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Protocol

An Interactive Voice Response and Text Message Intervention to Improve Blood Pressure Control Among Individuals With Hypertension Receiving Care at an Urban Indian Health Organization: Protocol and Baseline Characteristics of a Pragmatic Randomized Controlled Trial

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Abstract

Background: Efficient and effective strategies for treating chronic health conditions such as hypertension are particularly needed for under-resourced clinics such as Urban Indian Health Organizations (UIHOs).

Objective: The objective of the Controlling Blood Pressure Trial is to assess the impact of an interactive voice response and text message (IVR-T) intervention compared with usual care among individuals with hypertension receiving care at a UIHO in Albuquerque, New Mexico. This manuscript presents the baseline characteristics of individuals enrolled in the trial and compares their characteristics with those in the hypertension registry who did not enroll in the trial.

Methods: A hypertension registry developed from the clinic's electronic health record was used for recruitment. Potentially eligible participants were contacted by letter and then by phone. Those who expressed interest completed an in-person baseline visit that included a baseline survey and blood pressure measurement using standardized procedures. Individuals randomized to the intervention group could opt to receive either automated text messages or automated phone calls in either English or Spanish. The messages include reminders of upcoming appointments at First Nations Community HealthSource, requests to reschedule recently missed appointments, monthly reminders to refill medications, and weekly motivational messages to encourage self-care, appointment keeping, and medication taking for hypertension. Individuals in the IVR-T arm could opt to nominate a care partner to also receive notices of upcoming and missed appointments. Individuals in the IVR-T arm were also offered a home blood pressure monitor. Follow-up visits will be conducted at 6 months and 12 months.

Results: Over a 9.5-month period from April 2017 to January 2018, 295 participants were enrolled from a recruitment list of 1497 individuals. The enrolled cohort had a mean age of 53 years, was 25.1% (74/295) American Indian or Alaska Native and 51.9% (153/295) Hispanic, and 39.0% (115/295) had a baseline blood pressure greater than or equal to 140/90 mmHg. Overall, the differences between those enrolled in the trial and patients with hypertension who were ineligible, those who could not be reached, or those who chose not to enroll were minimal. Enrolled individuals had a slightly lower blood pressure (129/77 mmHg vs 132/79 mmHg; P=.04 for systolic blood pressure and P=.01 for diastolic blood pressure), were more likely to self-pay for

their care (26% vs 10%; *P*<.001), and had a more recent primary care visit (164 days vs 231 days; *P*<.001). The enrolled cohort reported a high prevalence of poor health, low socioeconomic status, and high levels of basic material needs.

Conclusions: The Controlling Blood Pressure Trial has successfully enrolled a representative sample of individuals receiving health care at a UIHO. Trial follow-up will conclude in February 2019.

Trial Registration: ClinicalTrials.gov NCT03135405; http://clinicaltrials.gov/ct2/show/NCT03135405 (Archived by WebCite http://www.webcitation.org/76H2B4SO6)

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KEYWORDS

Indians, North American; hypertension; urban health; pragmatic clinical trial; text messages

Introduction

Background

American Indians and Alaska Natives (AI/ANs) face pervasive health disparities in comparison with other racial and ethnic groups in the United States. Although disparities in diabetes have received national attention, cardiovascular disease (CVD) remains the primary cause of mortality in AI/ANs as in other groups [1]. Interventions to prevent CVD in AI/ANs have historically focused on individuals with diabetes (eg, the Special Diabetes Program for Indians Healthy Heart Demonstration Project) [2], with few studies of interventions to prevent CVD among AI/ANs without diabetes. Successful CVD prevention for AI/ANs requires the engagement of health care systems dedicated to this population. The health care system for AI/ANs includes federally operated Indian Health Service (IHS) facilities, tribally operated facilities, and 33 Urban Indian Health Organizations (UIHOs) across the United States. All face unremitting challenges in funding and staffing that jeopardize their mission to provide culturally appropriate health care, outreach, and referral services for AI/AN. Strategies for treating chronic health conditions are particularly problematic in UIHOs. Although 71% of AI/ANs live in urban areas, UIHOs only receive 1% of the IHS budget [3,4].

Treatment of hypertension is a pillar of CVD prevention. Hypertension is the most common chronic health condition in the United States [5]. Uncontrolled hypertension increases the risk of myocardial infarction, stroke, kidney failure, and congestive heart failure [6]. Hypertension rates are high, levels of control are low, and disparities in care are evident in AI/AN populations [1,7-9]. Communication technologies that extend care to patients “where they are,” outside the clinical setting, can facilitate hypertension control [10]. Such outreach may be particularly important for AI/ANs and other vulnerable populations that face logistical and cost barriers to receiving office-based care.

