aspiration feature in Cantonese consonants is similar to the voicing feature in English consonants [38]. With this logical replacement, it is anticipated that the SRT and MPT will be useful in differentiating between Cantonese speakers with and without CAS, as has been proven in English and Dutch speakers [11,15].
1. Tone accuracy will be calculated from perceptual judgments of correctness.
2. Tone consistency will be calculated using the consistency strength formula described in the study by Williams et al [19]. The 5 repetitions of each stimulus will be compared with the children’s own baseline one by one to determine the consistency strength of that production.
3. F0 values will be measured using Praat. F0 will be estimated at 5 evenly spaced time points (0%, 25%, 50%, 75%, and 100%) from the beginning to the end of the voiced segment of each syllable in the TST [39].
4. Acoustic durations will be measured in Praat from the onset of the first syllable to the end of the last syllable.

All assessment sessions will be conducted at a local university clinic or laboratory, and all data collection sessions will be conducted in the soundproof booth in the laboratory. Children’s performances on the MPT, SRT, and TST will be audio- and video-recorded. Two speech-language pathologists with experience in childhood disordered speech will perceptually transcribe children’s productions using narrow transcription and score their performance. Furthermore, 20% of the ratings will be rerated by the speech-language pathologists to determine intra- and interrater reliability.

| Table 2. Stimuli of tone sequencing task (TST) for the proposed study. |
|--------------------------|-------------------------|-------------------------|
| TST type | Structure | Vowel | Consonant-vowel |
| TSTmono<sup>a</sup> | [a<sub>1</sub>]<sup>b</sup>x5 | [pa1]<sup>c</sup>x5 |
| | [a2]<sup>d</sup>x5 | [pa2]<sup>c</sup>x5 |
| | [a4]<sup>e</sup>x5 | [pa4]<sup>c</sup>x5 |
| | [u1]<sup>c</sup>x5 | [hu1]<sup>c</sup>x5 |
| | [u2]<sup>c</sup>x5 | [hu2]<sup>c</sup>x5 |
| | [u4]<sup>c</sup>x5 | [hu4]<sup>c</sup>x5 |
| TSTtri<sup>f</sup> | [a1a2a4]<sup>c</sup>x5 | [pa1pa2pa4]<sup>c</sup>x5 |
| | [u1u2u4]<sup>c</sup>x5 | [hu1hu2hu4]<sup>c</sup>x5 |

<sup>a</sup>TSTmono: tone sequencing task for monosyllabic stimuli.
<sup>b</sup>The number 1 indicates high-level tone in Cantonese.
<sup>c</sup>Indicates word stimuli (the others are nonword stimuli).
<sup>d</sup>The number 2 indicates high-rising tone in Cantonese.
<sup>e</sup>The number 4 indicates low-falling tone in Cantonese.
<sup>f</sup>TSTtri: tone sequencing task for trisyllabic stimuli.

**Statistical Methods**

For the statistical analysis, linear mixed-effects models will be used. Our models will include group (CAS vs SSD vs S&LI vs TD) as a fixed effect and participants and items as random effects.

The sensitivity and specificity of the MPT, SRT, and TST in making a diagnosis of CAS in Cantonese-speaking children will be determined using the receiver operating characteristics curve [40]. The new cutoff scores of the MPT and SRT to diagnose CAS in Cantonese-speaking children will be compared with the existing cutoff scores recommended for English-speaking children. The cutoff scores for the TST will also be determined from the receiver operating characteristics curve.

**Ethics Approval**

An information sheet and informed consent form will be given to the parents or guardians of the child participants before the initial assessment or data collection sessions. All parents or guardians will be asked to provide consent by signing the informed consent form given. The parents or guardians of the participants will be informed that their participation is voluntary and that they can withdraw their children at any time without giving a reason and without any negative consequences. All the information provided by the participants and their parents or guardians will be handled confidentially and anonymously, which means that all the data from which the participants can be identified will be removed. All the data will be encrypted and stored in a repository with restricted access. Only researchers working on this study will have access to personal and research data for the purposes of this study. This study has received ethical approval from the Hong Kong Polytechnic University Institutional Review Board (HSEARS 20210125011 and HSEARS 20210330007). Responsible members of Hong Kong Polytechnic University may be given access for monitoring and auditing the research. Any important changes in the protocol will be informed to the Hong Kong Polytechnic University Institutional Review Board.
Results

Data collection started in January 2022 but was soon disrupted by the fifth wave of the COVID-19 pandemic in Hong Kong. As of August 2022, the project has recruited 4 children in the CAS group, 21 children in the non-CAS SSD group, 4 children in the S&LI group, and 53 children in the TD group. Data collection is ongoing and will continue until October 2023.

Discussion

Principal Findings

The proposed study will address an important clinical research gap owing to which there is an urgent need for a valid diagnostic tool for Cantonese speakers with CAS. In particular, we aimed (1) to show that the MPT and SRT can contribute to the diagnosis of CAS in Cantonese-speaking children, (2) to document differences in pitch-variation skills in Cantonese-speaking children with versus without CAS, and (3) to prove that TSTs are effective for diagnosing CAS in Cantonese-speaking children.

Comparison With Prior Work

With reference to previous investigations of the TST [17,20], it is anticipated that Cantonese-speaking children with CAS will have significantly poorer pitch-variation skills than the control groups. Specifically, Cantonese speakers with CAS will show less variations in F0 values, longer acoustic repetition durations, lower percentages of tones correct, and lower consistency than those in the control groups. It is further anticipated that TST, like MPT and SRT, will be shown to be effective for diagnosing CAS in Cantonese speakers, with appropriate sensitivity and specificity.

Strengths and Limitations

On completion, this study will provide 2 objective measures (ie, MPT and TST) and 2 measures that convert perceptual judgments into quantitative data (ie, SRT and TST) for diagnosing CAS in Cantonese speakers. The results will promote the standard of CAS diagnosis in Cantonese speakers from reliance on expert perceptual judgment based on a list of clinical features [41] to a combination of perceptual judgment and quantitative data. In addition, the short administration time of the measures proposed in this study (ie, approximately 15-20 minutes per measure) will provide clinicians with quick and accurate methods for CAS diagnosis in Cantonese speakers than approximately 2 hours of comprehensive assessment [18,41,42] of speech motor skills reported in the literature. Moreover, the results of this study will provide the basis for further investigations of pitch-variation skills in children with CAS who speak other tonal languages (eg, Mandarin, Vietnamese, and Thai) as well as in children with CAS who speak nontonal languages (eg, English). Finally, investigations of the effects of linguistic elements (such as the lexical status, syllable structure, number of syllables, and syllable position) on children’s pitch-variation skills or speech motor control will provide information on how the linguistic elements of Cantonese interact with speech motor planning and programming skills.

This study faces several challenges. First, data collection started in January 2022 but was disrupted owing to the fifth wave of the COVID-19 pandemic in Hong Kong. Restrictions on face-to-face interactions during the fifth wave forced the cessation of data collection for several months. Although the fifth wave is now over, the parents of participants are still concerned about mask-off activities during data collection, resulting in slow progress in data collection. Second, the study is recruiting either patients with CAS with an existing CAS diagnosis or individuals suspected of having CAS by a qualified speech-language pathologist. However, a recent study has shown that about half of the Hong Kong speech-language pathologist respondents to a questionnaire (36/77, 47%) had never worked with children with CAS or suspected CAS. Furthermore, a majority of the respondents (64/77, 83%) rated their understanding of Cantonese CAS as “a little” or “fair” [43]. This may be because of a possible low prevalence of CAS in Hong Kong or limited understanding of CAS among local clinicians. Both factors could have limited participant recruitment in this study. In an effort to solve these problems, the research team has provided continuing education opportunities for local speech-language pathologists to enhance their understanding of CAS among Cantonese speakers. In addition, the research team may extend participant recruitment to Macau, another special administrative region of China, because, as in Hong Kong, the people of Macau also use Cantonese as their primary language for oral communication. Third, coexisting developmental issues in the participants may limit the results of this study. Owing to the challenge of recruiting participants with CAS, the research team will not control for coexisting developmental conditions in the participants, such as intellectual disability and ASDs, which may affect the speech production skills of the participants. The research team is aware of this limitation and will balance the sample size and coexisting developmental conditions of the participants.

Dissemination Plan

This project will benefit the field of speech-language pathology locally and internationally. Locally, the results of this study will be shared with speech-language pathologists through continuing education seminars and conferences. Owing to the limited understanding of CAS in Cantonese speakers, the professional training of local speech-language pathologists currently does not adequately address this severe pediatric SSD. Postqualification continuing education is frequently requested. A study has shown that an understanding of CAS in Cantonese speakers is lacking. Even experienced speech-language pathologists are not confident in using criteria for making a differential diagnosis of CAS in Cantonese-speaking children [44]. The challenge of making such an accurate diagnosis will be ameliorated through the dissemination of these results. If this study finds that the 2 existing diagnostic tools (ie, MPT and SRT) and the potential tool (ie, TST) are effective in differentiating Cantonese-speaking children with CAS from those without CAS, local clinical practices will benefit directly from the study findings and the related assessment package. Speech-language pathologists will be more confident in diagnosing children with CAS and providing appropriate support and care.

https://www.researchprotocols.org/2022/10/e40465

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(page number not for citation purposes)
treatment, subsequently improving the quality of life of children with CAS and their families. In addition, the local professional training of speech-language pathologists will be enhanced with more data from the local population. The benefit will further extend to society as a medium-term impact, when the appropriate amount of speech-language therapy time is allocated according to valid CAS diagnoses.

Internationally, the results of this study will be shared with other academics through publications in international peer-reviewed journals with open-access and via international conferences. We anticipate that there will be an increased understanding of pitch-variation skills in Cantonese-speaking children with CAS. We also hope to provide a potential diagnostic tool for CAS. This will serve as the basis for further investigations of pitch-variation skills in children who speak other tonal languages, such as Mandarin, Vietnamese, and Thai, and may lead to the development of the TST as a diagnostic tool for CAS in children learning these languages. The results of this study may also provide insight into pitch-variation skills in children with CAS, regardless of their language background. Given that the same underlying deficits in speech motor planning and programming skills manifest differently among different languages [14], this project will have theoretical implications that will impact future international investigations. Ballard et al [21] stated that “exploring additional speaking contexts would be valuable in fully understanding how control of f0 develops over time in children.” If the results show that degraded pitch-variation skills are one of the deficits in children with CAS, the TST can be applied to speakers of English (or other nontonal languages) in an out-of-stress context. This application may shed light on the role of pitch control in out-of-stress contexts and confirm the existence of deficits in pitch control in speakers with CAS across languages.

### Future Investigations

The results of this study will also provide a basis for further investigations of pitch-variation skills in other disordered populations, such as ASDs, hearing impairment, developmental language disorders, acquired apraxia of speech, and aphasia. In the long term, theoretical knowledge about pitch-variation skills in disordered populations will be acquired and applied by frontline health care professionals. In addition to the MPT and SRT, the TST will become a vital component of the assessment process for children with communication disorders.

### Acknowledgments

The authors express their gratitude to the participants, their families, and the community for their support in this study. This study was funded by the General Research Fund (15605821) of the Research Grant Council of the Hong Kong Special Administration Region Government.

### Data Availability

The data sets generated and analyzed during this study are not publicly available but can be obtained from the corresponding author on reasonable request.

### Authors' Contributions

MNW is the principal investigator of this grant application, while ECHW and SLV are coinvestigators. ECHW took the lead in designing the study and writing the protocol, while MNW and SLV provided supervision. All authors read and approved the final manuscript and contributed to the drafting and revision of the manuscript. ECHW will take the lead in the collection, management, analysis, and interpretation of the data, writing of the report, and publication of the report. MNW will oversee the whole project and provide support for data collection and analysis. MNW and SLV will provide supervision in the analysis and interpretation of the data and in the writing and publication of the report.

### Conflicts of Interest

None declared.

### Multimedia Appendix 1

Peer-review reports from the General Research Fund and Early Career Scheme Research Grants Council of the Hong Kong Special Administration Region Government.

[PDF File (Adobe PDF File), 570 KB - resprot_v11i10e40465_app1.pdf ]

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Abbreviations

- ASD: autism spectrum disorder
- CAS: childhood apraxia of speech
- F0: fundamental frequency
- LI: language impairment
- MFD: maximum fricative duration
- MPT: maximum performance tasks
- MRRtri: maximum repetition rate for trisyllabic stimuli
- S&LI: speech and language impairment
- SRT: Syllable Repetition Task
- SSD: speech sound disorder
- TST: tone sequencing task
Developing an Immersive Virtual Reality Training System for Novel Pediatric Power Wheelchair Users: Protocol for a Feasibility Study

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Abstract

Background: Power wheelchairs can empower children with physical limitations to gain independence in their everyday lives; however, traditional methods of power wheelchair training are often limited by poor accessibility and safety concerns. Immersive virtual reality technology (IVRT) uses advanced display technology to place users in a fully immersive web-based environment that can support real-time skills training, often requiring less resources and fewer safety concerns than real-world methods. IVRT interventions have shown to be a feasible training option among adult power wheelchair users; however, there is still a need to understand the technical and clinical feasibility of developing an IVRT power wheelchair training tool for the pediatric population.

Objective: This proposed study aims to use expert feedback and an iterative design process to develop an IVRT training intervention for pediatric power wheelchair skill development.

Methods: This 3-phase feasibility study will be conducted within the assistive technology unit of a public pediatric hospital. Separate participant groups will be recruited for each phase, consisting of approximately 10 to 15 clinicians (phase 1), 10 pediatric power wheelchair users (phase 2), and 15 to 20 additional pediatric power wheelchair users (phase 3). Phase 1 will be conducted to gather feedback on the baseline IVRT training intervention. Clinicians will test the intervention and assess its usability and acceptability using qualitative and quantitative methods. Phase 1 participants will also be invited back for a subsequent session to reassess a revised version of the training intervention that has been updated based on their previous feedback. Phase 2 and phase 3 will also use mixed methods to gather feedback on the usability, acceptability, and user experience of the IVRT training intervention from current pediatric power wheelchair users. In addition, phase 3 participants will perform a skills transfer assessment to compare power mobility skill performance between the virtual reality and real-life environments. Data gathered in phase 2 will be used to further refine the IVRT intervention, whereas phase 3 data will be used to statistically evaluate the final version.

Results: This study was approved by the Izaak Walton Killam Health Centre research ethics board in August 2021. Phase 1 testing began in February 2022. The entire study is expected to be completed by 2023.

Conclusions: The results of this study will be used to create an IVRT training intervention for pediatric power wheelchair skill development through an iterative and collaborative design process. Results may also assist in directing future studies in this area.

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KEYWORDS

immersive virtual reality; power wheelchair; training; pediatric rehabilitation; feasibility
Introduction

Background

The inability to mobilize independently can have significant deleterious effects on the psychosocial development of children, often affecting their ability to participate in age-relevant activities [1,2]. For children with physical disabilities that limit their ability to ambulate, assistive devices such as power wheelchairs empower them to mobilize with independence and create great opportunities for play, leading to enhanced intrapersonal and interpersonal relationships [2-7]. Children who use power wheelchairs describe feeling liberated and gaining autonomy with powered mobility use, with some even reporting the device as an integral part of their identity and an extension of the self [6]. Despite the benefits of power wheelchair use, methods of its training can be highly variable and difficult to access [8]. Many children are unable to participate in training opportunities owing to common barriers such as limited access, safety concerns, and inadequate availability of resources [5,6]. Furthermore, the rate of skill acquisition is often not a linear process, and it can be difficult for training interventions to account for individual differences among clients, including skill level and age range [5-8]. Access to power wheelchair training opportunities is essential to develop the skills required for independent participation and overall development [1,2]. As such, there exists a need for an approach that offers effective training for novel power wheelchair users within a safe and accessible environment.

Virtual Reality for Rehabilitation

Virtual reality (VR) is emerging as a promising modality for therapeutic and rehabilitative interventions in health care [9,10]. VR interventions have been shown to help support the rehabilitative process, by improving functional and cognitive performance in diverse populations such as patients with Parkinson disease [11], patients with chronic stroke [12], older adults with cognitive impairment [13], and power wheelchair users [14]. The growing interest in VR may be owing to the unique opportunity that allows individuals to engage in task-specific interventions by interacting in a real-time simulation of a computer-controlled activity or environment [9,10,15]. The use of a computer interface can also allow clinicians to quickly adjust the intervention to suit the user’s current ability (eg, modification of the difficulty level), thus promoting user awareness and confidence [16,17].

Children who use a VR application to practice their power wheelchair skills have shown increased overall improvement when transferring their skills into real-world navigation compared with their pretraining scores or a control group with no training [16,18-20]. A study examining the efficacy of a desktop VR system in teaching novel power wheelchair skills found that the VR intervention improved children’s skills to a greater extent than the control group who had no VR training; however, statistical significance was not reached [20]. In this case, individual performance scores varied greatly owing to potential confounders (eg, sex differences and potential motivation discrepancies), and it was suggested that future VR interventions should consider individualizing their training methods to meet the varying needs and interests of participants [20].

Immersive VR Technology

Recent VR modalities such as immersive VR technology (IVRT) may elicit increased performance improvements over time compared with nonimmersive VR systems owing to an increase in user engagement [21-24]. IVRT is a specific subset of VR that uses display technology such as head-mounted display (HMD) goggles or multiple screen projections to make the user feel physically present in a 3D setting [25]. The use of screen projections to create a fully immersive environment can be resource-intensive, often requiring a large space and multiple pieces of technological equipment to achieve a realistic setting. In contrast, HMD technology requires less costly resources and small physical space and can be easily transported to allow for clinical or at-home use [26,27]. Therefore, IVRT interventions using HMD tend to be the primary choice for recent skills-based training applications [28].

One of the greatest benefits of IVRT is the sense of presence that can be experienced by users during gameplay. The feeling of truly being there in the VR environment is heightened within an immersive VR system compared with a nonimmersive system and has been linked to better performance [21-24]. In a 2017 study comparing wheelchair performance and visual technology devices, the sense of presence and driving performance were both increased among users who trained with the IVRT modality compared with those who trained with a computer monitor [21]. Studies have also shown that users participating in an IVRT simulator are able to naturally mimic the same wheelchair-specific movement patterns (eg, trunk posture and chair propulsion) as executed in the real world, thus demonstrating the feeling of realism that can be experienced in the immersive environment [29].

IVRT has shown promise as a feasible rehabilitation tool for power wheelchair users; however, most studies have been conducted only among the adult population [14]. A 2019 scoping review found that most published studies using HMD-based IVRT for power wheelchair simulation included only adult participants, whereas a limited number of studies have extended into the pediatric population [14,16,30]. Morère et al [30] used a 3D wheelchair simulator to conduct a chronic training intervention and identified a positive change in pediatric participants’ outdoor driving abilities after completion of the training period; however, this study included only 12 participants in total. Another pediatric study revealed improvements in real-world power wheelchair skills following training with HMD compared with pretraining levels, but this study was also limited in sample size [16].