Interactive Voice Response and Text Message (IVR-T) technology can be used to send targeted voice messages to landlines and voice or text messages to cell phones. IVR-T tools could improve hypertension care by sending reminders about appointments or medication refills, recalling individuals who have missed appointments, and providing educational and motivational messages [11]. Existing evidence suggests that such interventions can improve medication adherence [12-15], appointment keeping [16], and blood pressure control [14,17]. Randomized controlled trials (RCTs) of IVR-T interventions have demonstrated clinical benefit at a low marginal cost [18-21]. In resource-constrained UIHOs, IVR-T messages may substitute for costly and time-intensive personal outreach by staff members. In addition, home blood monitoring without additional support has been shown to have a modest effect of systolic blood pressure at 6 months, but little sustained effect [22,23].

Objectives

The specific aim of the Controlling Blood Pressure Trial is to assess the impact of an IVR-T intervention compared with usual care among individuals with hypertension receiving care at a UIHO in Albuquerque, New Mexico. The primary study endpoint is change in mean systolic blood pressure between baseline and 12 months. Secondary endpoints include change in diastolic blood pressure, self-reported adherence, and the proportion of missed clinic appointments between intervention and control groups.

Methods

Study Setting

This pragmatic clinical trial is taking place at First Nations Community HealthSource (FNCH), a nonprofit, urban Indian community-based health and human services organization incorporated in 1972. The health center is authorized through Title V of P.L. 94-437, and subsequent amendments, of the Indian Health Care Improvement Act to improve the health of urban Indians. FNCH has expanded its mission to serve the greater community, without losing its fundamental basis for existence, and now provides primary medical care to urban AI/ANs and other socially disadvantaged residents of the Albuquerque, New Mexico area. In 1997, the center was designated as a Federally Qualified Health Center, and it is an Accreditation Association for Ambulatory Health Care (AAAHC)-Accredited Health Center and Medical Home. Approximately 40% of FNCH clients are AI/AN; Diné (Navajo) is the most common tribal affiliation. Many other clients served by FNCH are undocumented immigrants. Housing insecurity and homelessness are common. Most clients speak either English or Spanish as their primary language. FNCH has 3 campuses in close geographic proximity in southeastern Albuquerque. The medical clinic is staffed by physicians, nurse practitioners,

and physician assistants with extensive support staff including public health nurses, diabetes educators, patient navigators, and on-site behavioral health clinicians. FNCH provides comprehensive primary medical, dental, behavioral health, and traditional healing and a range of preventive support services to address the health disparities experienced by its target population. Its mission is to provide a culturally competent, comprehensive health service delivery system integrating traditional values to enhance the physical, spiritual, emotional, and mental well-being of American Indian families and other underserved populations residing in Albuquerque and on tribal reservations.

The study team established an Advisory Council consisting of FNCH staff from pharmacy, public health nursing, and social services and 2 patients and their caregivers. The Advisory Council actively collaborated in designing the trial, including participant eligibility criteria, recruitment materials, incentives for participation, operationalization of the intervention, participant survey materials, and the timing and content of the IVR-T messages. The Advisory Council met 3 times before starting the study and has met at least twice annually during the study itself.

Eligibility and Recruitment

Consistent with principles of a pragmatic trial, study inclusion criteria are broad, to demonstrate the impact of the intervention in a "real world" setting [24]. Individuals who infrequently seek care or are nonadherent with medications are a specific target of the intervention.

Before the initiation of the trial, the study team developed a hypertension registry using information extracted from FNCH's electronic medical record, eClinicalWorks (Westborough, MA). FNCH began using eClinicalWorks in 2012. The registry was built using SAS version 9.4 (SAS Institute Inc, Cary, NC). This registry had several purposes, including characterization of the FNCH population, assessment of baseline blood pressure control, and recruitment for the randomized trial. Hypertension was identified using diagnosis codes (ICD-9 401-405; ICD-10 I10-I13, I15), orders for antihypertensive medication, and elevated blood pressures (≥140/90). We considered individuals to have hypertension if any 1 of the following criteria was met: (1) having 2 visits with a hypertension diagnosis on different days, (2) having 1 visit with a hypertension diagnosis and 1 medication order, (3) having 1 visit with a hypertension diagnosis and 1 elevated blood pressure, or (4) having 2 consecutive elevated blood pressures on different days [25]. For study recruitment, we additionally required (1) at least 2 prior visits to FNCH with blood pressure measurements, at least 1 of which took place in the 24 months before recruitment, and (2) aged 21 to 79 years at the time of recruitment. Individuals aged 80 years and above were excluded because of the need to individualize treatment targets in the elderly [6]. Clients were eligible for the study even if their hypertension was under control, with the rationale that even those with controlled hypertension at a single visit may not remain in control over time. We included patients receiving care at FNCH regardless of their racial or ethnic self-identification. Individuals who resided outside Albuquerque (such as rural Indian reservations) were eligible if they identified FNCH as their primary source of care.

Exclusion criteria include the following: another preferred site of primary care, significant impairment of vision and hearing, life-limiting illnesses such as advanced cancer, renal dialysis, receipt of home health care with blood pressure monitoring and/or assistance with administration of medications, hospice services or residence in a nursing home, dementia, pregnancy at the time of recruitment, current homelessness, no landline or cellular phone access, or inability to understand English or Spanish.

Potentially eligible participants were contacted by letter and then by phone. Those who expressed interest completed an in-person baseline visit that included the informed consent process, a baseline survey, and blood pressure measurement using standardized procedures. They were then randomized to either the IVR-T intervention or usual care.

Randomization

Individuals were randomized 1:1 to IVR-T intervention or usual care using block randomization with blocks of 4. A randomization table was generated by the study statistician (SX) using SAS software. The study coordinators were blinded to the randomization sequence.

Intervention

Since 2005, the Institute for Health Research at Kaiser Permanente Colorado has developed and managed an IVR-T system that initiates telephone calls to landlines or cellular phones and text messages to cellular phones. The system uses a commercial database to distinguish between cellular phones and landlines and to determine whether a cellular phone is text-enabled [11]. For this intervention, information from the hypertension registry and Research Electronic Data Capture (REDCap) were used to send IVR-T messages to individuals randomized to the IVR-T intervention arm. Individuals in the intervention arm could opt to receive either automated text messages or automated phone calls in either English or Spanish. The messages include reminders of upcoming appointments at FNCH; requests to reschedule recently missed appointments; monthly reminders to refill medications; and weekly motivational messages to encourage self-care, appointment keeping, and medication taking for hypertension (Table 1; Multimedia Appendix 1). The motivational messages for text or telephone were modified from existing messages in the literature [26-29] and tailored with the help of an American Indian psychologist and the FNCH Advisory Council to be culturally appropriate. Some of the messages were recorded by the participants' primary care clinician at FNCH. Individuals in the IVR-T arm could opt to nominate a care partner to also receive notices of upcoming and missed appointments. Individuals in the IVR-T arm were also offered a home blood pressure monitor. Blood pressure logs were not received or reviewed by the study team. The intervention is unblinded, although participants' FNCH clinicians were not informed by the study staff of any patient's group assignment. The protocol for IVR-T messages is shown in Table 1.

Table 1. Components of the interactive voice response and text message intervention.

Component	Description
Reminders for upcoming visits	Three days before and 1 day before each upcoming visit
"Recalls" after missed clinic visits	Recall 1 to 6 days after a missed visit
Reminders to refill medications	Monthly reminders to refill hypertension medications
Motivational adherence messages	Weekly, from the list in Multimedia Appendix 1
Inbound calling options	Direct dial options available to participants to reach scheduling staff, a member of the clinical team, or pharmacy to address urgent concerns during business hours

Study Visits

Participants complete in-person baseline, 6-month, and 12-month visits. At each visit, blood pressure measurements are collected and participants complete a survey. Blood pressure is measured in a standardized fashion during the research visits, using an Omron HEM 907XL IntelliSense Professional Digital Blood Pressure Monitor (an automated sphygmomanometer) [30]. After a 5 min waiting period, blood pressures are taken 3 times, 30 seconds apart. The average of the second and third blood pressures is used. The baseline survey can be self-administered or participants can request assistance from study coordinators. The baseline survey includes questions about general health, blood pressure treatment, adherence to blood pressure medications [31], comorbidities, perceived health competence (adapted from Smith et al [32]), depression (Patient Health Questionnaire-2) [33], discrimination (adapted from several sources [34-36]), health literacy and numeracy (adapted from Brega et al [37]), exercise and diet [38], demographics, and socioeconomic status and social needs (see Multimedia Appendix 2). The 6-month and 12- month visit surveys contain a subset of the questions from the baseline survey, with additional questions about attitudes toward the intervention. Survey answers and other study data are managed using REDCap software. Participants receive US $20 gift cards for each visit.