IVRT has the potential to become a valuable training tool for pediatric power wheelchair users, but there is a paucity of literature on this topic, with weak descriptions of methodology and limited sample populations [8,31]. Introducing IVRT training for pediatric power wheelchair users may help to enhance opportunities for safe and accessible skill development, leading to increased independence and improved early-life psychosocial development [2-7]. To develop an effective method of power wheelchair training, there exists a need for
collaborative studies in which expert-driven feedback can be used to design a training intervention that meets the needs of pediatric power wheelchair users.

**Objectives and Research Questions**

**Overview**

This proposed 3-phase feasibility study will collect feedback from experienced clinicians and pediatric power wheelchair users to collaboratively develop an HMD-based IVRT training platform designed for pediatric power wheelchair skill development. Participants will engage in the training intervention and provide feedback on the usability and acceptability of the intervention for novel skill development. In this study, usability refers to the ease with which participants can successfully engage in the IVRT training intervention [32]. Feedback related to usability will assist in identifying features of the intervention that may help to achieve specific goals easily and effectively with limited confusion during gameplay. Acceptability is the perceived appropriateness of the intervention to meet the needs of the target population (novel pediatric power wheelchair users) [33]. Acceptability feedback will describe features of the IVRT training intervention that may help to enhance clinical uptake and accurately capture the training requirements of the pediatric population. Clinicians will also assist in developing a list of potential power wheelchair skills to be targeted in the training intervention.

Feedback gathered during each of the 3 phases will be carefully implemented in the technical design to continuously refine the training platform and produce a final version that can be used as a practical training tool for effective skill development in the future [34]. The efficacy of the final IVRT training intervention for power wheelchair skills training will be measured in future studies. To the best of our knowledge, this is the first study as of April 2022 that will gather iterative feedback from clinicians and experienced power wheelchair users to develop an IVRT training intervention intended for pediatric power wheelchair skill development.

**Objective**

To determine the feasibility of using an IVRT training intervention for pediatric power wheelchair skill development, as determined by the following:

1. Expert opinion from clinicians experienced in working with pediatric power wheelchair users
2. User feedback and skill performance metrics gathered from current pediatric power wheelchair users

**Research Question 1**

What is the usability of the IVRT training intervention for novel skill development, from the clinician’s and current power wheelchair user’s perspectives?

**Research Question 2**

What is the acceptability of the IVRT training intervention for pediatric power wheelchair users, from the clinician’s and current power wheelchair user’s perspectives?

**Research Question 3**

What set of skills should be included in the IVRT training intervention for appropriate power wheelchair skill development, from the clinician’s perspective?

We hypothesized that iterative feedback gathered from clinicians and current power wheelchair users will create an IVRT training intervention that is appropriate for our target population and can be successfully used for future power wheelchair skill development.

**Methods**

**Study Design**

This is a 3-phase feasibility study that will assess the usability and acceptability of an IVRT training intervention that has been collaboratively designed to support power wheelchair skill development. Mixed methods will be applied to provide qualitative and quantitative data on the outcome measures.

**Study Setting**

This study will be conducted within the assistive technology unit of a public pediatric hospital, the Izaak Walton Killam Health Centre in Halifax, Nova Scotia, Canada. An experienced researcher will facilitate all in-laboratory IVRT sessions and collect training intervention data. All power wheelchair skills performed in the IVRT training system and in the real world during phase 3 will be independently assessed by a clinician trained in power wheelchair skills assessment.

**Participants and Recruitment**

Eligible participants for this feasibility study will belong to one of 2 population groups. The first population group will consist of clinicians with at least three months of experience in working with individuals who use power wheelchairs (by means of training or offering care services) and who practice in a health care profession such as physiotherapists, occupational therapists, or child life specialists. The second population group will consist of children (aged 4-18 years) who currently use power wheelchairs. The lower age limit is selected to ensure that the VR headset will properly fit all participants, whereas the upper limit is representative of the pediatric population. A complete list of inclusion and exclusion criteria is provided in Textbox 1.

For phase 1, our target sample size is approximately 10 to 15 participants, consistent with common sample sizes used in technology feasibility studies with an iterative design process [35-37]. The target sample size for phase 2 will be 10 participants, to gather user experience data and facilitate 1 round of iterative development based on user feedback. For phase 3, we aim to recruit 15 to 20 participants for the purpose of statistically assessing the final version of the IVRT training intervention through user feedback and skill transferability. The target sample size for phase 3 is consistent with large studies piloting non-VR power wheelchair training methodologies [38,39] and is also greater than that used in previous pediatric IVRT feasibility studies [16,30].

https://www.researchprotocols.org/2022/10/e39140

JMIR Res Protoc 2022 | vol. 11 | iss. 10 | e39140 | p.66

(page number not for citation purposes)
Clinicians will be recruited for phase 1 via web-based advertisements (email lists and web-based newsletters) and word of mouth. Pediatric participants will be recruited for phase 2 and phase 3 via web-based newsletters, poster advertisements displayed within the host hospital, and discussion with their care provider. Researchers will distribute study information forms to care providers, which will outline the study design, purpose, and contact information. Care providers will be encouraged to offer these forms to their patients if it is believed that they may be interested in participating. Then, the individuals will indicate their interest to a research team member via email or verbally, and eligible individuals will be invited to participate in the study.

Textbox 1. Inclusion and exclusion criteria for each participant group.

<table>
<thead>
<tr>
<th>Inclusion criteria for clinicians (phase 1)</th>
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<tbody>
<tr>
<td>• Overall, ≥3 months of experience in working with power wheelchair users</td>
</tr>
<tr>
<td>• Practices in a health care setting</td>
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<tr>
<td>• Able to communicate fluently in English (verbal and writing)</td>
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<tr>
<td>• Able to operate a standard power wheelchair joystick</td>
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<td>• History or suspicion of a photosensitive seizure disorder</td>
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<tr>
<td>• Unable to tolerate wearing head-mounted display goggles for prolonged periods of time</td>
</tr>
<tr>
<td>• Impairment in visual functioning that cannot be corrected with lenses or contacts (eg, 3D depth perception, cataracts, and oculomotor dysfunction)</td>
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<table>
<thead>
<tr>
<th>Inclusion criteria for current power wheelchair users (phases 2 and 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Aged 4-18 years</td>
</tr>
<tr>
<td>• Current power wheelchair user, with ≥1 year of experience in using power wheelchair as primary means of mobility</td>
</tr>
<tr>
<td>• Able to communicate verbally in English</td>
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</tr>
<tr>
<td>• Participated in phase 2 of this study (phase 3 participants only)</td>
</tr>
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</table>

Ethics Approval

This study has been approved by the Izaak Walton Killam Health Centre research ethics board (Office of Research Ethics 1026934) in Halifax, Nova Scotia, Canada. Informed consent will be obtained from all study participants before their participation; participants aged <18 years will complete the assent form, and participants aged ≥18 years will complete the consent form.

Procedure

**IVRT Equipment**

The IVRT training application has been built using Unity3D, a Unity Technologies game engine that allows developers to create and manage web-based gaming environments. Participants will engage in the IVRT training intervention using the HTC Vive Pro, a commercially available VR technology from HTC Corporation that places users in a fully immersive VR environment using the HMD headset, tracking devices, and controllers (Figure 1) [40]. The wheelchair joystick used for this study has been built by an engineering team using a 3D printer and specifications that closely match a real-world power wheelchair joystick. An HTC Vive Pro tracking device is attached to the top of the joystick to allow for accurate control of the power wheelchair within the IVRT environment (Figure 1). Henceforth, this joystick will be referred to as the “tracker joystick.” The user can also engage in hand-based activities (eg, turning on the power wheelchair) in the IVRT environment by moving a controller held in their nondominant hand.

In phase 1, participants will sit in a Rifton Equipment Activity Chair [41] that replicates the seating and joystick setup of a power wheelchair. The Activity Chair is a positioning chair that provides adaptable seating for a range of patient populations and has been slightly modified to accommodate an arm attachment for easy operation of the tracker joystick (Figure 1). In phase 2 and phase 3, participants will sit in their own power wheelchair, and the tracker joystick will be attached to their personal joystick controller stem. The tracker joystick is fitted to easily screw onto any standard-size joystick controller stem, allowing for users to participate in the IVRT intervention without the need to transfer to a new chair. During the IVRT simulation, users will progress through the intervention in a
power wheelchair that replicates the natural movement of a real power wheelchair. The in-game power wheelchair movement patterns (eg, acceleration and deceleration speeds and turning trajectories) have been designed in collaboration with an occupational therapist to ensure that all movements are simulated with accuracy.

**Figure 1.** An HTC Corporation tracker and IVRT joystick (A) attached to the Rifton Activity Chair (B) and in-use during gameplay of the training intervention (C). IVRT: immersive virtual reality technology.

**IVRT Intervention**

The IVRT training intervention has been designed to help users develop core power wheelchair skills in a motivating and engaging manner. The baseline version of the training intervention was created in collaboration with the research committee (consisting of power wheelchair rehabilitation experts, including a pediatric physiatrist and a pediatric occupational therapist) and software development team. The research committee identified power wheelchair tasks that were commonly taught to novel power wheelchair users as beginner to moderate–level skills (eg, moving forward, moving backward, and turning 90°) [42]. Then, the software development team integrated the skills into the IVRT system within an environment that was approved by the research team to be acceptable for the pediatric population (ie, containing age-appropriate graphics and characters). The baseline training intervention is intended to introduce participants to the potential of an IVRT system for pediatric power wheelchair training and gather expert feedback on how to improve the skills, environment, and overall user experience.

The intervention places participants in a colorful cartoon environment with robotic characters. Users begin the intervention in the main lobby, where the instructor of the game explains the instructions and wheelchair controls using audio and visual cues. Then, the participants are brought to the outside world to begin level 1, where they must use the tracker joystick to control their power wheelchair and move through specific areas in the game to complete each level. Users will be challenged to participate in tasks that integrate various power wheelchair skills, such as backing up in a narrow hallway, driving over a ramp, and following a figure-eight path (Figure 2). In addition, players are also provided with various opportunities to increase their scores during gameplay, including driving on the correct path and collecting fruits to power up their wheelchair. The inclusion of a reward system that allows for positive reinforcement has been shown to enhance a child’s attention and motivation when training within a VR environment [43-45]. Therefore, it is anticipated that these additional components will help to increase user engagement and improve performance outcomes.

The IVRT system offers a range of options to measure client performance, which will otherwise be difficult to capture in real-world training. In total, 4 different VR camera angles (overhead, follow camera, first-person view, and free camera) provide the operator with a variety of viewpoints to assess the user’s driving skills (Figure 2). Chart selections can also be accessed by the operator to evaluate in-game user behavior, such as *client focus* (measurement of attentional focus) and *pathways* (real-time charting of user’s driving patterns). Furthermore, client skills and goals can be easily tracked using the metrics options, which offer real-time speed, collision, and completion time statistics. Taken together, the IVRT system can provide an accurate and comprehensive assessment of driving performance without disrupting the in-game user experience.
Training Intervention—Phase 1

The aim of phase 1 is 2-fold: (1) to use clinician feedback to develop a list of potential power mobility skills to be implemented in future versions of the IVRT training intervention and (2) to assess the usability and acceptability of the intervention from the clinician’s perspective. Phase 1 participants, comprising health care clinicians, will be exposed to a baseline version of the IVRT training intervention and participate in a training session during which they will progress through each of the levels, with instructions to carefully evaluate various components of the intervention. Participants will also be given the option to freely explore the game environment following the completion of each level, if they wish to do so.

Participants will be asked to assess the ability of the intervention to teach a range of core power wheelchair skills. Currently, there are no standardized methods that have been established among professionals to assess power mobility skills among children [38]; however, 4 main measures are commonly used: Assessment of Learning Powered Mobility Use [46], Powered Mobility Program [47], Power Mobility Training Tool [48], and Wheelchair Skills Checklist [49]. In the adult population, the Wheelchair Skills Test for Powered Wheelchairs is well validated for the evaluation of power wheelchair capacity [42]. Owing to the lack of an established measurement tool for the pediatric population, the research team identified core skills frequently listed in both the Wheelchair Skills Test for Powered Wheelchairs and common pediatric assessment tools to create a comprehensive skills list for clinician use. This list was developed in consultation with a pediatric rehabilitation specialist to ensure that all skills were appropriate for inclusion.

Immediately following the IVRT training intervention, participants will be provided with a list of 28 individual power mobility skills and asked to indicate their level of agreement with the following statement: “Based on my experience working with power wheelchair users, I believe the immersive virtual reality technology (IVRT) application can be used to teach children and adolescents to (insert skill here).” Consensus on the application’s ability to assess each item will be defined as ≥75% of participants indicating that they agree (score=4 out of 5) or strongly agree (score=5 out of 5) for a given item, leading to the inclusion of the skill in subsequent phases. If ≥75% of participants indicate disagreement (score=2 out of 5) or strong disagreement (score=1 out of 5) for a particular item, this will be deemed as consensus that the intervention is not appropriate for the development of that skill, and it will not be included in future phases. If a neutral response (score=3 out of 5) is indicated by ≥75% of participants, the skill will be refined for future versions of the training intervention using participant feedback. If an item is rated <4 out of 5, participants will be asked to provide a specific recommendation for modification of the IVRT intervention pertaining to that skill. If a participant believes that a skill cannot be feasibly modified, they will provide no response in the recommendation section.

Participants will also be provided with 3 separate questionnaires to assess perceived usability, acceptability, and overall user experience. Quantitative data will be collected from (1) the Presence Questionnaire (PQ) [50], (2) an ad hoc usability and acceptability questionnaire, and (3) an ad hoc user experience questionnaire. Qualitative data will be collected from (1) an ad hoc user experience questionnaire; (2) participants’ informal in-game comments and reports, as recorded by the researcher; and (3) a semistructured interview (round 2 only). A complete list of the assessment measures included in each phase is provided in Table 1.

The PQ and ad hoc usability and acceptability questionnaire will be provided as paper-based materials. The PQ is a well-validated assessment tool used to measure presence within a VR environment. In this study, the PQ has been adapted to include the 4 subscales most relevant to the IVRT training intervention: realism, possibility to act, quality of interface, and self-evaluation of performance [50]. Participants will be asked to report their experience related to multiple components of each subscale using a 7-point Likert scale rating. The ad hoc usability and acceptability questionnaire has been adapted from the Perceived Usefulness and Perceived Ease of Use scales [51] and System Usability Scale [52]. This questionnaire will be used to explore participants’ attitudes toward using the IVRT intervention as a training tool for the pediatric population. Participants will be asked to rank each statement on the questionnaire from 1 to 5, ranging from “strongly agree” to “strongly disagree.”

![Figure 2. Screenshots of the training application showing stages of the figure-eight task from three different camera viewpoints: follow camera (A), free camera (B), and first-person view (C).](https://www.researchprotocols.org/2022/10/iss.10/e39140)
The ad hoc user experience questionnaire will be hosted on the secure web-based software platform, REDCap (Research Electronic Data Capture; Vanderbilt University) [53]. The web-based questionnaire format was chosen to allow participants to respond to open-ended questions by typing rather than writing; however, they will be provided the option to complete a paper-based questionnaire if it is preferred. This questionnaire will be used to assess participant demographics, user tolerance (a component of usability), and overall user experience. To capture user tolerance to the IVRT intervention, the presence of VR-induced symptoms and effects (VRISE) will be assessed during and after the intervention. VRISE includes symptoms such as nausea, dizziness, disorientation, and fatigue and can occur as a side effect of VR exposure [51]. VR systems using HMD have been found to increase the prevalence of VRISE compared with nonimmersive systems; however, our intervention’s length falls below the theoretical limit of exposure to VR for adults (55-70 minutes) [54,55]. Although our intervention session is approximately 20 to 30 minutes in length, it is anticipated that some participants may still experience VRISE symptoms. User experience will be assessed in this questionnaire using open-ended questions that have been developed to better understand participants’ experiences within the IVRT application, such as ease of use, appropriateness of tasks and graphics, and suggestions for improvement.

Following the completion of the study session, participant feedback data will be summarized, anonymized, and presented to the research committee. The committee will use these data to produce recommendations for a new iteration of the application, which will be implemented by the software development team.

Participants will be invited back to the laboratory to complete a second session during which they will engage in the IVRT training intervention that has been updated based on feedback from the first session. Participants will complete the updated IVRT training intervention, followed by a semistructured interview designed to gather in-depth details of the user experience. The interview questions will be developed based on data from round 1 and will aim to capture feedback regarding the system’s new updates (eg, opinions regarding any new skills or levels added and updated graphics or audio) and address any potential areas for further improvement. Finally, participants will also complete the same PQ, ad hoc usability and acceptability questionnaire, and ad hoc user experience questionnaire as in round 1. Participant feedback will be presented to the research committee, and if any items in the IVRT intervention are found to still require significant changes, they will be updated as necessary by the software development team.

Training Intervention—Phase 2

Phase 2 will assess the usability and acceptability of the IVRT system from the pediatric power wheelchair user’s perspective. Participants in phase 2 will be comprised of current pediatric power wheelchair users, who will test and evaluate the updated IVRT training system that has been adjusted based on feedback gathered from clinicians in phase 1.

During the IVRT trial, participants will be placed in the IVRT setup and provided with 5 to 10 minutes to freely explore and acclimate to the VR setting. Once the participants indicate that they are ready to begin, they will start the training intervention. The skills selected in phase 1 for inclusion will be integrated into the intervention, and participants will be encouraged to complete each skill as they progress through the levels. Following completion of the intervention, participants will be given the option to exit the system or continue exploring after a mandatory 10-minute break. After the break, participants may freely explore the VR environment for up to an additional 15 minutes at their own discretion. The mandatory 10-minute break has been included in the session to reduce consistent VR exposure and limit the potential of VRISE among children [58].

Immediately following the IVRT intervention, participants will complete the same 3 questionnaires as in phase 1, but with age-appropriate adaptations (eg, changes to wording or question structure). Age-appropriate adaptations will be approved by a child life specialist to ensure suitability for the pediatric age group.
population. All questionnaires will be asked aloud by the researcher, and the pediatric participant’s verbal responses will be recorded. As in phase 1, the questionnaires will explore the perceived usability and acceptability of the IVRT system for power wheelchair skill development, IVRT tolerability, and general user experience.

Participants will also engage in a semistructured user experience interview, in which questions will be asked aloud and responses will be audio-recorded for qualitative analysis. The semistructured interview intends to gather in-depth details on the perceived usability, acceptability, and experience in the IVRT environment (eg, most favorite and least favorite parts of the game and why and areas for improvement). The participant’s caregiver (parent or proxy) will also be encouraged to provide any additional details that the pediatric participant may not remember (eg, dates and early-life experiences).

Pediatric participants and their caregiver will also participate in a training methods questionnaire and interview during the session. The training methods questionnaire will use Likert scale questions (asked aloud by the researcher) to explore both the child’s and caregiver’s perceptions of previous power wheelchair training methods. Then, a semistructured interview will be conducted to further explore their experience with power wheelchair training (eg, most exciting or challenging parts of training and confidence in skills after training). This information will provide great understanding of past training techniques and experiences from 2 different perspectives. In all cases where pediatric participants cannot remember specific details, caregiver input will be sought to ensure completeness of the data set.

After all participants have completed their session, data will be collected, summarized, and presented in the same manner as in phase 1. The research committee will use this feedback to identify and implement changes to the application for the final phase.