Baseline Variables

In addition to information from the baseline survey, we also collected demographic characteristics, hypertension characteristics, comorbidities, and geographic variables using information from the FNCH electronic health record (EHR). Race and ethnicity were categorized using the following hierarchical categories: AI/AN, Hispanic, non-Hispanic white, non-Hispanic African American, non-Hispanic other, and missing. Individuals with missing ethnicity information were assumed to be non-Hispanic.

Comorbidities such as diabetes, cardiovascular disease, and depression were defined as the presence of at least one ICD-9 or ICD-10 diagnosis code within the previous 2 years (see Multimedia Appendix 3). Chronic kidney disease was defined as being present if the most recent estimated glomerular filtration rate in the previous 2 years was less than 60 mL/min/1.73m^2 using the CKD-EPI estimating equation [39].

Ever homeless was defined using EHR visit types specific to homeless services and include information on visits since the inception of the FNCH EHR in 2012. The multiple insurance payers for FNCH clients were categorized into 5 groups (commercial, IHS, Medicaid, Medicare, and self-pay). We then defined the dominant payer by determining which insurance category predominated over the previous 2 years. When 2 encounters had different insurance categories, we assumed that the insurance change occurred at the midpoint between the 2 encounters. We geocoded addresses and created maps to determine those in and out of the Albuquerque city limits and Bernalillo County limits using ArcMap 10.3.1. (Esri, Redlands, CA) on a secure system. We also mapped the addresses onto census tracks and reported median household incomes and educational levels, using census track information from the 2010 US census. We assessed diet quality using the diet metric from the American Heart Association Simple 7 score and physical activity using American Heart Association recommendations [38].

Endpoints

The primary outcome of the trial is the change in systolic blood pressure between baseline and 12-month research visits, comparing participants receiving the IVR-T intervention with those in usual care. Secondary outcomes are change in diastolic blood pressure between baseline and 12 months, self-reported adherence, and the proportion of missed clinic appointments.

The primary medication adherence measure is the self-reported Voils instruments administered at baseline and during both follow-up surveys [31,40-42]. The measure has 3 questions about the extent of nonadherence over the previous 7 days; the 5 response options range from missing medication "none of the time" to missing medication "all of the time." If 1 or more items suggest nonadherence, 21 questions probe reasons for nonadherence; the 5 response options for each question range from being "not at all" a reason for nonadherence to being "very much" a reason. In prior studies, Cronbach alpha for the 3 "extent" items was .84, and the scale correlated significantly with systolic blood pressure and diastolic blood pressure [40]. Although it would have been ideal to corroborate this measure with pharmacy refill adherence or pill counts, FNCH clients use multiple pharmacies that preclude comprehensive assessment of refill adherence [43], and performing regular pill counts was not feasible.

The measure of visit adherence is the proportion of scheduled appointments that are kept, missed, or canceled. This measure is assessed using the FNCH EHR and calculated as a proportion of all visits scheduled during the period from enrollment to the end of follow-up. This is a standard measure in interventional trials to improve appointment keeping [11]. All 3 visit outcomes

(kept, missed, and canceled) are important from an operational perspective, as timely visit cancellations allow FNCH to schedule other clients.

Data Management

Information from the hypertension registry and the randomization table was loaded into REDCap electronic data capture tools hosted at Kaiser Permanente Colorado. REDCap was then used for study data collection, data management, and completion of the study visit questionnaires. REDCap is a secure, Web-based app designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for importing data from external sources [44].

Analysis Plan

The primary analytic strategy will be intention to treat. As secondary analyses, we will also perform per protocol and as-treated analyses. Linear mixed models will be used to analyze repeated measures of systolic blood pressure (the primary outcome variable) and diastolic blood pressure (a secondary outcome variable) as continuous variables [45]. For each group, the changes from baseline at 6 and 12 months after randomization can be obtained after the linear mixed model is fit and all coefficients are estimated. Then, we will contrast the changes from baseline between the 2 groups to assess the influence of IVR-T intervention on systolic blood pressure and diastolic blood pressure. We also plan to analyze the secondary outcomes missed appointment and medication adherence status using nonlinear mixed models.

We anticipate that some outcomes will be missing because of missed appointments or attrition. By default, the linear mixed models accommodate missing data by assuming that data are missing at random (MAR). We will explore different ways to examine the assumption of MAR [46]. When the data are missing not at random, outcome measures and missingness will be jointly modeled with either random effects selection models or pattern mixture models, whichever is appropriate [47,48]. Multiple imputation methods will also be used to explore the sensitivity of the results to missingness [49].