**Training Intervention—Phase 3**

Phase 3 of this study will also assess the usability and acceptability of the IVRT system from the perspective of current pediatric power wheelchair users. In addition, participants will complete a real-world trial and an IVRT trial to compare power mobility skill transfer between the VR and real-life environments. Both trials will occur over 1 study session, and the order of trials will be counterbalanced among participants.

All phase 3 participants will test the IVRT training system that has been updated based on phase 1 and phase 2 feedback. To compare and assess participant’s skill transferability, an experienced clinician will review in-game and real-world performance. It is anticipated that the IVRT intervention will be designed to closely resemble a real-life setting; therefore, the skills transferability assessment will measure the similarity of participant’s skills performance across both the VR and real-life environments.

A computerized recording of the IVRT intervention will be independently assessed by the clinician following the completion of the session to compare in-application versus real-world performance metrics. During the real-world trial, participants will be asked to complete each skill that has been included in the IVRT intervention. Skills will be performed in an environment within the hospital grounds and assessed by an experienced clinician. In-game and real-life performance will be assessed for capacity level (skill performed: “yes” or “no” and skill proficiency rating from 0-3) and time to complete each skill.

Participants will also be asked to complete the same questionnaires and semistructured user experience interview as in phase 2 to explore their experience in the IVRT environment and the perceived usability and acceptability of the intervention. Caregivers will again be encouraged to assist in the user experience interview to provide further details as needed and to complete the same ad hoc training methods questionnaire and interview as in phase 2. Exploratory analyses are planned to be conducted with phase 3 data to further evaluate the final version of the IVRT intervention.

**Risk to Participants**

Previous studies have shown that IVRT can be administered to children and adults without inducing significant safety risks to participants [54,55,58]. The research team will actively monitor for the presence of VRSE or any signs of discomfort during exposure and provide medical follow-up as necessary. The risk of physical injury to pediatric participants is low and will be mitigated by including only experienced power wheelchair users and conducting the real-world skills assessment in a large open space within hospital grounds.

**Primary Outcomes**

**Acceptability**

Acceptability of the skills targeted in the IVRT training intervention will be defined and assessed by clinicians using a core power wheelchair skills list. A structured web-based survey will be presented to clinicians following the completion of the IVRT training intervention, outlining 28 potential skills for inclusion. Participants will be asked to indicate their rating for each of the listed skills using a 5-point Likert scale ranging from “strongly agree” to “strongly disagree” for inclusion. Respondents will also have the option to provide skill modification recommendations in an open text field.

Acceptability of the IVRT training intervention will be assessed in each of the phases using 3 separate questionnaires: the PQ, an ad hoc usability and acceptability questionnaire, and an ad hoc user experience questionnaire. The questionnaires will consist of questions from the same topic for each phase; however, the wording of the questions will be adjusted to suit individual participant groups. Qualitative data will be collected using the questionnaires to investigate the perceived effectiveness of the intervention, suitability for the pediatric population, and sense of presence. Qualitative data will further explore users’ attitudes and experiences with IVRT. Open-ended question prompts in the first round of phase 1 (eg, perceived safety, appropriateness of graphics, and areas for improvement) will further evaluate the suitability of the intervention for our target population, whereas semistructured interview responses will capture in-depth qualitative data to check for accuracy and validity related to the updated IVRT intervention.
Usability

Usability of the IVRT training intervention will be determined through the ad hoc usability and acceptability questionnaire, ad hoc user experience questionnaire, and skills transfer assessment (phase 3 only). Phase 3 participants will complete the same skills in their real-world power wheelchair as those in the IVRT intervention and will be assessed by an experienced clinician to compare wheelchair skill performance. In doing so, skill transferability between the VR and real-world environments can be analyzed to identify similarities or discrepancies in user performance across environments. It is anticipated that this study will not be powered to detect any clinically significant discrepancies in skill transferability; however, data will be used to explore IVRT versus real-world skill transfer.

Participants will complete the ad hoc usability and acceptability questionnaire and user experience questionnaire to explore their attitudes toward the system’s effectiveness and complexity. Quantitative data will define perceived ease of use, user confidence, and level of satisfaction, whereas qualitative data will help to identify potential barriers or facilitators in using the intervention, such as presence of in-game confusion, uncertainty of tasks, and particular areas of frustration or excitement. Tolerability of the IVRT intervention will be assessed during gameplay and through a VRISE section on the user experience questionnaire to determine any symptoms experienced during or after the intervention. Informal notes taken by the researcher will also record comments or questions asked by the user during the intervention to further measure usability.

Secondary Outcomes

Pediatric participants and their caregivers will be asked to describe their previous experience with power wheelchair training methods and perceived abilities of the power wheelchair user. A semistructured interview and Likert scale questions will inquire about the location, length, and satisfaction of previous wheelchair training methods; confidence in abilities; and support received or challenges faced with training. Responses will be used to further understand the experiences with power wheelchair training from both the pediatric user and caregiver perspectives and integrate this information into future iterations of the IVRT system.

Statistical Analysis Plan

The data analysis plan for phase 1 focuses on descriptive and thematic analyses to compare the usability and acceptability of the IVRT intervention across participants and to create a list of potential power wheelchair skills for inclusion in subsequent phases. Phase 2 analysis will focus on descriptive and thematic analyses to understand user experience via system usability, acceptability, and previous training data. Phase 3 will use a descriptive and thematic analysis approach similar to phase 2 to examine system usability, acceptability, user experience, and descriptive and inferential statistics to assess performance outcomes and compare skill transferability from the real world to the IVRT intervention.

This study will define consensus based on clinical suggestions from Nair et al [59]. Phase 1 consensus for the inclusion of items in the power mobility skills list will be reached if a minimum of 75% (9/12) of participants agree (score=4 out of 5) or strongly agree (score=5 out of 5) on a given skill. Skills that do not achieve consensus will not be included in the IVRT intervention for future phases. The inclusion of skills in the phase 2 version of the IVRT intervention will be based on the perceived usefulness and necessity of the skill (as determined by phase 1 participants) and technical feasibility of integrating the skill into the IVRT environment (as determined by the software developers). Descriptive statistics will also be calculated for each skill item and presented to the panel members as feedback in phase 1.

All questionnaire responses to closed questions and Likert-type rating scales will be analyzed using RStudio. In phase 3, real-world and IVRT skill performance data will use “completed” or “not completed” scores and ratings of capacity from 0 to 3 to assess participants’ performance outcomes for each specific skill. Then, a composite score will be created and included in the descriptive analysis to compare the performance metrics across participants and environments. In phase 3, inferential statistical testing will also be conducted to evaluate skill transferability: it is anticipated that Wilcoxon signed-rank test will be used to compare real-world and in-application performance data among participants.

Open-ended questionnaire and semistructured interview responses will be thematically analyzed using NVivo (version 12; QSR International) [60]. Questions have been developed in consultation with a pediatric rehabilitation specialist to ensure clarity and appropriateness for each population group. The semistructured interview questions in each phase will be developed to reflect topics of interest (eg, highly variable responses or recurring topics) that arise from the initial feedback round and subsequent rounds. Results will be formatted in a document file and presented to the research panel after the completion of each round.

Results

Institutional review board approval was received in August 2021, and recruitment for phase 1 of this study began in February 2022. As of September 2022, a total of 12 participants enrolled in round 1 and 5 (42%) participants returned for round 2. Phase 1 is expected to be completed in October 2022.

Preliminary data analysis was conducted on phase 1–round 1 data in June 2022. Qualitative data explored the clinician’s user experience and revealed a positive perception of the IVRT system as a feasible tool for the pediatric population; however, adjustments in the system’s graphics and audio were suggested to reduce overstimulation, complex language, and nausea. Quantitative data further supported the clinical usability of the system and determined potential skills for inclusion into future versions. It is expected that full analysis for phase 1 data will begin in October 2022.

Phase 2 and phase 3 are anticipated to begin in fall of 2022 and winter of 2023, respectively, and it is expected that the entire study will be completed by summer 2023. Results are planned to be published in a peer-reviewed journal in early 2024.
used to develop a future research trial that will test the efficacy of the IVRT training intervention.

**Discussion**

**Overview**

Providing pediatric power wheelchair users with adequate skills training is fundamental when looking to improve their independence and well-being [1,2]. Unfortunately, many children are often restricted from accessing traditional training opportunities owing to physical and environmental barriers [5,6]. Without the knowledge of basic power mobility skills, children with physical disabilities are often unable to participate in activities that help to foster long-term social and cognitive development [1,2]. Therefore, it is essential to create an avenue through which children can develop power mobility skills in a manner that is accessible, easy to use, and safe.

VR is an innovative technique that can create expansive power wheelchair training opportunities within a setting that is often safer and less resource-intensive than a traditional training environment. HMD-based IVRT offers significant training benefits owing to the system’s fully immersive components and low resource requirements [26-28]. Although IVRT is beginning to emerge as a potential approach to power mobility training for children, current studies are still in their infancy [8,31]. This study will use the knowledge of multiple expert groups to collaboratively assess and design an IVRT training system that can be used for power wheelchair skill development in the future.

The IVRT application developed through this project will be deliberately designed for engaging pediatric populations; however, by assessing core power wheelchair skills relevant to novel users of all ages, future versions of the IVRT training system may be tailored for a variety of populations. In the future, we also hope to integrate machine learning engines into IVRT technology. These engines will apply real-time data output to generate specific tasks and graphics that can be tailored to match the individual needs of each user.

The short-term goal of this study is to develop an IVRT training intervention that has high usability and acceptability ratings among clinicians and pediatric power wheelchair users. The long-term goal is to provide novel power wheelchair users with a high-quality clinical training intervention that can be easily accessed to safely develop their power wheelchair skills. We also anticipate that the findings from this study will contribute to enhancing the current knowledge on IVRT for clinical practices, as IVRT is currently an underused technology that has the potential to improve patient outcomes by increasing user motivation [15,16], reducing resource requirements [26,27], and enhancing opportunities for task individualization [42-44].

**Strengths and Limitations**

A main strength of this study lies within the involvement of multiple participant groups to collectively critique and develop the IVRT training intervention. Although it is more time intensive to include both pediatric power wheelchair users and clinician participant groups, collecting data from people across various professions, ages, and life experiences will ensure that diverse opinions can be integrated into the development process. In addition, the use of consensus testing in this study will ensure that the final skills chosen for inclusion in the training intervention are relevant to our pediatric population and approved by experienced clinicians. The use of a mixed methods technique also strengthens our study by providing a detailed understanding of the perspectives, barriers to, and facilitators of IVRT skills training, as recognized by each participant group. Mixed methods can be a particularly useful tool when working in disability and rehabilitation research, as it uses multiple techniques to capture information for both population-based and individual analysis that may be otherwise missed when using only one structured method [61,62]. Given the novelty of our IVRT training intervention, it is particularly important to understand user experience from various angles to develop a final product that has been assessed by multiple expert groups.

A primary weakness of this study is the potential homogeneity of participants’ attitudes toward the use of technology for rehabilitative purposes. It is possible that individuals who decline to participate in the study may have differing opinions on the usefulness or acceptability of IVRT compared with participants who agree to participate. We aim to mitigate this potential bias by intentionally recruiting participants with a range of demographics (eg, age and profession) to gather diverse perspectives. The limited sample size in this study will also affect the generalizability of the findings and undermine any inferential statistical analysis performed. Therefore, statistical analyses will be interpreted with caution and used to inform future development of the IVRT intervention rather than to define any conclusive results. Similarly, our pediatric sample is limited by the exclusion of participants who are nonverbal. To obtain comprehensive user feedback in this study, all participants must be able to communicate verbally; however, we hope to include both participants who are verbal and those who are nonverbal in future IVRT studies to gather training data that can be generalized to both population groups. Finally, the visually immersive quality of the IVRT intervention may create feelings of fatigue or motion sickness among users, possibly affecting in-game user performance or postgame assessment measures. The IVRT application is equipped with antinausea settings that can be added to the user’s visual field to help reduce VRISE. Aspects of VRISE will also be measured after exposure to identify any distress that may be further alleviated and minimized in future versions.

**Conclusions**

This proposed feasibility study aims to develop and assess an HMD-based IVRT training intervention intended to benefit children with mobility limitations by creating a safe and accessible means of power wheelchair skill development. Exploring the acceptability and usability of the intervention is the first step in creating a final version that may be further tested in future studies and eventually implemented as part of clinical practices in rehabilitation health care. Given the limited number of pediatric studies using HMD-based IVRT for power wheelchair training currently published [16,30], findings from this study may also be used to inform the methodology, study procedures, and assessment protocol of future large-scale IVRT trials.
Acknowledgments

This research project received financial support from the Izaak Walton Killam Health Centre’s Innovation Services department and an independent virtual reality technology company, MARS VR Lab Inc [63]. The funders had no role in the design of the study; collection, analysis, and interpretation of data; writing of the manuscript; or decision to submit the manuscript for publication. The authors would like to thank Mandy Rice for her ongoing contribution to study recruitment and the immersive virtual reality technology training intervention design.

Data Availability

Data sharing is not applicable to this paper, as no complete data sets were generated at this stage of the study. However, upon completion of this study, the data generated and analyzed will be available from the corresponding author (SD) upon reasonable request. Results are also expected to be published in a peer-reviewed journal.

Authors’ Contributions

All authors contributed to the study design and refinement of the study protocol and procedures. LP and SD prepared and submitted relevant materials for ethics approval. SD is implementing the protocol with input from JS and ST. SD wrote the manuscript with support from LP. All authors read and approved the final manuscript.

Conflicts of Interest

The Izaak Walton Killam (IWK) Health Centre has a collaboration agreement with MARS VR Lab Inc [63], which includes provisions for the potential payment of royalties in the event of successful commercialization of virtual reality products tested as a part of the study. These royalties are payable to the IWK Health Centre. There are no plans to share profits directly with the study participants. Any royalties will be received by the IWK Health Centre, not by individual researchers, and will be directed back to the hospital’s research and operations consistent with its mission and mandate, including innovation, research, and education within the pediatric rehabilitation program. None of the researchers have previous or current direct relationships with MARS VR Lab Inc beyond that outlined in the collaboration agreement. The study design was developed without input from MARS VR Lab Inc. The conduct, analysis of results, and reporting will be performed independently by the research team, without input from MARS VR Lab Inc.

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Abbreviations

HMD: head-mounted display
IVRT: immersive virtual reality technology
IWK: Izaak Walton Killam
PQ: Presence Questionnaire
REDCap: Research Electronic Data Capture
VR: virtual reality
VRISE: virtual reality–induced symptoms and effects

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Understanding Racial Disparities in COVID-19–Related Complications: Protocol for a Mixed Methods Study

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Abstract

Background: In the United States, the COVID-19 pandemic has magnified the disproportionate and long-standing health disparities experienced by Black communities. Although it is acknowledged that social determinants of health (SDOH) rather than biological factors likely contribute to this disparity, few studies using rigorous analytic approaches in large, information-rich community-based data sets are dedicated to understanding the underlying drivers of these racial disparities.

Objective: The overall aim of our study is to elucidate the mechanisms by which racial disparities in severe COVID-19 outcomes arise, using both quantitative and qualitative methods.

Methods: In this protocol, we outline a convergent parallel mixed methods approach to identifying, quantifying, and contextualizing factors that contribute to the dramatic disparity in COVID-19 severity (ie, hospitalization, mortality) in Black versus white COVID-19 patients within the integrated health care system of Kaiser Permanente Georgia (KPGA). Toward this end, we will generate two quantitative cohorts of KPGA members with a confirmed COVID-19 diagnosis between January 1, 2020, and September 30, 2021: (1) an electronic medical record (EMR) cohort including routinely captured data on diagnoses, medications, and laboratory values, and a subset of patients hospitalized at Emory Healthcare to capture additional in-hospital data; and (2) a survey cohort, where participants will answer a range of questions related to demographics (eg, race, education), usual health behaviors (eg, physical activity, smoking), impact of COVID-19 (eg, job loss, caregiving responsibilities), and medical mistrust. Key outcomes of interest for these two cohorts include hospitalization, mortality, intensive care unit admission, hospital readmission, and long COVID-19. Finally, we will conduct qualitative semistructured interviews to capture perceptions of and experiences of being hospitalized with COVID-19 as well as related interactions with KPGA health care providers. We will analyze and interpret the quantitative and qualitative data separately, and then integrate the qualitative and quantitative findings using a triangulation design approach.

Results: This study has been funded by a Woodruff Health Sciences grant from December 2020 to December 2022. As of August 31, 2022, 31,500 KPGA members diagnosed with COVID-19 have been included in the EMR cohort, including 3028 who were hospitalized at Emory Healthcare, and 482 KPGA members completed the survey. In addition, 20 KPGA members (10 Black and 10 white) have been interviewed about their experiences navigating care with COVID-19. Quantitative and qualitative data cleaning and coding have been completed. Data analysis is underway with results anticipated to be published in December 2022.
Conclusions: Results from this mixed methods pilot study in a diverse integrated care setting in the southeastern United States will provide insights into the mechanisms underpinning racial disparities in COVID-19 complications. The quantitative and qualitative data will provide important context to generate hypotheses around the mechanisms for racial disparities in COVID-19, and may help to inform the development of multilevel strategies to reduce the burden of racial disparities in COVID-19 and its ongoing sequelae. Incorporating contextual information, elucidated from qualitative interviews, will increase the efficacy, adoption, and sustainability of such strategies.

International Registered Report Identifier (IRRID): RR1-10.2196/38914

(Keywords: COVID-19; social determinants of health; race; mixed methods; equity; disparity; health; pandemic; disease severity; mortality; racial; ethnicity; complications)

Introduction

Background

In the United States, the COVID-19 pandemic has magnified the disproportionate and long-standing health disparities experienced by Black communities. Substantive data now demonstrate that Black Americans experience infection, hospitalization, and death from COVID-19 at disproportionality high rates [1-5]. For example, in the state of Georgia, Black Americans represent 31% of the population, yet they account for approximately 40% of total COVID-19 deaths [6]. Now, as we approach our third year of the pandemic, an abundance of extant literature points to the heavily racialized effects of COVID-19, yet there has been scarce discourse and few interventions addressing the disproportionate toll among Black populations due to a lack of actionable evidence needed to inform such responses. Unpacking the role of structural racism (through the multilevel processes that interact with one another to generate and reinforce disparities faced by racialized communities) on the risk of COVID-19 complications, including severe COVID-19 infections requiring hospitalization and “long COVID-19,” remains crucial to inform pandemic responses among Black communities.

Social determinants of health (SDOH), rather than biological differences, are hypothesized to impose a greater risk for both infection and severe disease from COVID-19 (ie, hospitalization) among Black communities [7]. These include a myriad of factors operating at the level of the individual (eg, chronic disease burden), interpersonal (eg, patient-provider relationship), community (eg, health care availability), and social and economic structure (eg, poverty rate, racial segregation). Although it is acknowledged that these factors likely contribute, few studies using rigorous analytic approaches in large, information-rich community-based data sets are dedicated to understanding the underlying drivers of these racial disparities.

Objective

In this protocol, we outline a mixed methods approach to identifying, quantifying, and contextualizing the specific medical and SDOH factors that contribute to the dramatic disparity in COVID-19 complications in Black versus white COVID-19 patients within an integrated health care system. The specific aims of this planned research are to: (1) quantitatively examine the individual, community, and structural factors contributing to (ie, mediating) disparities in COVID-19 complications in Black versus white COVID-19 patients using electronic medical record (EMR) data and primary survey data; (2) conduct semistructured qualitative interviews among Black and white patients hospitalized with COVID-19 to explore personal experiences with COVID-19, and contextualize factors that facilitate and impede health-seeking behaviors at the interpersonal, family, community, and health care levels; and (3) compare and contrast the qualitative interviews about personal experiences with COVID-19 with perceptions on the quantitative survey and routinely collected EMR data (Figure 1). This mixed methods approach will provide a robust understanding of the multifactorial challenges faced by adults diagnosed with COVID-19, and compare these challenges between Black and white patients to inform future interventions and policies that may reduce barriers and improve equity.
Figure 1. Convergent parallel mixed methods design to understand racial disparities in COVID-19–related complications. EMR: electronic medical record; KPGA: Kaiser Permanente Georgia.

### Methods

#### Conceptual Framework

Our approach is informed by the National Institute of Minority Health and Health Disparities (NIMHD) Research Framework (Table 1) [8]. This framework considers the complex interplay among individual, interpersonal, community, and structural factors that influence health and health outcomes. In this study, the NIMHD Framework informed our quantitative EMR cohort and survey development, as well as the qualitative interview guide.

#### Table 1. The National Institute on Minority Health and Health Disparities Research Framework [8].

<table>
<thead>
<tr>
<th>Levels of influence</th>
<th>Biological</th>
<th>Behavioral</th>
<th>Physical/built environment</th>
<th>Sociocultural environment</th>
<th>Health care system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural</td>
<td>Population exposure</td>
<td>Policies and laws (eg, social distancing)</td>
<td>Societal structure</td>
<td>Societal norms; society; structural discrimination; media</td>
<td>Quality of care; health care policies</td>
</tr>
<tr>
<td>Community</td>
<td>Community exposure</td>
<td>Community functioning</td>
<td>Community environment; community resources</td>
<td>Community norms; local structural discrimination</td>
<td>Availability of health services; safety net services</td>
</tr>
<tr>
<td>Interpersonal</td>
<td>Family microbiome; caregiver-child interaction</td>
<td>Family functioning; school/work functioning</td>
<td>Household environment; school/work environment</td>
<td>Social networks; family/peer norms; interpersonal discrimination</td>
<td>Patient-provider relationships; medical decision-making</td>
</tr>
<tr>
<td>Individual</td>
<td>Preexisting conditions</td>
<td>Health behaviors (including social distancing; coping strategies)</td>
<td>Personal environment</td>
<td>Sociodemographic; cultural identity; response to discrimination</td>
<td>Insurance coverage; health literacy; trust in health care system</td>
</tr>
</tbody>
</table>

#### Community Advisory Board

Evidence suggests that a community-engaged approach leads to the development of more efficacious and readily adoptable interventions [9], the long-term objective of our work. For this study, we have formed a community advisory board (CAB; N=5) comprised of patients, caregivers, and researchers. CAB members were recruited through established community engagement networks, academic institutions, local community organizations, and health care systems. The composition of the CAB is 70% women and 100% nonwhite. To date, the CAB has helped inform the development of the qualitative interviews. It is anticipated that results arising from the study will be disseminated to the CAB, which will be essential to contextualizing results and informing the development future multilevel intervention studies to reduce COVID-19–related racial disparities.

#### Study Population and Data Sources

**Kaiser Permanente Georgia**

Kaiser Permanente Georgia (KPGA) is a large health insurance database of more than 260,000 current adult members (>40% Black) across 2230 US Census tracts in the metropolitan Atlanta area as well as North Georgia. To be enrolled in the database, participants must have insurance with KPGA. The large...
proportion of Black members (in the general Georgia population, the proportion of people identifying as Black is 32.6%) and variability in SDOH indices (household income, social vulnerability index) will allow us to investigate racial disparities and effect modification by individual circumstances, health care site, and neighborhood. KPGA has an extensive EMR data repository, including information related to patient demographics (with some individual measures of SDOH such as insurance status), diagnoses, procedures, claims, lab values, and prescribed medications. In addition, community-level SDOH variables were drawn from an extensive database of characteristics at the county, census-tract, and zip code levels to characterize social vulnerability factors at the community and system levels. Data on community- and system-level factors were obtained from publicly available sources (eg, American Community Survey), which were geocoded and linked to patient EMR data using information of the patient address.

EMR Cohort (Quantitative)

To develop the EMR cohort, all adult (aged ≥18 years) members enrolled in KPGA as of January 1, 2020, with a minimum of 1-month continuous enrollment and with a confirmed diagnosis of COVID-19 were included (N=31,500). COVID-19 was defined by a positive COVID-19 polymerase chain reaction test or an International Classification of Diseases-10th revision (ICD-10) diagnosis code (U07.1, B97.29, B34.2, B97.21, or J12.81). To ascertain granular information on in-hospital outcomes (eg, intensive care unit [ICU] admission), KPGA EMR data were linked to Emory Healthcare for the subset of KPGA members hospitalized with COVID-19 at Emory Healthcare (n=3028). KPGA does not offer inpatient services and Emory Healthcare represents >50% of all hospitalizations among KPGA members in metropolitan Atlanta. Linkage of KPGA to Emory Healthcare data was done using an algorithm of date of birth, first name, last name, and sex, with a linkage rate greater than 90%.

COVID-19 Survey Cohort (Quantitative)

For the COVID-19 survey, adult (aged ≥18 years) KPGA members with a confirmed COVID-19 diagnosis; a valid email address; and current KPGA enrollment with a minimum of 1-month continuous enrollment as of June 1, 2021, were invited to participate via email. The cohort eligible for the survey was populated on June 1, 2021, and research staff began emailing eligible adults a recruitment email with an embedded survey link. Emails were sent in batches of 500 between July 1, 2021, and August 15, 2021. In total, 482 people completed the survey with a response rate of 3%, similar to other Kaiser Permanente email-administered surveys. All participants provided informed consent.

Interview Cohort (Qualitative)

For semistructured interviews, Black and white adult (aged ≥18 years) KPGA members with a confirmed COVID-19 diagnosis and hospitalized with COVID-19 with a discharge date between March 2020 and March 2021 were eligible to be recruited. KPGA members were recruited via the KPGA patient portal (Health Connect), email, phone, and mail. Upon initial contact, we additionally screened individuals to ensure we only recruited those who self-identify as Black or white and ensured an equal distribution of participants by race (ie, 10 Black and 10 white participants). Using this recruitment method, and anticipating a 10%-20% response rate [10], we invited approximately 200 KPGA members to achieve our sample size of 20. Based on guidance, completing 20 interviews among a racially balanced cohort will be adequate for ensuring an appropriate saturation of themes [11].

Table 2 describes the four distinct populations in this study, and respective measurements and study outcomes.
Table 2. Study populations, measurements, and outcomes of interest.

<table>
<thead>
<tr>
<th>Study population</th>
<th>Study population description</th>
<th>Participants, n</th>
<th>Measurement(s)</th>
<th>Outcome(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quantitative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMR cohort</td>
<td>All adult KPGA members diagnosed with COVID-19 between January 1, 2020, and June 1, 2021</td>
<td>31,500</td>
<td>EMR data, including demographics, neighborhood-level SDOH, comorbidities, medications, and lab values</td>
<td>Hospitalization within 30 days of COVID-19 diagnosis; readmission (30, 60, and 90 days); mortality; long COVID</td>
</tr>
<tr>
<td>Survey cohort</td>
<td>We invited those in the EMR cohort with a valid email address (n=17,500) to complete a COVID-19 survey</td>
<td>482</td>
<td>Survey questions related to demographics (eg, race, education), usual health behaviors (eg, physical activity, smoking), impact of COVID-19 (eg, job loss, caregiving responsibilities), and medical mistrust. Survey data were supplemented with EMR data</td>
<td>Hospitalization within 30 days of COVID-19 diagnosis; readmission (30, 60, and 90 days); mortality; long COVID</td>
</tr>
<tr>
<td>KPGA-Emory cohort</td>
<td>All adult KPGA members hospitalized at Emory Healthcare with COVID-19 between January 1, 2020, and June 1, 2021</td>
<td>3028</td>
<td>KPGA EMR data, supplemented with data on in-hospital medications and lab values from Emory Healthcare</td>
<td>In-hospital outcomes: mechanical ventilation, COVID-19 treatment, ICU use</td>
</tr>
<tr>
<td>Qualitative: interview cohort</td>
<td>We invited those in the EMR cohort with a valid email address (n=17,500) to participate in a 60-minute one-on-one interview</td>
<td>10</td>
<td>Semistructured interviews</td>
<td>Themes</td>
</tr>
</tbody>
</table>

*EMR: electronic medical record.
KPGA: Kaiser Permanente Georgia.
SDOH: social determinants of health.
ICU: intensive care unit.
ECMO: extracorporeal membrane oxygenation.

Quantitative Methods and Analysis: EMR Cohort

**Primary Exposure: Race**

Race is a social construct describing groups that have associated racial meanings that affect their economic, political, and social lives [7,12]. Racial inequalities are influenced by class differences and SDOH [12,13]. In this study, the primary independent variable will be race, determined from KPGA patient self-report data, and will focus on Black and white adults. Based on guidance by Ioannidis et al [14] and Lin and Kesley [15], the use of race in the current context is appropriate, as other SDOH factors often fail to associate (with sufficient precision) when race is used as the placeholder, and the development of our models will carefully consider other explanatory biological and sociologic variables that may explain race-based signals. Further, due to persistent structural inequities that exist across multiple levels, studying the magnitude of disparities between Black and white individuals in EMR data is often difficult because of missing race/ethnicity data. Therefore, to address missing data on self-identified race (~24% among adults in KPGA), we will apply a Bayesian method integrating surname and geocoded information to impute self-reported race [16]. This approach has previously shown high correlation (76%) with self-reported race with other Kaiser Permanente databases [16]. Analyses will be performed with and without imputed race. Quantitative findings of factors contributing to racial disparities will be merged with the perceptions and experiences from semistructured interviews using a triangulation design. Of note, the current study protocol is restricted to examine differences between Black and white individuals and does not include other racial or ethnic groups, or those identifying as multiracial. This is because the reasons for racial and ethnic disparities in health outcomes across groups are complex and must be carefully considered against each group’s historical, social, and economic circumstances. Here, we focus on Black versus white disparities to better ensure that the research provides specific and actionable insight for this important subgroup. Future work will incorporate other racial and ethnic groups.

**Covariates**

A list of the multilevel variables that will be considered as confounders and/or mediators based on our conceptual model, along with their respective data sources, is detailed in Table 3. We will consider these variables in the context of individual-, community-, and system-level factors, but acknowledge that these are not always mutually exclusive and that many risk factors have upstream causes for which solutions should also be upstream.

https://www.researchprotocols.org/2022/10/1/e38914
Table 3. Quantitative study variables and data sources.

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Data Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Individual-level factors</strong></td>
<td></td>
</tr>
<tr>
<td>Demographics (eg, race, age, sex, ethnicity)</td>
<td>KPGA(^a) EMR(^b)</td>
</tr>
<tr>
<td>Insurance coverage</td>
<td>KPGA EMR</td>
</tr>
<tr>
<td>Primary language spoken at home</td>
<td>KPGA EMR</td>
</tr>
<tr>
<td>COVID-19 diagnosis date</td>
<td>KPGA EMR</td>
</tr>
<tr>
<td>Pre-existing conditions</td>
<td>KPGA EMR</td>
</tr>
<tr>
<td>Medical treatment</td>
<td>KPGA EMR</td>
</tr>
<tr>
<td>Vital signs and lab data</td>
<td>KPGA EMR</td>
</tr>
<tr>
<td>In-hospital lab values</td>
<td>Emory Healthcare</td>
</tr>
<tr>
<td>In-hospital medications</td>
<td>Emory Healthcare</td>
</tr>
<tr>
<td>Marital status</td>
<td>COVID-19 Survey</td>
</tr>
<tr>
<td>SDOH(^c) (eg, education, household income)</td>
<td>COVID-19 Survey</td>
</tr>
<tr>
<td>Locus of control</td>
<td>COVID-19 Survey</td>
</tr>
<tr>
<td>Health behaviors (eg, exercise, smoking, drinking) pre- and post-COVID-19</td>
<td>COVID-19 Survey</td>
</tr>
<tr>
<td>COVID-19 symptoms</td>
<td>COVID-19 Survey</td>
</tr>
<tr>
<td>Health care-seeking behavior</td>
<td>COVID-19 Survey</td>
</tr>
<tr>
<td>Impacts of COVID-19 pandemic (eg, job loss)</td>
<td>COVID-19 Survey</td>
</tr>
<tr>
<td>Vaccine hesitancy</td>
<td>COVID-19 Survey</td>
</tr>
<tr>
<td>Medical mistrust</td>
<td>COVID-19 Survey</td>
</tr>
<tr>
<td><strong>Community- and structural-level factors</strong></td>
<td></td>
</tr>
<tr>
<td>Neighborhood deprivation index</td>
<td>American Community Survey</td>
</tr>
<tr>
<td>Median household income</td>
<td>American Community Survey</td>
</tr>
<tr>
<td>Social vulnerability index</td>
<td>American Community Survey</td>
</tr>
<tr>
<td><strong>Outcome variables</strong></td>
<td></td>
</tr>
<tr>
<td>30-day hospitalization</td>
<td>KPGA EMR</td>
</tr>
<tr>
<td>Readmission (30-day, 60-day, 90-day)</td>
<td>KPGA EMR</td>
</tr>
<tr>
<td>ICU(^d) admission</td>
<td>Emory Healthcare</td>
</tr>
<tr>
<td>Mechanical ventilator use</td>
<td>Emory Healthcare</td>
</tr>
<tr>
<td>COVID-19 treatment</td>
<td>Emory Healthcare</td>
</tr>
<tr>
<td>ECMO(^e) use</td>
<td>Emory Healthcare</td>
</tr>
<tr>
<td>Long COVID complications: cardiovascular (CAD(^f), HF(^g), MI(^h), stroke, PVD(^i)); respiratory (fibrotic lung disease, bronchiectasis, pulmonary vascular disease; mental health (depression, anxiety, substance abuse)</td>
<td>KPGA EMR</td>
</tr>
<tr>
<td>Mortality</td>
<td>KPGA EMR</td>
</tr>
</tbody>
</table>

\(^a\)KPGA: Kaiser Permanente Georgia.
\(^b\)EMR: electronic medical record.
\(^c\)SDOH: social determinants of health.
\(^d\)ICU: intensive care unit.
\(^e\)ECMO: extracorporeal membrane oxygenation.
\(^f\)CAD: coronary artery disease.
\(^g\)HF: heart failure.
\(^h\)MI: myocardial infarction.
\(^i\)PVD: peripheral vascular disease.
Outcomes

COVID-19–Related Hospitalizations
Hospitalizations will be considered to be COVID-19–related if they occurred within 30 days of the COVID-19 diagnosis date and include an ICD-10 code for COVID-19.

Hospital Readmissions
Hospital readmissions will be defined as readmissions at 30, 60, and 90 days following the first hospital discharge date.

In-Hospital Outcomes
ICU admission, COVID-19 treatment, and ventilator status will be defined based on KPGA and Emory Healthcare data.

Long COVID
Long COVID will be defined through multiple outcome domains: cardiovascular (coronary artery disease, heart failure, myocardial infarction, stroke, peripheral vascular disease); metabolic (diabetes); kidney (acute kidney injury); respiratory (fibrotic lung disease, bronchiectasis, pulmonary vascular disease); mental health (depression, anxiety, substance abuse). Long COVID outcomes will be defined using ICD-10 codes as appropriate. To minimize misclassification of acute COVID-19 complications, as well as previously undiagnosed conditions, long COVID will be defined as symptoms >30 days following the initial COVID-19 infection date.

Mortality
Vital status is updated on a quarterly basis by a dedicated team at KPGA. We will consider COVID-19–specific deaths and all-cause deaths in this group (Tables 2-3).

Statistical Analysis

Overview
In this open cohort study, we will follow individuals in our cohort from the date of first COVID-19 infection, through to each outcome of interest (ie, hospitalization, postacute sequelae of COVID-19, death, or end of enrollment). All primary analyses will consider time to first event (ie, first COVID-19–related event). In sensitivity analyses, we will consider multiple events (ie, >1 event). In addition, given the various waves of COVID-19 (ie, emergence of the Delta and Omicron variants), all analyses will be stratified by calendar period.

Summary Statistics
The study population characteristics will be described with summary statistics as appropriate for the EMR cohort. The χ², t, and Wilcoxon rank-sum tests will be used to test for differences in baseline characteristics by race as appropriate. We will fit multivariable Poisson regression models, negative binomial regression, and generalized Poisson regression to estimate the excess risk of COVID-19 outcomes in Black versus white adults, and determine the multilevel factors associated with this excess risk using a stepwise approach [17]. All models will consider variability across calendar time. Given the known sex disparity in COVID-19 (ie, men have higher risk of severe COVID-19 compared with women) [18], we will additionally stratify all results by sex. Findings will also be stratified by age and vaccination status to examine the effect modification on their association with severe COVID-19 outcomes. Study variables obtained from EMR data, excluding race, are expected to be available for >95% of participants based on prior analyses. Therefore, our primary approach will be a complete case analysis. However, we will perform sensitivity analyses using hot-deck imputation, replacing missing values with imputed values as estimated from respondents with matching covariates [19].

Decomposition Analysis
Following a social-ecological approach, we will apply the Oaxaca-Blinder decomposition technique to quantify the contribution of individual, community, and structural exposures to racial disparities in COVID-19 outcomes. This regression-based counterfactual method was originally developed in economics with recent applications in epidemiology [20,21]. We will use this method to partition the disparity in outcomes between Black and white KPGA members into the portion that is explained by differences in the levels of exposures across race, differences in the associations of the exposures across race, and the portion that is unexplained by exposures included in the model (ie, other unmeasured factors such as racism). The output from the decomposition analysis will provide insight on the expected residual disparity in outcome if Black and white adults experienced the same level of exposures (eg, equal health care access), sample exposure effects (eg, equal effects on outcomes once health care is accessed), and the interaction between level and effects of exposures. This technique will enable us to quantify the confounder-adjusted potential impact of targeting specific exposures and exposure combinations (which may be differentially distributed by race but also have differential effects on outcomes for each race) on the Black-white disparity in study outcomes. This quantification can be used to prioritize future intervention efforts. Finally, effect modification by area-level characteristics will be evaluated through stratified decomposition analysis among adults residing in counties with high and low vulnerability scores following established percentile-based indices (high: >75th percentile). All analyses will be performed using Stata version 16.1 (StataCorp).

Sample Size and Power Calculation
The EMR cohort is expected to follow 31,500 adults (~47.2% Black). For the rarest outcome, COVID-19 mortality (159 per 100,000 white adults) [22], we expect to be able to detect relative risks (between Black and white adults) of 1.4 with 0.9 power at the 5% significance level. Based on previous applied studies using decomposition analysis (sample size range 24 to 22,666,142), our study will have a modest sample size to conduct decomposition analysis, and based on a range of uncertainty estimates, we anticipate having 80% assurance for 80% power or higher [23].