In our analyses of the baseline data, we compared individuals in the recruitment pool who did and did not enroll in the trial using SAS version 9.4. Statistical significance was computed using Fisher exact test for categorical variables and Mann-Whitney for discrete ordinal variables and continuous variables. A *t* test was used to compare with Mann-Whitney *P* values as a check, and the results were similar except for distance to clinic. Due to outliers for distance to clinic, we report the medians. To compare agreement between the EHR and the study survey for specific comorbidities, we used the prevalence and bias adjusted kappa [50].

Power

Our initial target sample size for this study was 512, based on the following assumptions: (1) 1800 individuals in the FNCH hypertension registry, (2) 36% of eligible FNCH clients would agree to enter the study, and (3) 80% of those would complete the trial. This would have yielded 80% statistical power to detect a 5 mmHg reduction in systolic blood pressure with a Cronbach alpha of .05 and estimated SD in systolic blood pressure of 18 mmHg [51].

Ethical Oversight

This study was approved by the Kaiser Permanente Colorado Institutional Review Board (KPCO IRB). The Colorado Multiple Institutional Review Board, which governs research activities at the University of Colorado Anschutz Medical Campus, ceded to the KPCO IRB. The National Indian Health Service Institutional Review Board determined that it did not have oversight of the study and deferred to local authorities. The study was registered at clinicaltrials.gov (#NCT03135405) on April 27, 2017.

Results

Participant Recruitment

Recruitment for the study took place from April 12, 2017, to January 31, 2018. Out of a recruitment list of 1497, a total of 295 eligible individuals completed the informed consent process and were randomized. An additional 6 individuals were randomized but were then found to be ineligible, as they had not had a qualifying visit at FNCH in the previous 2 years. These individuals will be excluded from all analyses. Individuals were not enrolled because of the following reasons: could not be contacted (n=508 or 35.0%), declined to participate (n=496 or 33.1%), were ineligible (n=106 or 7.1%), or never completed a baseline visit (n=92 or 6.1%; see Multimedia Appendix 4).

Comparison of Eligible and Enrolled Individuals

A total of 1497 potentially eligible individuals were identified through the hypertension registry. Overall, the differences were small between those enrolled in the RCT and FNCH patients with hypertension who were ineligible, could not be reached, or chose not to enroll (Table 2). There was a slightly greater proportion of women in the enrolled group. The enrolled group also had a higher proportion of Hispanic individuals. Enrolled individuals had a slightly lower blood pressure than those not enrolled, but the mean difference was small (2.6/1.7 mmHg). The largest difference between the groups is that the enrolled group was more likely to self-pay for their care (26.1% vs 10.0%) and had a more recent primary care visit at FNCH (164 days vs 231 days). Although we excluded individuals who were homeless at the time of enrollment, 14.2% of individuals had received homeless services from FNCH since 2012.

Baseline Characteristics of the Study Cohort

Baseline characteristics of the study cohort are reported in Tables 2-4. Table 2 is derived from the FNCH EHR, whereas Tables 3 and 4 are self-reported information from the baseline survey. The number of missing responses per survey question was 8 or less, except for income (number missing=30), the perceived health competence scale (number missing=15), and specific items of the basic material needs assessment (see footnote to Table 4).

Table 2. Individuals in the First Nations Community Health Source hypertension registry, by enrollment status (N=1497).

Characteristics	Enrolled in the RCT[a] (study cohort; n=295)	Not enrolled in the RCT (n=1202)	Total (recruitment pool; n=1497)	*P* value
Demographics				
Age (years), n (%)				.71
18-44	71 (24.1)	278 (23.1)	349 (23.3)	—
45-64	169 (57.3)	674 (56.1)	843 (56.3)	—
≥65	55 (18.6)	250 (20.8)	305 (20.4)	—
Age (years), mean (SD)	53.4 (11.3)	53.6 (12.5)	53.6 (12.2)	.52
Female, n (%)	176 (59.7)	637 (53.0)	813 (54.3)	.04
Race, n (%)				<.001
AI/AN[b]	65 (22.0)	358 (29.8)	423 (28.3)	—
Hispanic	155 (52.5)	442 (36.8)	597 (39.9)	—
Non-Hispanic white	47 (15.9)	248 (20.6)	295 (19.7)	—
Non-Hispanic African American	18 (6.1)	83 (6.9)	101 (6.8)	—
Other	7 (2.4)	53 (4.4)	60 (4.0)	—
Missing	3 (1.0)	18 (1.5)	21 (1.4)	—
BMI[c], mean (SD); number of people with missing values	32.6 (7.3); 1	32.2 (7.9); 23	32.2 (7.8); 24	.21
Time between last clinic visit and randomization date in days, mean (SD)	164.3 (174.8)	230.9 (217.9)	217.8 (211.8)	<.001
Insurance, n (%)				<.001
Commercial	111 (37.6)	544 (45.3)	655 (43.8)	—
IHS[d]	9 (3.1)	82 (6.8)	91 (6.1)	—
Medicaid	46 (15.6)	207 (17.2)	253 (16.9)	—
Medicare	46 (15.6)	227 (18.9)	273 (18.2)	—
Self-pay	77 (26.1)	120 (10.0)	197 (13.2)	—
Unknown	6 (2.0)	22 (1.8)	28 (1.9)	—
Ever homeless, n (%)	47 (15.9)	165 (13.7)	212 (14.2)	.35
Hypertension characteristics				—
Hypertension diagnosis in EHR[e], n (%)	271 (91.9)	1074 (89.4)	1345 (89.8)	.24
Hypertension medication order in EHR, n (%)	260 (88.1)	1042 (86.7)	1302 (87.0)	.56
Most recent SBP[f,g], mmHg, mean (SD)	129.3 (13.9)	131.9 (17.3)	131.4 (16.7)	.04
Most recent DBP[g,h], mmHg, mean (SD)	77.0 (9.8)	78.7 (10.6)	78.4 (10.5)	.01
SBP≥140 or DBP≥90, n (%)	72 (24.4)	373 (31.0)	445 (29.7)	.03
Comorbidities, n (%)				—
Diabetes	97 (32.9)	385 (32.0)	482 (32.2)	.78
Cardiovascular disease	14 (4.7)	39 (3.2)	53 (3.5)	.22
Depression	77 (26.1)	256 (21.3)	333 (22.2)	.09
Chronic kidney disease	31 (12.7)	117 (13.1)	148 (13.0)	.91
Geographic variables[i]				—
Census track median household income, mean (SD)	US $35,900 (14,199.9)	US $35,735 (16,186.5)	US $35,768 (15,808.6)	.27
Percent of census track with less than high school education, mean (SD)	17.6 (0.11)	17.4 (0.11)	17.4 (0.11)	.59

Characteristics	Enrolled in the RCT[a] (study cohort; n=295)	Not enrolled in the RCT (n=1202)	Total (recruitment pool; n=1497)	*P* value
Distance from home address to clinic (miles), median (IQR[j])	3.89 (1.62-6.76)	3.91 (1.64-7.56)	3.91 (1.63-7.47)	.65
Live in the City of Albuquerque, n (%)	269 (91.2)	1,070 (89.0)	1,339 (89.4)	.29
Live in Bernalillo County, n (%)	283 (95.9)	1,122 (93.3)	1,405 (93.9)	.11

[a]RCT: randomized controlled trial.

[b]AI/AN: American Indian or Alaska Native.

[c]BMI: body mass index.

[d]IHS: Indian Health Service.

[e]EHR: electronic health record.

[f]SBP: systolic blood pressure.

[g]Primary care visits only.

[h]DBP: diastolic blood pressure.

[i]12 individuals had addresses that could not be geocoded, 1 in the RCT group and 11 in the not enrolled group.

[j]IQR: interquartile range.

Table 3. Baseline demographic characteristics of the study cohort (N=295).

Characteristics	Statistics
Gender, n (%)	
Male	117 (39.7)
Female	175 (59.3)
Other	3 (1.0)
Primary language: Spanish, n (%)	116 (39.3)
Race, n (%)	
American Indians and Alaska Natives	74 (25.1)
Hispanic	153 (51.9)
Non-Hispanic white	43 (14.2)
Non-Hispanic African American	14 (4.8)
Other	11 (3.7)
Marital status, n (%)[a]	
Married	95 (32.3)
Marriage-like relationship	37 (12.6)
Separated or divorced	83 (28.2)
Widowed	20 (6.8)
Never married	59 (20.1)
Education, n (%)[a]	
8th grade or less	79 (26.9)
Some high school	32 (10.9)
High school grade or General Equivalent Development Test	61 (20.8)
Some college	79 (26.9)
4-year college degree	25 (8.5)
More than 4-year college degree	18 (6.1)
Employment, n (%)	
Employed for wages	106 (35.9)
Self-employed	20 (6.8)
Out of work for 1 year or more	19 (6.4)
Out of work for less than 1 year	12 (4.1)
Homemaker	32 (10.9)
Student	4 (1.4)
Retired	50 (17.0)
Unable to work	52 (17.6)
Household income, n (%)[a]	
Nothing	27 (10.2)
Less than US $10,000	75 (28.3)
US $10,000 to US $14,999	50 (18.9)
US $15,000 to US $19,999	26 (9.8)
US $20,000 to US $24,999	35 (13.2)
US $25,000 to US $34,999	22 (8.3)
US $35,000 to US $49,999	17 (6.4)

Characteristics	Statistics
US $50,000 to US $74,999	10 (3.8)
More than US $75,000	3 (1.1)
Household income, mean (SD)	US $17,170 (17,058)

[a]Numbers do not sum to 295 due to missing values. The number of missing values are as follows: marital status=1, education=1, household income=30.