Quantitative Methods and Analysis: COVID-19 Survey Cohort

Survey Development
We collected additional individual-level patient information on COVID-19–positive patients via an electronic survey to explore specific factors, including SDOH, that may be associated with...
COVID-19 complications not captured in EMR data. Variables included in the survey (see Multimedia Appendix 1 and Table 3) were based on a priori knowledge as well as emerging questions specific to COVID-19, and obtained from a variety of sources, including the National Institute of Health’s Office of Behavioral and Social Sciences Research resource list of COVID-19–relevant domains for clinical or population research [24]. The survey, administered through Emory University’s RedCap system, was pilot-tested among a sample (N=15) of non-COVID-19 non-KPGA members, and estimated to take, on average, 8 (range 5-10) minutes to complete.

**Race**

Race, as described above for the EMR cohort, will be collected via self-report on the survey. We will define individuals as non-Hispanic Black and non-Hispanic white. Within the design of the survey, all individuals must answer questions on race before progressing in the survey. Therefore, we do not have any missing data on race for the COVID-19 survey.

**Outcome**

KPGA members who completed the COVID-19 survey were linked to the KPGA EMR using name, date of birth, and medical record number with an almost 100% match rate. This means that all COVID-19 survey participants will also have EMR data on comorbidities, lab values, and medications as per the EMR cohort. The primary outcome for COVID-19 survey participants will be 30-day hospitalization as ascertained by the KPGA EMR (Table 3).

**Statistical Analysis**

**Overview**

The analytic approach for the COVID-19 survey cohort will be similar to that described for the EMR cohort under the Summary Statistics subsection above. We do not have sufficient power to perform a decomposition analysis on this sample.

**Sample Size and Power Calculation**

Using a Poisson regression for our primary outcome of COVID-19–related hospitalization within 30 days of infection among 482 survey participants, 38.6% of whom identify as Black, we estimate having 93% power at a .05 significance level to detect a minimum relative risk of 1.4. This sample size estimate is adjusted for covariates of age, gender, neighborhood vulnerability index, and median income.

**Qualitative Methods and Analysis**

**Overview**

Examining racial disparities in COVID-19 using large EMR systems such as KPGA will provide quantitative data to explore the contribution of several multilevel factors to known racial disparities. However, this approach in isolation may overlook the complex interaction of contextual factors, cultural and personal values, social resources, and individual motivations that influence a person’s ability to seek health care and navigate the health care system. Therefore, this mixed methods project concurrently conducted in-depth semistructured interviews, guided by the theoretical framework outlined in Table 1 and with feedback from the CAB, to capture perceptions of and experiences of being hospitalized with COVID-19 as well as related interactions with KPGA health care providers. Qualitative methods such as this are well-suited to produce rich, contextual information from individuals deemed knowledgeable about specific issues [25]. Furthermore, capturing the patient experience and integrating this information into the design and development of future interventions, as our long-term objective, is known to increase the efficacy, adoption, and sustainability of such interventions [26].

**Data Collection**

Semistructured interviews were conducted among a cohort of 10 Black and 10 white participants diagnosed with COVID-19. According to the principles of qualitative research, we believe that a sample size of 20 will be sufficient to reach saturation for thematic analyses [27]. All interviews were conducted via telephone and audio-recorded. Each interview lasted ~60 minutes and was conducted by trained social behavioral scientists at KPGA with extensive experience in qualitative interviewing. The interview guide focused on factors related to health disparities and the multilevel factors associated with racial disparities in health and health care. This includes social environment (neighborhood-level access to quality care), medical mistrust, patient-provider interaction, and changes in employment or housing circumstances (Multimedia Appendix 2). We included a process for referring participants to counseling through KPGA’s Behavioral Health Department for any patients who report challenges during the interview. The interview guide and procedures were pilot-tested with a subset (n=2-3) of the study population prior to enrolling study participants. Participants were offered a nominal financial incentive (US $20 Amazon gift card) for participating in the interview.

**Data Analysis**

Semistructured interviews were audio-recorded and transcribed verbatim by two trained research assistants (one identifying as Black and the other as white) and overseen by a trained social behavioral scientist (identifying as Black). A random sample of transcripts were checked against the audio recordings for accuracy. We then developed a codebook using open coding to identify themes that emerged, followed by axial coding to categorize the themes that emerged to code the interview transcripts [26]. Two coders independently coded each interview transcript and any discordance between the primary coders was discussed with the group until a resolution was reached. Intercoder agreement will be assessed using κ values. We used NVivo 12.0 software to code data and organize results. Thematic analysis will be used to describe themes within the study domains and constructs. We will use modeling techniques to visualize relationships between themes that emerge among each group of participants.

**Mixed Methods Integration**

This study will follow the checklist for mixed methods research proposed by Fetters and Molina-Azorin [28]. We will analyze and interpret quantitative and qualitative data separately, and then integrate the qualitative and quantitative findings using a triangulation design approach to directly compare and contrast quantitative statistical results with qualitative findings, and to...
validate quantitative findings with qualitative data. We will present quantitative data and qualitative data separately, and together in a joint display table (Figure 1).

Ethics Approval and Dissemination
The KPGA Institutional Review Board (IRB; #0000406) and Emory University IRB (#MOD004-STUDY00001631) reviewed and approved this study. Online informed consent was obtained from all participants in the survey cohort. Verbal informed consent was obtained from all participants involved in qualitative interviews.

The Emory and KPGA IRBs waived the requirement of written Privacy Rule Authorization for use of protected health information for recruitment purposes, for the secondary data analysis portion of the study, and waived the requirement of written Privacy Rule authorization and the requirement to obtain a signed consent form for the survey and interview portions of the study.

Study findings will be disseminated with key stakeholders, including CAB members, KPGA, and Emory Healthcare, and will be presented at academic conferences and published in peer-reviewed journals.

Data and Material Availability
The data that support the findings of this study are available from KPGA, but restrictions apply to the availability of these data, which were used under license for this study and so are not publicly available. However, data are available from the authors upon reasonable request and with permission of KPGA.

Results
This study has been funded by a Woodruff Health Sciences grant from December 2020 to December 2022. As of August 31, 2022, 31,500 KPGA members diagnosed with COVID-19 between January 1, 2020, and September 30, 2021, have been included in the EMR cohort, including 3028 who were hospitalized at Emory Healthcare, and 482 KPGA members completed the survey. In addition, 20 KPGA members (10 Black and 10 white) have been interviewed about their experiences navigating care with COVID-19. Quantitative and qualitative data cleaning and coding have been completed. Data analysis is underway with results anticipated to be published in December 2022.

Table 4 describes the basic demographics of our three distinct study populations. In brief, the EMR cohort was more likely to be Black, female, and younger as compared to the general KPGA population. The survey cohort was less likely to be Black and male, and more likely to be older as compared to the general KPGA population. Finally, the interview cohort was more likely to be Black and male relative to the general KPGA population.

Discussion
Principal Findings
Results from this mixed methods pilot study in a diverse integrated care setting in the southeastern United States will provide insights into the mechanisms underpinning racial disparities in COVID-19 complications. We hypothesize that Black KPGA members will have an increased risk for COVID-19–related complications such as hospitalization, ICU admission, and ventilator use relative to white KPGA members. We also anticipate that a higher proportion of comorbidities among Black KPGA members will explain some, but not all, of the observed disparities, and that SDOH, including racism, will also contribute significantly to race-based disparities. The quantitative and qualitative data in this study will provide important context to generate hypotheses around the mechanisms for racial disparities in COVID-19, and may help to inform the development of multilevel strategies to reduce the burden of racial disparities in COVID-19 and its ongoing sequelae.

Incorporating contextual information, elucidated from qualitative interviews, will increase the efficacy, adoption, and sustainability of such strategies.

Comparison to Prior Work
Previous work examining racial disparities in COVID-19–related outcomes has largely been limited to quantitative approaches describing the relative risk of COVID-19 or COVID-19–related outcomes in one race or ethnic group relative to another. Few studies to date have employed a mixed methods approach to comprehensively explore the underlying mechanisms of racial disparities in COVID-19–related outcomes. One known study, using data from the “Health, Ethnicity and Pandemic Survey” (N=2506), a nationally representative survey conducted in October 2020, reported that Black respondents were 6 times more likely to report experiences of racism during COVID-19 [29]. The experience of racism was related to where people lived (eg, “red” vs “blue” states, and racially homogenous neighborhoods), as well as individual-level factors such as being male, low education, and lack of access to the internet [29].

Table 4. Demographic characteristics of the three unique study populations diagnosed with COVID-19 included in this mixed methods study as compared to the general KPGA population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>EMR(^a) cohort</th>
<th>Survey cohort</th>
<th>Interview cohort</th>
<th>KPGA(^b) population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants recruited, n</td>
<td>31,500</td>
<td>482</td>
<td>20</td>
<td>264,681</td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>14,868 (47.2)</td>
<td>186 (38.6)</td>
<td>10 (50.0)</td>
<td>110,107 (41.6)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>13,261 (42.1)</td>
<td>157 (32.5)</td>
<td>12 (60.0)</td>
<td>120,430 (45.5)</td>
</tr>
<tr>
<td>Aged&gt;60 years, n (%)</td>
<td>5260 (16.7)</td>
<td>192 (39.8)</td>
<td>0 (0)</td>
<td>63,259 (23.9)</td>
</tr>
</tbody>
</table>

\(^a\)EMR: electronic medical record.
\(^b\)KPGA: Kaiser Permanente Georgia.
This study highlighted the importance of examining the multilevel factors contributing to racism, but did not expand this research to examine mechanisms and associations with COVID-19–related outcomes, a focus of the current research.

**Strengths and Limitations**

The key strength of this study is the use of a large integrated health care system (KPGA) with a rich EMR data infrastructure that includes individual, interpersonal, community, and structural factors, providing a unique opportunity to disentangle the key multilevel mechanisms underscoring racial disparities in COVID-19 for which few other data sets are equipped to address. Furthermore, KPGA is a longitudinal data set, and includes inpatient, outpatient, and general health encounters, leading to greater generalizability than most hospital-based COVID-19 studies performed to date. Our research team has extensive expertise using EMR data for research purposes [30-35], including validation studies [36], and is well-equipped to address the nuances of EMR data in research settings.

However, there are some limitations of this study to consider. First, KPGA has a higher proportion of Black adults compared to the Georgia population (41.6% and 32.6%, respectively), higher socioeconomic status (ie, median income and social vulnerability) [37], and does not include uninsured or Medicaid patients. Therefore, results from this study cannot be generalized to the broader Georgia population, but rather to those within an integrated health care system such as KPGA. Despite this, pervasive racial, ethnic, and socioeconomic disparities exist within the KPGA population. For example, Kaiser Permanente has previously reported racial and socioeconomic disparities with respect to health and well-being [38], gastric cancer [39], smoking cessation [40], and diabetes care [41], and preliminary evidence suggests that Black members are twice as likely to experience housing instability, indicating that a social gradient exists within this integrated health system. Understanding the underlying mechanisms contributing to racial disparities in COVID-19 in a population with comparatively uniform access to care is the focus of this work, for which the KPGA data infrastructure is well-suited.

Second, there are known limitations to the use of EMR data for research purposes, not least of which pertains to diagnosis bias: there is likely a race-based bias in terms of who is being screened, tested, and subsequently diagnosed with comorbidities. However, EMR data outperform claims and self-reported data. Moreover, the use of EMR data from a large population allows us to tease out underlying mechanisms of racial disparities in COVID-19 that would not be possible in a smaller, more select cohort population.

Third, our survey response rate was only 3%, similar to other email-based recruitment surveys. Consequently, our survey population is more likely to be white, female, and older as compared to the general KPGA population, thus limiting the external generalizability of our findings. However, the internal validity of our analyses examining the relative contribution of various SDOH factors and COVID-19–related disparities within this population is unlikely to be comprised by this selection bias, and thus the results will still be informative and generate important hypotheses for future work.

Finally, qualitative findings will be limited to a small number of COVID-19–related contexts due to the sample size. Here, we have prioritized understanding the context of health care navigation among Black and white KPGA members with COVID-19, as interventions to improve access, and thus reduce racial disparities, within an integrated health care system may be more readily addressed.

**Future Directions**

In this pilot study, we hope to generate new knowledge regarding underlying mechanisms of race-based disparities in COVID-19 outcomes to inform the development of future multilevel interventions aimed at reducing inequalities within integrated care settings. Further, KPGA shares the same data infrastructure with 18 other health systems across the United States (in 13 states and serving >28.4 million patients). This will allow us to expand our work to a multisite study across the United States examining the impact of COVID-19 in communities of color in the southeast and nationally.

**Conclusion**

In conclusion, this study will investigate race-based disparities in COVID-19 outcomes, and the contributing roles and mediating pathways of individual-level and social (eg, structural racism, neighborhood environment) factors among a racially and socioeconomically diverse population of people enrolled within an integrated health system. A rigorous examination of social contexts and racial disparities in COVID-19 outcomes will contribute to the identification of factors that can inform continuing efforts to address racial disparities in the United States in the context of COVID-19.

**Acknowledgments**

This work is funded by a Woodruff Health Sciences 2020 CURE award for COVID-19 research. The use of REDCap in this project is supported by grant UL1TR000424. The funders played no role in the design or interpretation of the study. The study team would like to thank all Kaiser Permanente Georgia (KPGA) members who participated in this study, the Community Advisory Board (CAB), and the research staff at KPGA without whom this work would not be possible. We would also like to thank Mengyu Di for her sample size power calculations.
Authors' Contributions

JLH conceptualized the study, contributed to design, and wrote the manuscript. SAP, JG, and TD contributed to conceptualization, study design, and reviewed-edited the manuscript. REP, BM, DW-W, RJ, and LT contributed to study design and reviewed-edited the manuscript. All authors have read and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Quantitative survey questions.

[PDF File (Adobe PDF File), 220 KB - resprot_v11i10e38914_app1.pdf ]

Multimedia Appendix 2

Qualitative interview guide.

[PDF File (Adobe PDF File), 156 KB - resprot_v11i10e38914_app2.pdf ]

References


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Abbreviations

CAB: community advisory board
EMR: electronic medical record
ICD-10: International Classification of Diseases, 10th revision
ICU: intensive care unit
IRB: Institutional Review Board
KPGA: Kaiser Permanente Georgia
NIMHD: National Institute of Minority Health and Health Disparities
SDOH: social determinants of health

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Biomarkers of Exposure and Potential Harm in Exclusive Users of Nicotine Pouches and Current, Former, and Never Smokers: Protocol for a Cross-sectional Clinical Study

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Abstract

Background: Tobacco harm reduction (THR) aims to reduce the health burden of cigarettes by encouraging smokers to switch to using alternative tobacco or nicotine products. Nicotine pouches (NPs) are smokeless, tobacco-free, oral products that may be beneficial as part of a THR strategy.

Objective: This 2-center, cross-sectional confinement study conducted in Denmark and Sweden aimed to determine whether biomarkers of exposure (BoEs) to tobacco toxicants and biomarkers of potential harm (BoPHs) in exclusive users of NPs show favorable differences compared with current smokers.

Methods: Participants were healthy NP users (target n=100) and current, former, or never smokers (target n=40 each), as confirmed by urinary cotinine and exhaled carbon monoxide concentrations. During a 24-hour confinement period, participants were asked to use their usual product (NP or cigarette) as normal, and BoEs and BoPHs were measured in blood and 24-hour urine samples, with compliance determined using anabasine, anatabine, and N-(2-cyanoethyl)valine. BoEs and BoPHs were compared between NP users and current, former, and never smokers. Urinary total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (BoE to nicotine-derived nitrosamine ketone) and urinary 8-epi-prostaglandin F2α, type III, exhaled nitric oxide, blood carboxyhemoglobin, white blood cell count, soluble intercellular adhesion molecule-1, and high-density lipoprotein cholesterol (BoPHs) were evaluated as primary outcomes. Other measures included urinary 11-dehydrothromboxane B2, forced expiratory volume, carotid intima-media thickness, self-reported quality of life, and oral health.

Results: The results of this study were received in mid-2022 and will be published in late 2022 to early 2023.

Conclusions: The results of this study will provide information on toxicant exposure and biomarkers associated with the development of smoking-related diseases among users of NPs compared with smokers, as well as on the potential role of NPs in THR.

Trial Registration: International Standard Randomised Controlled Trial Number (ISRCTN) ISRCTN16988167; https://www.isrctn.com/ISRCTN16988167

International Registered Report Identifier (IRRID): DERR1-10.2196/39785

(JMIR Res Protoc 2022;11(10):e39785) doi:10.2196/39785

KEYWORDS
biomarkers of exposure; biomarkers of potential harm; nicotine pouches; tobacco harm reduction; cross-sectional clinical study
Introduction

Background

Cigarette smoking is associated with several health risks, including the development of lung cancer and cardiovascular disease [1]. Although the addictive properties of cigarette smoking are primarily due to the tobacco constituent nicotine [2,3], its disease mechanisms, including DNA damage and oxidative stress [4,5], are associated with the long-term inhalation of smoke from the combusted tobacco [1,6]. This knowledge has led to the concept of tobacco harm reduction (THR), whereby smokers are encouraged to replace cigarette smoking with the use of alternative nicotine products with potentially fewer health risks [7]. Such an approach might reduce the health burden of tobacco use [8] and is currently supported by a number of health and regulatory bodies [9-11], although THR is not universally implemented or accepted [12]. Furthermore, for THR to realize its full potential, complete switching from the more harmful product, typically tobacco cigarettes, to the less harmful product is required [13].

Commericially available since the mid-2010s, nicotine pouches (NPs; Figure 1) are nicotine-containing oral, smokeless, tobacco-free pouches [14,15]. Although NPs are growing in popularity [16,17], use of NPs is relatively low; in a representative monthly survey of British adults conducted between November 2020 and October 2021, only 0.26% used NPs [18]. Similar to Swedish snus, which is a smokeless tobacco product that has been recognized to have reduced health risks compared with combustible cigarettes [19,20], NPs are placed between the gum and top lip, where nicotine is released from the cellulose matrix in the pouch and absorbed through the oral mucosa.

Figure 1. Illustration of a typical nicotine pouch: (A) as sold in container with lid, and (B) individual pouch. It is from “Chemical characterization of tobacco-free “modern” oral nicotine pouches and their position on the toxicant and risk continuums” by David Azzopardi, Chuan Liu & James Murphy David Azzopardi, Chuan Liu & James Murphy (2021) taken from Drug and Chemical Toxicology (2022), Vol45:5, Informa UK Limited, trading as Taylor & Francis Group (2022), reprinted by permission of the publisher.

Because of their relatively simple composition, that is, pharmaceutical-grade nicotine added to a cellulose-based matrix rather than a nicotine-containing tobacco matrix, NPs contain fewer toxicants compared with snus and may therefore present similar or fewer health risks. This has been demonstrated in a recent toxicant analysis in which 24 to 26 compounds (23 to 25 of which were harmful and potentially harmful constituents [HPHCs]) were measured in snus, NPs, and a nicotine replacement therapy (NRT) gum and lozenge. In total, 22 out of 25 of the measured HPHCs were not quantified in the NPs, whereas only 11 out of 23 HPHCs were not quantified in Swedish snus [15]. In addition, studies have demonstrated that extracts from NPs are significantly less toxicologically active in vitro than extracts from Swedish snus or cigarette smoke [21,22].