Self-reported race/ethnicity differed somewhat from race/ethnicity data from the EHR, although the overall agreement was 90.2% (266/295). The study cohort was 25.1% (74/295) AI/AN and 51.9% (153/295) Hispanic. Among the AI/AN participants, 8 (10.8%) also identified as Hispanic. Almost all participants reported having hypertension (94.5%), whereas 79.8% reported taking blood pressure medication. Only 17.4% had a home blood pressure monitor. Nearly all individuals in the intervention group (144/148, 97%) opted to receive a blood pressure monitor as part of the study intervention. Over one-third (39.0%) had a baseline blood pressure greater than or equal to 140/90 mmHg. Our self-reported medication adherence rate was 36.4%. Concordance between the medical record and the survey was relatively good for most chronic health conditions, with prevalence and bias adjusted kappa for diabetes, CVD, chronic kidney disease, and depression of 0.81, 0.71, 0.73, and 0.55, respectively.

Over three-quarters of the sample reported a poor diet. Our study cohort reported poor general health, with only 46% reporting good or better health. Self-reported socioeconomic status was low. Over one-third of participants had less than a high school education, and over one-quarter of individuals were unemployed or unable to work. Over one-third of participants reported annual household incomes of less than US $10,000, with a mean annual household income of US $17,170 and median household income of US $12,500. Basic resource needs were very common. High percentages of participants reported they did not always have enough money to buy food, health care, or utilities.

Individuals who did not answer or who chose the “does not apply” option were included in the denominator as not having that particular social need; this number varied widely between the different options (clothes=1, place to live=2, utilities=17, childcare=227, debts=87, transportation=4, and Supplemental Nutrition Assistance Program=1).

Our recruitment pool from the FNCH hypertension registry was 17% smaller than originally estimated (1497 instead of 1800). We successfully recruited 295 individuals or 20%. Multimedia Appendix 5 shows the number of individuals recruited as a function of time; we were able to recruit 8 participants per week through most of the study period. By the end of the recruitment period, we had exhausted the recruitment pool, with very few individuals being added to the recruitment registry each week. With our final sample of 295 participants, we have 80% statistical power to detect a 6.5 mm Hg reduction in systolic blood pressure with a Cronbach alpha of .05 and an estimated SD in systolic BP of 18 mmHg.

Table 4. Baseline health status and psychosocial characteristics of the study cohort (N=295).

Characteristics	Statistics
Hypertension characteristics	
Report having hypertension, n (%); number of people with missing values	277 (94.5); 2
Taking blood pressure medications, n (%); number of people with missing values	233 (79.8); 3
Having a home blood pressure monitor, n (%); number of people with missing values	51 (17.4); 2
Systolic blood pressure at enrollment visit (mmHg), mean (SD)	133.6 (19.5)
Diastolic blood pressure at enrollment visit (mmHg), mean (SD)	81.5 (12.6)
Elevated blood pressure (SBP≥140 or DBP≥90 mmHg), n (%)	115 (39.0)
Adherent to blood pressure medications (Voils adherence scale), n (%); number of people with missing values	82 (36.4); 8
Self-reported comorbid conditions	
Prediabetes, n (%)	57 (19.3)
Diabetes, n (%)	87 (29.4)
Heart disease, n (%)	51 (17.3)
Kidney disease, n (%)	25 (8.5)
Depression, n (%)	109 (36.9)
Positive screening Patient Health Questionnaire-2, n (%); number of people with missing values	69 (23.8); 5
Arthritis, n (%)	72 (24.4)
Back pain, n (%)	123 (41.7)
Health status and self-care behaviors	
General health, n (%)[a]	
Excellent	4 (1.4)
Very good	29 (9.9)
Good	101 (34.6)
Fair	130 (44.5)
Poor	28 (9.6)
AHA[b] Healthy 7–diet component, n (%)[a]	
Poor	221 (75.2)
Intermediate	68 (23.1)
Ideal	5 (1.7)
Physical activity, n (%)[a]	
None	28 (9.5)
Intermediate	177 (60.2)
Ideal	89 (30.3)
Health literacy (possible range 1-5), mean (SD)	3.85 (0.95)
Health numeracy (possible range 0-1), mean (SD); number of people with missing values	0.61 (0.28); 8
Perceived health competence scale (possible range 1-5), mean (SD); number of people with missing values	3.31 (0.60); 15
Discrimination due to race or ethnicity	
Experience discrimination, n (%)	
Never	116 (39.3)
Once or twice	50 (17.0)
A few times	86 (29.2)
Many times	37 (12.5)