The aforementioned findings indicate that NPs may have a potential role to play in a THR approach, as recently suggested by Palmer et al [23]. However, at present, there are no data on a user’s actual exposure to toxicants from these products. It should be noted that a reduction in toxicant exposure from alternative nicotine product use compared with continued smoking may not correspond to a reduction in overall harm, and further studies on longer-term use of these products are required to support this. In this regard, clinical studies measuring biomarkers in human samples can provide information on whether NP users are exposed to reduced levels of toxicants and whether this translates to a potential for reduced risk compared with continued smoking. In particular, biomarkers of exposure (BoEs), which indicate a user’s internal exposure to tobacco toxicants, and biomarkers of potential harm (BoPHs), which reflect changes in their wider biological system [24], are now being used to evaluate the risk reduction potential of e-cigarettes and tobacco heating products [25-29].

Objectives

The aim of this study was to assess whether the lower number and levels of toxicants found in NPs compared with those found in tobacco smoke translate to lower levels of selected BoEs as well as favorable differences in selected BoPHs and physiological measures of health between adults who use NPs and adult current, former, and never smokers.
The primary objective was to quantitatively assess differences between NP users and current smokers in one BoE (total 4-[methylN-nitrosamino]-1-[3-pyridyl]-1-butanol [NNAL]) and six BoPHs (fractional exhaled nitric oxide [FeNO], 8-epi-prostaglandin F2α type III [8-epi-PGF2α type III], carboxyhemoglobin [COHb], white blood cell (WBC) count, soluble intercellular adhesion molecule-1 [sICAM-1], and high-density lipoprotein [HDL]).

The secondary objectives were to quantitatively assess differences between NP users and current smokers in the BoEs’ total nicotine equivalents (nicotine, cotinine, 3-hydroxycotinine, and their glucuronide conjugates); monohydroxybutenylmercapturic acid; 3-hydroxy-1-methylpropylmercapturic acid (HMPMA); 3-hydroxypropylmercapturic acid; total N-nitrosornornicotine; 3-hydroxybenzo[a]pyrene; S-phenylmercapturic acid; the BoPH 11-dehydrothromboxane B2 (11-dTX B2); the physiological measures forced expiratory volume in 1 second as percentage of predicted (FEV1%pred), carotid intima-media thickness (CIMT), and oral health; and a quality-of-life questionnaire. In addition, all study end points were compared between NP users and former smokers and between NP users or former smokers and never smokers.

Methods

Study Design

This cross-sectional multicenter confinement study was conducted among exclusive NP users and current, former, and never smokers attending 1 of 2 centers in Herlev, Denmark, and Uppsala, Sweden, between March 2021 and January 2022. Written informed consent was obtained from all participants before screening and enrollment.

Ethics Approval

Ethics approval for the study was obtained from the Scientific Ethics Committees for the Capital Region, Denmark (H-21021424) and the Ethical Review Authority, Sweden (2021-01810). The study was conducted in accordance with the Declaration of Helsinki and will be reported based on the guidelines of the International Council on Harmonisation. The trial has been registered on the ISRCTN registry (ISRCTN16988167).

Biomarker Selection

The BoEs chosen for analysis are based on the 9 priority smoke toxicants recommended for mandatory lowering by the World Health Organization [30], which provide an indication of exposure to toxicants present in the gas and particulate phases of tobacco smoke (Table 1). For two of these toxicants (acetaldehyde and formaldehyde), there are no reliable BoEs at present; therefore, levels of crotonaldehyde were assessed (through HMPMA) instead. The BoPHs 11-dTX B2 [31-33], 8-epi-PGF2α type III [34,35], CIMT [36-38], COHb [39-41], FeNO [35,42], FEV1%pred [43], HDL [44-46], sICAM-1 [47-49], and WBC count [50-53] were selected to cover a range of associated smoking-related diseases, including lung cancer, cardiovascular disease, and chronic obstructive pulmonary disease, as well as underlying disease processes such as oxidative stress (Table 2). Note that urinary NNAL, a biomarker for nicotine-derived nitrosamine ketone exposure, is also considered a BoPH associated with lung cancer [54,55].
Table 1. Biomarkers of exposure measured in the study.

<table>
<thead>
<tr>
<th>Biomarker of exposure</th>
<th>Associated toxicant</th>
<th>Matrix</th>
<th>Method</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td><strong>Primary end point</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Total NNAL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NNK&lt;sup&gt;b&lt;/sup&gt;</td>
<td>24-hour urine</td>
<td>LC-MS/MS&lt;sup&gt;c&lt;/sup&gt;</td>
<td>[54-57]</td>
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<tr>
<td><strong>Secondary end points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-HPMA&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Acrolein</td>
<td>24-hour urine</td>
<td>LC-MS/MS</td>
<td>[56,58]</td>
</tr>
<tr>
<td>3-OH-B[a]P&lt;sup&gt;e&lt;/sup&gt;</td>
<td>B[a]P&lt;sup&gt;f&lt;/sup&gt;</td>
<td>24-hour urine</td>
<td>LC-MS/MS</td>
<td>[59]</td>
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<tr>
<td>HMPMA&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Crotonaldehyde</td>
<td>24-hour urine</td>
<td>LC-MS/MS</td>
<td>[56,58]</td>
</tr>
<tr>
<td>MHBMA&lt;sup&gt;h&lt;/sup&gt;</td>
<td>1,3-Butadiene</td>
<td>24-hour urine</td>
<td>LC-MS/MS</td>
<td>[56,58]</td>
</tr>
<tr>
<td>S-PMA&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Benzene</td>
<td>24-hour urine</td>
<td>LC-MS/MS</td>
<td>[58]</td>
</tr>
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<td>TNeq&lt;sup&gt;j&lt;/sup&gt;</td>
<td>Nicotine</td>
<td>24-hour urine</td>
<td>LC-MS/MS</td>
<td>[56]</td>
</tr>
<tr>
<td>Total NNN&lt;sup&gt;k&lt;/sup&gt;</td>
<td>NNN</td>
<td>24-hour urine</td>
<td>LC-MS/MS</td>
<td>[56]</td>
</tr>
</tbody>
</table>

<sup>a</sup>NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol. Urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol is associated with lung cancer risk [57]; therefore, it is also considered a biomarker of potential harm for lung cancer [54,55].

<sup>b</sup>NNK: nicotine-derived nitrosamine ketone.

<sup>c</sup>LC-MS/MS: liquid chromatography with tandem mass spectrometry.

<sup>d</sup>3-HPMA: 3-hydroxypropylmercapturic acid.

<sup>e</sup>3-OH-B[a]P: 3-hydroxybenzo[a]pyrene.

<sup>f</sup>B[a]P: benzo[a]pyrene.

<sup>g</sup>HMPMA: 3-hydroxy-1-methylpropylmercapuric acid.

<sup>h</sup>MHBMA: monohydroxybutenylmercapturic acid.

<sup>i</sup>S-PMA: S-phenylmercapturic acid.

<sup>j</sup>TNeq: total nicotine equivalents (nicotine, cotinine, 3-hydroxycotinine, and their glucuronide conjugates).

<sup>k</sup>NNN: N-nitrosonornicotine.
Table 2. Biomarkers of potential harm measured in the study.

<table>
<thead>
<tr>
<th>Biomarker of potential harm</th>
<th>Associated biological process</th>
<th>Matrix</th>
<th>Method</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-Epi-PGF2α type III&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Oxidative stress</td>
<td>24-hour urine</td>
<td>LC-MS/MS&lt;sup&gt;b&lt;/sup&gt;</td>
<td>[34,35,60]</td>
</tr>
<tr>
<td>COHb&lt;sup&gt;c&lt;/sup&gt;</td>
<td>CVD&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Whole blood</td>
<td>HS GC-MS&lt;sup&gt;e&lt;/sup&gt;</td>
<td>[39-41,61]</td>
</tr>
<tr>
<td>FeNO&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Airway inflammation</td>
<td>Exhaled breath</td>
<td>Chemical field-effect transistor</td>
<td>[35,42,62]</td>
</tr>
<tr>
<td>HDL&lt;sup&gt;g&lt;/sup&gt;</td>
<td>CVD</td>
<td>Blood</td>
<td>Enzyme colorimetric</td>
<td>[28,44-46]</td>
</tr>
<tr>
<td>sICAM-1&lt;sup&gt;h&lt;/sup&gt;</td>
<td>CVD</td>
<td>Serum</td>
<td>ELISA&lt;sup&gt;i&lt;/sup&gt;</td>
<td>[28,47-49]</td>
</tr>
<tr>
<td>WBC&lt;sup&gt;j&lt;/sup&gt; count</td>
<td>Inflammation</td>
<td>Blood</td>
<td>Flow cytometry</td>
<td>[50-53,63]</td>
</tr>
<tr>
<td>Secondary end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-dehydrothromboxane B2&lt;sup&gt;k&lt;/sup&gt;</td>
<td>CVD</td>
<td>24-hour urine</td>
<td>LC-MS/MS</td>
<td>[31-33,60]</td>
</tr>
<tr>
<td>CIMT&lt;sup&gt;l&lt;/sup&gt;</td>
<td>CVD</td>
<td>Physiological measurement</td>
<td>Ultrasound</td>
<td>[36-38,64]</td>
</tr>
<tr>
<td>FEV₁%pred&lt;sup&gt;m&lt;/sup&gt;</td>
<td>COPD&lt;sup&gt;n&lt;/sup&gt;</td>
<td>Physiological measurement</td>
<td>Spirometry</td>
<td>[43,65,66]</td>
</tr>
</tbody>
</table>

<sup>a</sup>8-Epi-PGF2α type III: 8-Epi-prostaglandin F2α type III.
<sup>b</sup>LC-MS/MS: liquid chromatography with tandem mass spectrometry.
<sup>c</sup>COHb: carboxyhemoglobin.
<sup>d</sup>CVD: cardiovascular disease.
<sup>e</sup>HS GC-MS: headspace gas chromatography–mass spectrometry.
<sup>f</sup>FeNO: fractional exhaled nitric oxide.
<sup>g</sup>HDL: high-density lipoprotein.
<sup>h</sup>sICAM-1: soluble intercellular adhesion molecule-1.
<sup>i</sup>ELISA: enzyme-linked immunosorbent assay.
<sup>j</sup>WBC: white blood cell.
<sup>k</sup>11-dehydrothromboxane B2.
<sup>l</sup>CIMT: carotid intima-media thickness.
<sup>m</sup>FEV₁%pred: forced expiratory volume in 1 second as percentage of predicted.
<sup>n</sup>COPD: chronic obstructive pulmonary disease.

Study Participants

All participants were healthy adult men or women aged 19 to 55 years. For all other inclusion and exclusion criteria, refer to Textbox 1. Exclusive NP users as well as current, former, and never smokers were recruited in Sweden and Denmark, with an equal split of Swedish and Danish participants in each arm. Participants were selected either from a database of individuals who were registered at the participating clinics for the purpose of undertaking clinical studies or through study-specific advertising (eg, social media). Because of difficulties in recruiting NP users by the study clinics alone, an external recruitment agency assisted in identifying potential participants from its database and referred interested individuals to the study clinics without releasing any personal information.

For the NP user group, participants were self-reported solus users of at least three Lyft NPs (currently marketed as Velo; British American Tobacco) per day and had used these NPs for a minimum of 6 months before screening. For the current smoker group, participants were self-reported solus smokers of at least 10 factory-made cigarettes (FMCs) per day and had smoked for at least one year before screening. For the former smoker group, participants were self-reported former smokers of FMCs who quit smoking at least six months before screening. For the never smoker group, participants had never smoked (<100 cigarettes in their life and none within the 6 months before screening). Compliance with long-term smoking abstinence in the NP and former smoker groups was verified by analysis of N-(2-cyanoethyl)valine (CEVal) in erythrocytes [67]. Urinary levels of anabasine (AB) and anabatine (AT) were also used to determine short-term abstinence from smokeless tobacco use.

https://www.researchprotocols.org/2022/10/e39785
Textbox 1. Inclusion and exclusion criteria.

**Inclusion criteria**

- Participants who are healthy men or women, aged 19 to 55 years
- Participants who have a BMI of 18.5 to 30.0 kg/m\(^2\) (body weight exceeding 52 kg [men] or 45 kg [women])
- Participants who are in good health as judged by the principal investigator (PI) or the appropriately qualified designee based on medical history, physical examination, vital signs assessment, 12-lead electrocardiogram, clinical laboratory evaluations, and lung function spirometry test
- Participants who have given their written informed consent to participate in the study and have agreed to abide by the study restrictions
- Participants who can demonstrate the ability to comprehend the informed consent form, are able to communicate well with the PI or the appropriately qualified designee, can understand and comply with the requirements of the study, and can be judged suitable for the study in the opinion of the PI or the appropriately qualified designee
- Participants who will refrain from consuming alcohol within 24 hours before screening and admission
- Participants who will refrain from consuming cruciferous vegetables as well as grilled, fried, or barbequed food and avoid being in the presence of the cooking of cruciferous vegetables as well as grilled, fried, or barbequed food for 48 hours before screening and admission
- **Arm A:** exclusive nicotine pouch (NP) users
  - Participants who are regular (daily) users of at least three Lyft NPs (British American Tobacco) per day
  - Participants who have used Lyft for a minimum of 6 months before screening
  - Participants who have a urinary cotinine level ≥200 ng/mL and an exhaled carbon monoxide (eCO) level <7 ppm at screening and admission
- **Arm B:** current smokers
  - Participants who are regular solus smokers of commercially manufactured filter cigarettes
  - Participants who have smoked for at least one year before screening
  - Participants who typically smoke at least 10 cigarettes per day and have a urinary cotinine level ≥200 ng/mL and an eCO level ≥7 ppm at screening and admission
- **Arm C:** former smokers
  - Participants who are former smokers of commercially manufactured filter cigarettes who quit smoking at least six months before screening
  - Participants who have a urinary cotinine level <200 ng/mL and an eCO level <7 ppm at screening and admission
- **Arm D:** never smokers
  - Participants who have never smoked (<100 cigarettes in their life and none within the 6 months before screening)
  - Participants who have a urinary cotinine level <200 ng/mL and an eCO level <7 ppm at screening and admission

**Exclusion criteria**

- Female participants who are pregnant or breastfeeding (confirmed at screening)
- Participants who have donated ≥400 mL of blood within 90 days before screening, plasma in the 7 days before screening, and platelets in the 6 weeks before screening
- Participants who have had an acute illness (eg, upper respiratory tract or viral infection) within 4 weeks before screening as judged by the PI
- Participants who have a significant history of alcoholism or drug or chemical abuse (apart from known smoking and vaping history) within 24 months before screening as determined by the PI or the appropriately qualified designee
- Participants who have a positive urine drugs of abuse panel or breath alcohol screen result (confirmed by repeat) at screening or admission
- Participants who have serum hepatitis or are carriers of the hepatitis B surface antigen or are carriers of the hepatitis C antibody; have a positive result for the test for HIV antibodies; have symptoms of a COVID-19 infection, have a positive result in the COVID-19 test at screening or admission indicating current, active infection (Sweden only), or not providing proof of a negative COVID-19 test taken within 48 hours of admission (Denmark only)
- Participants who have used prescription or over-the-counter bronchodilator medication (eg, inhaled or oral β-adrenergic agonists) to treat a chronic condition within the 12 months before screening
- Participants who have received any medications or substances (other than nicotine) that interfere with the cyclooxygenase pathway (eg, anti-inflammatory drugs, including aspirin and ibuprofen) within 14 days before screening or are known to be strong inducers or inhibitors of cytochrome P450 enzymes within 14 days or 5 half-lives of the drug (whichever is longer) before screening
- Participants who would need to take prescription medication not approved by the PI during the period beginning with screening and ending with discharge (for female participants, hormonal contraceptives are acceptable, and for all participants, painkillers [eg, paracetamol] are permitted)
• Participants who are unwilling or unable to comply with the study requirements
• Employees and immediate relatives of the tobacco industry or the clinical site
• Participants who have any clinically relevant abnormal findings on the physical examination, medical history, electrocardiogram, lung function tests, or clinical laboratory panel, unless deemed not clinically significant by the PI or the appropriately qualified designee
• Participants who have been diagnosed with a significant history of urticaria or asthma (childhood asthma is acceptable)
• Participants who have, or who have a history of, any clinically significant neurological, gastrointestinal, renal (including urinary tract infection or nephrolithiasis), hepatic, cardiovascular, psychiatric, respiratory, metabolic, endocrine, hematological, or other major disorder that, in the opinion of the PI or the appropriately qualified designee, would jeopardize the safety of the participant or have an impact on the validity of the study results
• Participants who have previously been diagnosed with any form of malignancy or carcinoma in situ
• Participants who are currently participating in another clinical trial (including follow-up)
• Participants who, in the opinion of the PI or the appropriately qualified designee, should not participate in this study
• Arm A: exclusive NP users
  • Participants who have used any form of tobacco or nicotine-containing product, other than the Lyft NP products, within 6 months before screening
• Arm B: current smokers
  • Participants who are self-reported noninhalers (smokers who draw smoke from the cigarette into the mouth and throat but who do not inhale)
• Arms C and D: former and never smokers
  • Participants who have used any form of tobacco or nicotine-containing product within the 6 months before screening

Investigational Products
No investigational products were provided; instead, participants were required to bring their own supply of NPs or cigarettes for use during the study confinement period. However, all participants recruited to the NP group were self-reported solus users of Lyft NPs; those recruited to the current smoker group could be smokers of any brand of FMCs.

Study Procedures
Potential participants were invited to attend the clinic to assess study eligibility. They received verbal and written information about the study and were asked to sign the informed consent form before undergoing any procedures. Screening consisted of physical, oral, and vital signs examinations, as well as routine laboratory testing. Tests for alcohol and drug consumption as well as pregnancy (women only) were also conducted, and extent of nicotine use and smoking status were determined through a questionnaire.

Individuals deemed eligible based on the screening assessments were invited back to the clinic for admission into the study within 7 days of screening. They were asked to bring with them a sufficient supply of their usual NPs (Lyft brand) or usual cigarettes to last the whole screening and confinement period. In addition, NP users were asked to bring excess pouches to enable the analysis of unused pouches for nicotine content. Those who successfully completed the admission assessments (Table 3) were enrolled in the study (day 1) and given a unique study number. Participant data were collected on a paper case report form (CRF) or entered directly on an electronic case report form (eCRF). After enrollment, participants began a period of 24-hour urine collection and were confined to the clinic during this time. The remaining study assessments, including blood sampling and physiological assessments, were performed during the remainder of the confinement period before discharge on day 2 (Table 3). During the confinement period, participants were requested to use their NPs or cigarettes as they would normally, except where product use might interfere with on-study assessments. This approach facilitated the measurement of short-term BoEs that reflected the participant’s product use outside the clinic. In the case of NP users, pouches were collected after use for assessment of residual nicotine content. On 3 random occasions, participants in the NP group were asked to record the duration of pouch use to the nearest minute. They commenced timing upon placing the pouch under the lip and ended timing on removal of the pouch. Participants were discharged from the clinic on day 2 after completion of both the 24-hour urine collection period and study and discharge assessments. No later than 1 week after discharge, a poststudy follow-up was performed by telephone call to collect information on the status of any ongoing adverse events (AEs) at discharge and any new AEs experienced after discharge.
<table>
<thead>
<tr>
<th>Assessment</th>
<th>Screening</th>
<th>Admission (day 1)</th>
<th>On study (days 1-2)</th>
<th>Discharge (day 2)</th>
<th>Poststudy follow-up&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants are free to use NP&lt;sup&gt;b&lt;/sup&gt; or smoke as usual&lt;sup&gt;c&lt;/sup&gt;</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Participants collect used NPs&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Unused pouch collection</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Informed consent</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Inclusion and exclusion criteria</td>
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<td></td>
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<td></td>
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<td>Sociodemographic data</td>
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<td></td>
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<tr>
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<td>Prior and concomitant medications</td>
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<td>✓</td>
<td>✓</td>
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<td>Tobacco and nicotine use history questionnaire</td>
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<td></td>
</tr>
<tr>
<td>Pregnancy test (urine and serum)&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>✓</td>
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<tr>
<td>COVID-19 test (Sweden only)</td>
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<tr>
<td>Height, weight, BMI, and waist circumference</td>
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<tr>
<td>Vital signs&lt;sup&gt;f&lt;/sup&gt;</td>
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<td>✓</td>
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<tr>
<td>12-lead ECG&lt;sup&gt;g&lt;/sup&gt;</td>
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<td>Physical examination&lt;sup&gt;h&lt;/sup&gt;</td>
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<td>Urinary cotinine screen (dipstick)</td>
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<td>Urine drugs of abuse panel and alcohol screen&lt;sup&gt;i&lt;/sup&gt;</td>
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<tr>
<td>Serum biochemistry and hematology</td>
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<td>Urinalysis</td>
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<tr>
<td>Virology (hepatitis B and C and HIV)</td>
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<td></td>
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<tr>
<td>Exhaled carbon monoxide measurement&lt;sup&gt;j&lt;/sup&gt;</td>
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<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>Spirometry (without bronchodilator)&lt;sup&gt;k&lt;/sup&gt;</td>
<td></td>
<td></td>
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<tr>
<td>FeNO&lt;sup&gt;l&lt;/sup&gt; measurement&lt;sup&gt;m&lt;/sup&gt;</td>
<td></td>
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<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>24-hour urine collection</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Blood sampling for biomarker analysis&lt;sup&gt;n&lt;/sup&gt;</td>
<td></td>
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<td>Carotid intima-media thickness assessment</td>
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<td>Quality-of-life questionnaire</td>
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<td>Oral health assessment</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

<sup>a</sup>Within 7 days of discharge.

<sup>b</sup>NP: nicotine pouch.

<sup>c</sup>At any time, unless it would interfere with study assessments.

<sup>d</sup>All pouches used during confinement collected from participants in arm A commencing just before the start of 24-hour urine collection.

<sup>e</sup>Urine pregnancy test only at admission.

<sup>f</sup>Includes pulse rate, systolic and diastolic blood pressure, respiratory rate, and tympanic temperature.

<sup>g</sup>ECG: electrocardiogram.

<sup>h</sup>Full physical examination at screening; symptom-driven physical examination at admission and discharge, if deemed necessary.

<sup>i</sup>By breath test (alcometer).

<sup>j</sup>No food, smoking, or nicotine pouch use within 30 minutes before assessment.

<sup>k</sup>No food within 2 hours before assessment; no smoking or nicotine pouch use within 1 hour before assessment.

<sup>l</sup>FeNO: fractional exhaled nitric oxide.

<sup>m</sup>No food or drink within 1 hour before assessment; no smoking or nicotine pouch use within 30 minutes before assessment.
Blood sampling for the following biomarker analysis: N-(2-cyanoethyl)valine, carboxyhemoglobin (drawn between 6 PM and 8 PM), lipid panel (for high-density lipoprotein analysis), soluble intercellular adhesion molecule-1, and white blood cell count.

Reporting begins at provision of informed consent.

At any point, participants were able to withdraw from the study for any reason, or they may have been withdrawn at the discretion of the principal investigator (PI) or study sponsor (e.g., for health reasons or protocol deviations). The reason for premature discontinuation would be clearly documented in the participant’s eCRF. The PI could suspend or terminate the study for any reason after consultation with the sponsor; the sponsor could also suspend or terminate the study for any reason. If the study was terminated, the reasons would be fully documented.

Study Assessments

Overview

Routine clinical laboratory testing was conducted at screening to exclude individuals with significant medical conditions. Urine collection began on day 1, immediately after enrollment; all urine voided was pooled at the end of the 24-hour period and mixed before analyses. Blood samples were obtained on days 1 and 2 through direct venipuncture or a cannula inserted in a forearm vein. The blood sample for COHb analysis was drawn between 6 PM and 8 PM. A maximum of 100 mL was drawn and used for both laboratory tests and biomarker evaluations. Physiological assessments were performed on days 1 and 2 before discharge.

Compliance

For participants in the NP and former smoker groups, compliance with long-term abstinence from smoking before the study was assessed by measurement of CEVal in erythrocytes derived from 5 mL of whole blood [68]. In addition, short-term abstinence from smokeless tobacco use was assessed by measurement of urinary AB and AT. CEVal, AB, and AT were measured at Analytisch-Biologisches Forschungslabor (ABF) in Munich, Germany. AB and AT were analyzed by LC-MS/MS as follows. In brief, 60 µL deuterated internal standard (IS) solutions (AB-D4 and AT-D4, 12 ng each) and 900 µL formic acid were added to 0.6 mL urine and the mixture subjected to solid phase extraction on Oasis MCX cartridges (60 mg, 3 mL; Waters). After washing with 1.8 mL 0.5% formic acid, 3.2 mL water, 1.8 mL methanol, and 1.8 mL acetonitrile/methanol (6:4, volume:volume), and elution with 1.2 mL 2% aqueous ammonium hydroxide/59% acetonitrile/39% methanol, evaporation of the eluate, and reconstitution with 100 µL 10 mM aqueous ammonium acetate/acetonitrile (9:1, volume:volume), 10 µL was injected into an LC-MS/MS system (HP 1100 HPLC [Agilent Technologies] coupled to an API 4000 [Sciex]). Chromatography was conducted with a Gemini C18 (2) column (150x3 mm, 3 µm particle size; Phenomenex) by applying a gradient consisting of 10 mM aqueous ammonium acetate (A) and acetonitrile (B) under the following conditions: 0.5 mL/minute, 50 °C; 0 to 3 minutes: 10% to 75% B; 3 to 4 minutes: 75% B; 4 to 4.1 minutes: 75% to 10% B; and 4.1 to 9 minutes: 10% B. Mass spectrometric analysis was conducted in positive electrospray ionization mode using multiple reaction monitoring. Mass-to-charge ratios (m/z) for quantifier/qualifier transitions: AB: 163→80/163→92, AB-D4: 167→84/–, AT: 161→144/161→107, and AT-D4: 165→148/–. Limit of detection and lower limit of quantification for AB and AT in urine were 0.13/0.39 ng/mL and 0.08/0.24 ng/mL, respectively.

Measuring BoEs

Total NNAL [56], total nicotine equivalents [56], monohydroxybutenylmercapturic acid [56,58], HMPMA [56,58], 3-hydroxypropylmercapturic acid [56,58], total N-nitrosomornicotine [56], S-phenylmercapturic acid [58], and 3-hydroxybenzo[a]pyrene [59] in urine were analyzed by ABF using validated LC-MS/MS methods as previously described.

Measuring BoPHs

HDL was measured at Nordic Bioscience (Herlev, Denmark) and Clinical Chemistry and Pharmacology laboratory at Uppsala University Hospital in Uppsala, Sweden, using Advia Chemistry System–Direct HDL. Cholesterol (Siemens Healthcare) and Cobas Pro (Roche Diagnostics International), in accordance with the manufacturer’s protocol, respectively. Total WBC count was measured at Sanos Clinic (Herlev, Denmark) and Clinical Chemistry and Pharmacology laboratory (Uppsala University Hospital, Uppsala, Sweden) using the XN-550 and XN-20 systems (Sysmex), respectively.

Urinary 8-epi-PGF2β type III and 11-dTX B2 measurements were carried out at ABF as previously described [60]. Plasma sICAM-1 was measured at Celerion (Zurich, Switzerland) by an enzyme-linked immunosorbent assay kit (DuoSet; R&D Systems).

COHb analysis was carried out at ABF by headspace gas chromatography–mass spectrometry as previously described [61], with modifications. In brief, 100 µL of whole blood was spiked with 50 µL of IS solution (saturated whole blood containing 13COHb) and 1.4 mL of water. Carbon monoxide was released with the addition of 200 µL of potassium hexacyanoferrate solution 200 g/L at 55 °C for 30 minutes. Next, 1 mL of the head space was injected into a model 6890 gas chromatograph interfaced to a model 5973 mass selective detector (Agilent Technologies) using a multipurpose autosampler (Gerstel). Chromatographic separation was conducted on an Rtx-Msieve 5A porous layer open tubular capillary column (30 m x 0.32 mm inner diameter, 30 µm film thickness; Restek). The injector temperature was set to 150 °C with a split of 9:1 and a constant helium flow of 1.9 mL/minute. An isothermal temperature program (45 °C) was applied for chromatographic separation. Mass spectrometry detection was performed in the selected ion monitoring mode with electron impact ionization. The transfer line temperature was set to 280 °C with a source temperature of 230 °C and a quadrupole temperature of 150 °C. The mass fragment m/z 28 (IS: 29) was used for quantification, with m/z 12 (IS: 13) as qualifier.

For CIMT, ultrasound assessment was performed on a 10-mm section of the distal portion of the common carotid artery, on both sides of the neck, at least 5 mm from the carotid bulb. The mean, SD, and maximum thickness of the intima-media were...
recorded using the Acuson P500 Ultrasound System (Siemens Healthcare).

FEV₁ %pred was measured by spirometry assessment (without a bronchodilator) using the EasyOne Pro (Sweden) or Easy on-PC (Denmark) spirometers (NDD Medical Technologies) in accordance with the procedures outlined by the American Thoracic Society and European Respiratory Society [65]; values were standardized to predictive values of the Global Lung Function Initiative [66]. Participants were not allowed to eat for 2 hours and 1 hour, or to use NPs or smoke for 1 hour and 30 minutes, before spirometry and FeNO assessments, respectively. FeNO was measured using the Vivatmo Pro device (Bosch Healthcare Solutions).

**Other Assessments**

Oral health was assessed with the Oral Health Assessment Tool [69,70]. Quality of life was assessed with the 36-Item Short Form Health Survey questionnaire (RAND Corporation) [71].

**Nicotine Content in Used NPs**

Unused NPs brought by the participants for nicotine content analysis were stored at 2 °C to 8 °C. NPs used during the confinement period were collected into a single container and stored at 2 °C to 8 °C until analysis. The NPs were analyzed for nicotine content by gas chromatography with flame ionization detector at Labstat International Inc in Kitchener, Ontario, Canada. In brief, 3 unused pouches (approximately 2 g) or all of the participants’ used pouches were cut in half, and both the contents and the pouch material were added to an extraction vessel. Next, 5 mL of 2N sodium hydroxide was added to the extraction vessel, which was subsequently sealed and allowed to stand for 15 minutes. Subsequently, 50 mL of an extraction solution of 10 mL of quinoline primary stock (10 g of quinoline accurately weighed into a 250-mL volumetric flask and diluted to volume with methyl t-butyl ether) diluted to volume with methyl t-butyl ether was added to the extraction vessel, which was then sealed. The extraction vessel was shaken in a linear shaker in a horizontal position for 2 hours, after which it was placed in the dark in a vertical position to allow the phases to separate (maximum 2 hours). The organic phase (top layer) was then transferred to an amber autosampler vial.

**Safety**

Participant safety during the study was monitored by physical examination, vital signs, 12-lead electrocardiogram, and laboratory assessments, including hematology, virology, biochemistry, and urinalysis. Any AEs or serious AEs were monitored throughout the confinement period and by telephone follow-up up to 1 week after discharge. If the study was stopped because of an AE, it would not be restarted without consultation with the study ethics committee.

All AEs were recorded on the eCRF, coded in accordance with the latest version of the Medical Dictionary for Regulatory Activities, and tabulated by system organ class and preferred term. Severity was classified as mild (does not cause significant discomfort or change in activities of daily living; symptoms are easily tolerated), moderate (causes inconvenience or concern to the participant; interferes with activities of daily living but such activities may be continued), or severe (significantly interferes with activities of daily living to the point where they cannot be continued, or the participant is incapacitated). Numbers and percentages of participants reporting at least one AE, one serious AE, or an AE leading to withdrawal, as well as numbers and percentages of participants with AEs by severity were reported.

Participants who developed an AE at any time during the study, including the period between discharge and follow-up, were followed until assessments had returned to baseline, or the PI had determined that these events were no longer clinically significant. Provided there were no AEs that required further attention, the participant’s involvement in the study was complete. The ethics committee was informed of study completion within 90 days of the last participant’s final study procedures.

**Statistical Analysis**

In the absence of any NP biomarker data, the sample size was based on data from former and current smokers for sICAM-1, which shows the most variability in values in the literature. Assuming a ratio of mean values between NP users and smokers of 0.847 and a coefficient of variation of 27.1% to 32.8% based on data from Haswell et al [72], PROC POWER in SAS software (version 9.4; SAS Institute) was used to calculate that 84 to 120 participants would be the minimum needed to demonstrate a statistically significant difference with β=.2 and α=.05. The split between NP users and current smokers was not planned to be equal; therefore, a minimum sample size of 120 was fixed for the 2 groups combined. To allow for attrition and noncompliant NP users, 100 participants was the target to be recruited to the NP user group, 40 to the current smoker group (because the values are less variable and better described in the literature), and 40 to each of the former and never smoker groups to characterize biomarker levels in these groups. If withdrawal from the NP user group led to a substantial drop in sample size, new participants could be recruited to ensure that minimum values were met.

**Data Analysis**

The data were analyzed using SAS version 9.4. For continuous variables, the number of participants, mean, SD, median, minimum, and maximum were tabulated by study arm and overall. Categorical variable frequencies (number and percentages) were tabulated by study arm.

The group means of each of the primary end points were compared between participants who were solus users of Lyft NP products (arm A) and participants who were solus conventional cigarette smokers (arm B) in both the per-protocol population and the CEVal-, AB-, and AT-compliant populations. This was performed using a multiple linear regression model with the respective biomarker (Yᵢ) as the dependent variable and the arm (X₁) as the independent variable. The variables age (X₂), sex (X₃), and site (X₄) were added to the model in a stepwise manner and kept in the final model if they showed significance on an α level of .05. A final model for each biomarker (primary end point) was estimated; for example, the final model could differ among the end points because of the
steepwise approach. If the assumption of the model was not valid (normally distributed residual data), then the biomarker data were log-transformed, that is, log(Yj). If the data were log-transformed and the residuals remained not normally distributed, the Mann-Whitney U test was used to ensure an accurate testing method. To adjust for multiple testing for the primary end points, Bonferroni correction was applied. The α level was divided by 7 (7 primary end points): \(0.05/7 = 0.007143\). Because of the adjustments, the 99.286% CIs for the estimated least square means were presented. The same approach was applied for the secondary end points as previously described for the primary end points but without Bonferroni adjustment.

Data Management
The protocol for data management is described in full in a data management plan, which was finalized before any data were collected. Completeness of the participants’ records, accuracy of recording on the eCRFs, adherence to both the study protocol and good practice guidelines, and progress of enrollment were checked throughout the study by an independent clinical research associate. The eCRFs served as the source documents for reviewing data collection procedures.

Data that were initially collected on paper documents were entered in the electronic data capture system by staff at each clinical site. Data entry underwent quality control checks, and any discrepancies in the database were resolved. After all data validation steps, the PI or designee electronically signed the completed electronic data before database lock. All primary sources and copies of data generated by each study site (eg, data sheets, CRFs, electronic records, correspondence, laboratory records, and photographs) required for construction and evaluation of the study report will be retained in the archives of the 2 study sites for 25 years after study completion.

Results
The results of this study were received in mid-2022 and will be published in late 2022 to early 2023.

Discussion
Overview
NPs, a modern oral nicotine product, have been commercially available in a number of countries since the mid-2010s. Recent surveys of retail sales [17] and product use [16] show that NPs are gaining popularity in the United States, and some authors have suggested that they may form part of a THR approach [23]. To date, however, there are few data available on these relatively new products [14,15,21,22,73-78].

In terms of use and appearance, NPs are very similar to Swedish snus, an oral smokeless tobacco product that has been traditionally used in Scandinavia for more than 100 years. Although overall tobacco product use in Sweden is comparable with that in the rest of Europe, smoking-associated deaths are much lower because most tobacco consumers use snus [19]. This has been termed the “Swedish experience” [79], and the lower risks of harm from snus compared with combustible cigarettes have been recognized by the US Food and Drug Administration [20]. Of note, a recent analysis of the toxicant content of NPs compared with that of snus has demonstrated that most of the measured HPHCs (22 of 25) are unquantifiable in NPs, whereas only approximately half of the measured HPHCs (11 of 23) are unquantifiable in Swedish snus [15], raising the possibility that, similar to Swedish snus, NPs may have reduced health risks compared with cigarette smoking. To determine whether the low number and levels of HPHCs in NPs translate to a reduction in toxicant exposure and potential risk for users compared with cigarette smokers, this cross-sectional study compared BoEs and BoPHs between individuals who have been exclusively using NPs for 6 months and current smokers. The results from this study will provide an indication of the exposure of NP users to tobacco and tobacco smoke toxicants arising from NP use and relative levels compared with current, former, and never smokers. In addition, this study will provide an indication of the real-world levels of BoPHs in regular NP users compared with current, former, and never smokers. Furthermore, the study will generally add to the scientific characterization of these relatively new nicotine products with additional subjective, physiological, and behavioral data.

Biomarker studies are frequently used to evaluate exposure to environmental and occupational toxicants and have recently been applied to assess the effects of switching from smoking combustible cigarettes to using alternative nicotine and tobacco products. Reductions in several BoEs and BoPHs have been documented when smokers switch to using e-cigarettes [27,80,81], tobacco heating products [25,26,28,56], and NRT [27], helping to establish the relative health risks of these products. This study will continue to build on data from these other tobacco and nicotine product categories. To the best of our knowledge, this is the first time that BoEs and BoPHs have been measured in NP users, providing information on 17 BoEs and BoPHs in NP users in comparison with current, former, and never smokers. The findings should add to our overall knowledge on NPs by providing the relative levels of exposure to tobacco toxicants as well as an insight into the potential risk from use of these modern tobacco-free NP products compared with cigarette smoking.

Strengths
This study includes some strengths. First, participants who self-reported as solus NP users and former smokers were confirmed as not having used combustible tobacco products through CEVal assessment [28,67]. Furthermore, as snus use is popular in Scandinavia, particularly in Sweden, an attempt was made to confirm that the NP users and former smokers did not use snus. Although snus is recognized as a reduced risk product [20], it has been shown to contain a higher number of toxicants than NPs [15]. Therefore, snus use could have potentially affected BoEs and BoPHs if participants in the NP group used snus but failed to report this, which was a possibility given the similarities between use and physical characteristics of NPs and snus. Hence, a further compliance assessment of AB and AT was included because CEVal, a biomarker for acrylonitrile exposure, cannot detect snus use. These alkaloids have been suggested as biomarkers to detect tobacco consumption during NRT use [82,83] and were suggested as potential compliance biomarker candidates to detect short-term...
smokeless tobacco use during this study by experts from a bioanalytical laboratory, although an assessment of these alkaloids in NPs has not been made. A second strength of this study is that it measured BoEs and BoPHs in individuals who are regular users of NPs through their own choice, rather than in individuals who are asked to try the product for a few days [27,81], and should therefore provide information specific to this user group. Third, this cross-sectional approach recruited regular users of NPs, an approach which may better reflect real-world NP use compared with an approach that asks smokers to switch to NPs as part of a longitudinal design. Fourth, this cross-sectional approach limits the chance of participant withdrawals. Fifth, because of the cross-sectional study design, the sample size of 220 is considerably higher than that in some previous product-switching trials [80]. Finally, an additional strength of the study is that the confinement period allowed 24-hour urine samples to be collected (as opposed to spot urine collection) and blood samples to be collected at consistent times to help minimize variability in the biomarker data.

Limitations
The study also includes some limitations. First, the cross-sectional study design enables the study population to be assessed at a single point in time, but unlike in longitudinal studies, in which the same individuals are assessed multiple times over a longer study period (eg, up to 12 months [26,28]), information about changes over time will not be obtained. On the basis of the results from longitudinal studies, 6 months of NP use was deemed sufficient for changes in BoEs and particularly in BoPHs to have occurred in this study [28]. Second, the cross-sectional design approach means that no baseline assessments were made. Therefore, this may lead to greater variability in the biomarker results because comparisons were made between different populations as opposed to investigating biomarker-level changes within populations as per a longitudinal study approach. Third, some of the BoPHs assessed in this study (eg, WBCs, HDL, and sICAM-1) are not specific biomarkers of smoking-related disorders and may also be influenced by environmental exposure and lifestyle choices such as diet and exercise [84]. Finally, although compliance measures were implemented, these have limitations in terms of their sensitivity to detect tobacco cigarette and smokeless tobacco use, and they cannot detect use of other nicotine products such as e-cigarettes. In addition, participants self-reported product use (quantity and length of time that they have, or have not, been using the products), which cannot be corroborated fully with the current compliance and screening procedures (ie, eCO). Therefore, we cannot guarantee that current and past product use requirements will be fully met. This information is likely to be controlled better in a longitudinal study in which there is a defined switching period and regular contact with the participants.

Data Availability
British American Tobacco is committed to the responsible sharing of data with the wider research community. Data access is administered for this study through an internal data-sharing committee on reasonable request after completion of a data-sharing request form and, if applicable, a data access agreement. Requests for data sharing in the first instance should be emailed to the corresponding author.

Authors' Contributions
DA, LEH, MM, NG, JT, and GH contributed to the design of the study, JT and FM provided statistical expertise, including the sample size calculation and statistical analysis plan review. DA led the study, supported by JF. DA wrote the first draft of the manuscript. All authors read, edited, and approved the final manuscript.

Conflicts of Interest
British American Tobacco (BAT) was the sponsor of this study and provided funding. All authors were employees of BAT at the point of manuscript submission, except for JT who was a BAT employee during the design of the study and throughout the clinical phase. BAT is a company that manufactures tobacco and nicotine products.

References


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Abbreviations

11-dTX B2: 11-dehydrothromboxane B2
8-Epi-PGF2α type III: 8-Epi-prostaglandin F2α type III
AB: anabasine
ABF: Analytisch-Biologisches Forschungslabor
AE: adverse event
AT: anatabine
BAT: British American Tobacco
BoE: biomarker of exposure
BoPH: biomarker of potential harm
CEVal: N-(2-cyanoethyl)valine
COHb: carboxyhemoglobin
CRF: case report form
eCO: exhaled carbon monoxide
eCRF: electronic case report form
FeNO: fractional exhaled nitric oxide
FEV1%pred: forced expiratory volume in 1 second as percentage of predicted
FMC: factory-made cigarette
HDL: high-density lipoprotein
HMPMA: 3-hydroxy-1-methylpropylmercapuric acid
HPHC: harmful and potentially harmful constituent
IS: internal standard
LC-MS/MS: liquid chromatography with tandem mass spectrometry
m/z: mass-to-charge ratio
NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NP: nicotine pouch
NRT: nicotine replacement therapy
PI: principal investigator
sICAM-1: soluble intercellular adhesion molecule-1
THR: tobacco harm reduction
WBC: white blood cell

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Soil-Transmitted Helminth Infection in Malaysia: Protocol for a Scoping Review

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Abstract

Background: Soil-transmitted helminth (STH) infection is 1 of the 20 notable neglected tropical diseases according to the Centers for Disease Control and Prevention and World Health Organization. In 2010, it is estimated that 1.73 billion people are infected with STH globally, of which 70% of cases occur in Asia. To date, there is a dearth of published literature on the prevalence of STH infection throughout Malaysia.

Objective: The objectives of this study are to review research activity on STH infection in Malaysia, to estimate the prevalence of STH infection among Malaysians, and to identify significant risk factors associated with the infection. This review aims to provide the current state of evidence pertaining to STH infections, focusing on the main areas, limitations, and biases of research and mapping out the morbidity distribution of the diseases and their causative agents, and to identify significant risk factors for preventive measures.

Methods: We will conduct a scoping review based on the 6-stage structured framework developed by Arksey and O’Malley. A comprehensive search strategy focusing on STH infection will be executed using electronic databases (Scopus, PubMed, Web of Science, and Embase). A systematic approach for searching, screening, reviewing, and data extraction will be applied based on the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines. Mendeley software and Microsoft Excel will be used to manage the references and to remove duplicates. Relevant data from selected articles will be extracted using a standardized data extraction form.

Results: A total of 164 potential manuscripts were retrieved. Data extraction is currently in progress and completion is expected by the end of 2022.

Conclusions: Our scoping review will summarize the current state of research in this field and provide comprehensive information regarding STH infections in Malaysia for future reference.

Trial Registration: National Medical Research Register NMRR-20-2889-54348; https://nmrr.gov.my/research-directory/e52ea778-d31c-4eb4-9163-a45bb3680bbf
International Registered Report Identifier (IRRID): DERR1-10.2196/36077

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KEYWORDS

STH; soil-transmitted helminth; PRISMA-ScR; Malaysia; helminth; tropical disease
Introduction

Soil-transmitted helminth (STH) infection is among the most common diseases worldwide, primarily affecting those living in poor tropical and subtropical regions, especially households with inadequate sanitation facilities [1]. STH contamination can occur due to high soil moisture content in cramped living quarters, shared toilets, uncovered latrine pits, unhygienic practices, and pet (cat and dog) ownership, which increases the risk for zoonotic transmission [2]. STHs are nematodes including roundworms (Ascaris lumbricoides), whipworm (Trichuris trichiura), and anthropophilic hookworms (Necator americanus and Ancylostoma duodenale). STHs can infect humans through contact with parasitic eggs or larvae in soil [3].

According to the World Health Organization (WHO; 2005), STHs and schistosomes caused nearly 1.5 billion infections worldwide up to 2015. STH—namely, Ascaris spp, Trichuris spp, and hookworms—can affect physical and mental development in children, also contributing to poor nutritional status in the community [4,5]. Although it is known that hookworms can cause iron deficiency and protein malnutrition due to intestinal blood loss, STH infection does not necessarily cause death if early intervention and treatment are taken. STH infection can also cause anemia, where the intensity of hookworm infection is correlated to the depletion of host iron stores [6]. The prevalence of STH infections worldwide is overwhelming. According to Pullan et al (2014) [7], more than 50% of STH cases were recorded in South Asia and sub-Saharan Africa, with prevalence rates of A lumbricoides, T trichiura, and hookworm reported to be 819 million, 464 million, and 439 million, respectively. STH infection is very common in South Asia due to this region having tropical and moist climate areas, where these worms are endemic. It can also occur in several underdeveloped and developing countries in South Asia, which still do not have adequate clean water supply and do not have systematic sanitation infrastructure in some regions [8]. The highest prevalence of STH infections in South Asia was documented in India (21%) and China (18%), with the continent of Asia contributing to 67% of the global prevalence of STH infections [9]. Thirty-nine studies in India showed that A lumbricoides infection was the most prevalent parasite, with more than 50% prevalence reported in several states [10]. Conversely, the survey data of STH infection in China showed that the prevalence of STH infection in China considerably decreased from 2005 onward [11].

Although Malaysia is a developing country with rapid growth in socioeconomic and infrastructure in both urban and rural areas, the government is still grappling with the problem of STH infections, especially among very rural populations and indigenous communities. Many STH studies conducted in Malaysia focused on the indigenous people of Malaysia. Even though the government had built numerous resettlement areas for these indigenous tribes, they are still heavily dependent on the forest for their daily needs and sustenance, thereby retaining a high risk for intestinal parasitism [12]. A study by Sinniah et al (2014) [13] showed that STH infection was more common among those living in rural areas (32.3%), followed by urban squatters (20.6%) and those residing in flats or apartments (5.4%). The prevalence rate of STH infection among urban settlers, residents, and those living in flats showed a dramatic decrease, whereas STH infection prevalence in indigenous communities was over 90% previously (1970s) and is currently fluctuating below 70% (2000-2013) [13]. Another study revealed that the most prevalent types of STH in Malaysia are T trichiura (2.1%-98.2%), followed by A lumbricoides (4.6%-86.7%) and hookworm (0%-37%).

There are many recommendation documents published by the WHO to eliminate STH as a public health problem. The strategic plan for STH elimination included routine control activities in low-transmission areas, intensive control of STH infection in areas of high transmission (WHO 2001), and the delivery of anthelmintic treatment in school-age children to reduce worm loads (WHO 2012) [14]. In 1974, Malaysia launched a worm control program aimed at controlling STH infection [15]. The program targeted schoolchildren aged 7-15 years; a total of 1486 schools with more than 220,000 pupils were involved in this program. The national mass deworming program in Malaysia, which used a single dose of pyrantel pamoate once or twice per year, was discontinued in 1983 due to the drug’s low effectiveness against Trichuris and hookworm. Albendazole tablets are still given to children in some rural areas. The government also attempted to improve sanitation in rural households by providing pour-flush latrines and safe drinking water to diminish STH infection [16].

This review aims to provide the current state of evidence pertaining to STH infections, focusing on the main areas, limitations, and biases of research and mapping out the morbidity distribution of the diseases and their causative agents, and to identify significant risk factors for preventive measures.

Methods

Protocol Design

This study protocol is registered at the National Medical Research Register (NMRR-20-2889-54348) [17]. This scoping review will adhere to the 6-stage structured framework proposed by Arksey and O’Malley [18], which was further developed by Levac et al [19] and the Joanna Briggs Institute [20], where it is recommended that the review process be structured in at least 5 stages. These stages include (1) identifying the research question; (2) identifying relevant studies; (3) selecting studies; (4) charting the data; and (5) collating, summarizing, and reporting the results. Although stage 6 (consulting with relevant stakeholders) would be beneficial in terms of getting insights and updates on the present circumstances of STH infection in Malaysia, this scoping review will not include this stage due to time and budget constraints. However, experts with scoping review–writing experience and statisticians (for data analysis) may be consulted throughout the preparation of this scoping review. This protocol was not submitted to PROSPERO (International Prospective Register of Systematic Reviews), as they do not currently accept scoping review protocols. The report will follow the 22 items in the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) [21] guidelines. Clinical trial
Stage 1: Identifying the Research Questions

An exploratory review of the literature on STH infection in Malaysia was conducted to refine the scope of this protocol and develop the research questions. Based on this review and through consultation with the research team, the following research questions were identified:

1. What types of research activity on STH infection have been carried out in Malaysia?
2. What is the prevalence of STH infection in Malaysia?
3. What are the significant risk factors associated with STH infection in Malaysia?

Stage 2: Identifying Relevant Studies

A comprehensive search strategy will be executed by a team of investigators. Website sources will include published scientific journals, grey literature, and annual reports as below:

1. Electronic databases including PubMed, Scopus, Web of Science, and Embase
2. Relevant research websites such as ClinicalTrials.gov, the WHO, Global Atlas of Helminth Infections, Ministry of Health Malaysia, and Virtual Library Ministry of Health
3. Grey literature including website searches of universities, Google Scholar, and research institutes

A systematic approach to searching, screening, reviewing, and data extraction will be applied based on PRISMA-ScR guidelines. Titles, abstracts, and keywords will be examined for eligibility independently by 2 investigators. The proposed initial search strategy, keywords, and search terms for a search for relevant articles are attached. Medical Subject Headings (MeSH) terms were applied to assist the keyword search for related databases used (Multimedia Appendix 1). All selected search results will be downloaded and imported into Microsoft Word and Excel (Microsoft Corp) in duplicate; they will then be shared through Google Drive. Mendeley software and Microsoft Excel will be used to manage the references and to remove duplicates.

A hand search of the grey literature will be conducted through university visits and meetings with academics for further data retrieval and consultation, whenever relevant. The reference lists of publications by WHO-Western Pacific will be screened for additional sources of information.

Stage 3: Study Selection

Overview

The study selection will be based on the objectives of this review, which are (1) to identify the trend of research activity (the extent and nature of study), (2) to estimate the prevalence of STH infection, and (3) to identify significant risk factors associated with STH infection in Malaysia. We will include all original articles, either observational (cohort study, case-control study, cross-sectional study, case report, ecological report, and descriptive report) or interventional (randomized and nonrandomized). The first level for the review process consists of the screening of titles and abstracts. Investigators will independently screen the title and abstract from all retrieved citations that meet the minimal inclusion criteria. Abstracts that do not meet the scope of the study will be excluded. The second level of screening will take place once relevant abstracts are selected. The full-text review will include any articles that are considered significant and applicable to the research question. Cohen κ statistic will be applied to determine interobserver agreement and ensure consistent application of the eligibility criteria for inclusion in the review [22]. The third investigator will review any full-text article assessment that does not meet perfect agreement (κ ≤ 1), and the discordance will be resolved through discussion until full consensus is reached.

Inclusion Criteria

The following principles will be used to determine the studies that meet the criteria:

1. Studies that present evidence that was published between 2000 and 2020.
2. Studies that present evidence that was carried out in Malaysia with the Malaysian population.
3. Studies that present evidence on STH infection incidents in Malaysia.

Exclusion Criteria

Studies with the following characteristics will be excluded:

2. Studies with no evidence on STH infection incidents in Malaysia.
3. Studies published in languages other than English.

Stage 4: Charting the Data

The significant study characteristics from the articles will be extracted by a standardized data extraction framework using Google Sheets. It includes 7 sections that assist in data information extraction from the full review articles retrieved. Section 1 will provide standard bibliographical information (title, author, journal, year of publication, language, location of the study, sample size, and period of study), together with details pertaining to the specific STH involved in the study (parasite species of focus, predominant species, mixed infection, if a study was describing more than a single species of parasite, and the intensity of infection if mentioned). Sections 2 to 7 will describe the type of study, primary outcome, risk factors, treatment efficacy, laboratory investigation, and other valuable information, respectively. These sections will provide significant information about the study and facilitate data analysis (Multimedia Appendix 2). The data extraction framework will be distributed to all investigators through a link and can be easily accessed through email and mobile apps. Each investigator will be assigned articles in duplicate, and the results of the data extraction will be cross-checked with other investigators in the research team to ensure data extraction accuracy. Any aberrant findings and disagreements will be further discussed to ensure consistency and achieve consensus between investigators. A thorough discussion will be conducted whenever any questions or uncertainties arise throughout the whole data extraction process.
Stage 5: Collating, Summarizing, and Reporting the Results

Results will be retrieved and downloaded through a spreadsheet generated using Google Sheets. All relevant information will be collated into its appropriate category and will be reported according to the selection criteria. The characteristics of the outcome from the selected articles will be described based on the types of interventions, study design, settings, tools used, and the outcomes of each study. The findings of this study will summarize all data and information from the relevant articles and emphasize the scope of STH infection in Malaysia. Topics and areas that have been under-studied and may require further attention might be identified and will be highlighted in this study.

Ethical Considerations

Since the scoping review analysis seeks to synthesize information from publicly accessible publications and no primary data will be collected, formal ethical approval regarding dissemination activities is not necessary for this study.

Results

The search was performed in December 2021, in the abovementioned electronic databases; a total of 164 results were retrieved. Data extraction from all potential manuscripts will be completed by the end of 2022. Data will be summarized descriptively in tabular form including types of interventions, study design, settings, tools used, and the outcomes of each study.

Discussion

Overview

Many publications focus on the prevalence and distribution of STH infections among the indigenous population in Malaysia based on sociodemographic characteristics. There are limited publications that specify the general population, laboratory investigation, and treatment efficacy. Those studies highlighted a single issue and were not as collaborative. There were also Knowledge, Attitude, and Practice studies that emphasized risk factors and disease prevention measures; however, those studies will not be selected for data collection in this scoping review. To ensure the report’s quality and reliability, only significant findings with $P \leq 0.05$ will be included in this study.

This scoping review will determine the types of research activities that have been carried out in Malaysia, whether epidemiological, clinical, treatment efficacy, preventive measures, or others, related to the research topic. It will include all studies published between 2000 and 2020, as this time frame will provide adequate data to compare and summarize. We would like to provide further evidence on the prevalence of STH in terms of the parasite species that predominately cause the infection and the intensity of the infection. Prevalence figures provided by selected studies were calculated, considering each study’s sample size. Prevalence maps will be produced based on the geographical coordinates of the studies’ sites. Finally, we will present the significant risk factors that contribute to STH infection and discuss prevention measures taken by considering the government and private sector’s involvement toward curbing this issue. We hope that the findings of this scoping review will provide information for policy makers and strengthen policy guidelines to eradicate STH infection, as well as for researchers to further study and investigate any STH-related issue in Malaysia.

Dissemination

An article detailing the scoping review findings will be submitted to a scientific journal for publication and will be presented at relevant meetings and conferences, as well as for continuous medical education at the departmental level. The scoping review results are expected to provide a comprehensive overview of the available evidence on the prevalence of STH infection in Malaysia and to highlight areas of controversy or where evidence is lacking. It will also offer essential information to policy makers and health practitioners involved in designing, funding, and delivering evidence-based and effective strategies to prevent STH infection. The findings will also be disseminated as part of future seminars and workshops.

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Authors’ Contributions

MFMH conceived the idea, developed the research question, developed the study methods, was involved in data extraction, and contributed to the drafting and editing of the manuscript. FHA, HMH, NAL, NY, ENM, and RA aided data extraction and contributed to the drafting and editing. NAM supervised the preparation of the protocol and reviewed the manuscript. All authors have approved the final manuscript.

Conflicts of Interest

None declared.
References


Abbreviations

MeSH: Medical Subject Headings

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

STH: soil-transmitted helminth

WHO: World Health Organization