Characteristics	Statistics
All the time	6 (2.0)
Experience discrimination in health care setting, n (%)	
Never	220 (74.6)
Once or twice	45 (15.3)
A few times	21 (7.1)
Many times	9 (3.1)
All the time	0 (0)
Family members experience discrimination, n (%)[a]	
Never	137 (47.1)
Once or twice	43 (14.8)
A few times	61 (21.0)
Many times	44 (15.1)
All the time	6 (2.1)
Family members experience discrimination in health care setting, n (%)[a]	
Never	219 (75.0)
Once or twice	34 (11.6)
A few times	31 (10.6)
Many times	7 (2.4)
All the time	1 (0.3)
Substance use	
Alcohol, n (%)	
Never	149 (50.5)
Monthly or less	66 (22.4)
2 to 4 times per month	45 (15.3)
2 to 3 times per week	20 (6.8)
4 or more times per week	15 (5.1)
Tobacco, n (%)[a]	
Yes	75 (25.5)
Yes, only ceremonial purposes	9 (3.1)
No, I quit within the last year	11 (3.7)
No, I quit over a year ago	58 (19.7)
Never	141 (48.0)
Illegal drugs, n (%)	
Never	266 (90.2)
Sometimes	23 (7.8)
Often	3 (1.0)
Very often	3 (1.0)
Basic resource needs, n (%)[c]	
Food	99 (33.6)
Health care	123 (41.7)
Clothes	74 (25.1)
Place to live	50 (16.9)

Characteristics	Statistics
Utilities	158 (53.6)
Childcare	37 (12.5)
Debts	144 (48.8)
Transportation	74 (25.1)
Enrolled in Supplemental Nutrition Assistance Program	142 (48.1)

[a]Numbers do not sum to 295 due to missing values. The number of missing values are as follows: general health=3, AHA healthy 7-diet component=1, physical activity=1, family members experience discrimination=4, family members experience discrimination in health care setting=3, and tobacco=1.

[b]AHA: American Heart Association.

[c]Individuals who did not answer or who chose the "does not apply" option were included in the denominator as not having that particular social need. This number was: clothes=1, place to live=2, utilities=17, childcare=227, debts=87, transportation=4, and Supplemental Nutrition Assistance Program=1.

Discussion

Improving the health of underserved populations requires effective, low-resource interventions. The Controlling Blood Pressure Trial will evaluate the effectiveness of an IVR-T intervention to improve blood pressure, medication adherence, and visit keeping among individuals with hypertension who receive care at a UIHO. The study has enrolled 295 individuals with hypertension. Important design features of this trial include (1) registry-based recruitment, which allows the assessment of generalizability to the source population, and (2) a pragmatic design that minimizes exclusions.

A recent review of the representativeness of major cardiology randomized clinical trials found that "real-world" cardiology patients tend to have higher risk characteristics, to be older, to be more likely to be female, to have clinical impairments and comorbidity disease, and to be treated less frequently with guidelines-recommended therapy, compared with individuals enrolled in cardiology RCTs. In many studies, over 50% of "real-world" patients would be ineligible for trials [52]. However, in many cases, the actual source population for a given study is unknown, and assumptions must be made in extrapolating the characteristics of study participants to the source population [53,54]. Through registry-based recruitment, we were able to precisely define the source population for our trial. We efficiently recruited individuals through the use of an EHR-based registry. Overall, the study population is representative of the eligible clinic population in its level of blood pressure control and most sociodemographic characteristics, although it does represent a group that is more likely to self-pay for their care and has been seen more recently at FNCH.

The study is designed to be pragmatic [55], with inclusive eligibility criteria. We designed the intervention itself to be flexible, allowing participants to choose the mode of delivery (text messages or phone calls), language of delivery (English or Spanish), whether to include a care partner, and whether to receive a home blood pressure monitor. The intervention included both mandatory comments (educational messages and visit reminders), and optional components (care partner and home blood pressure monitors), which replicates clinical practice. Due to the pragmatic nature of the trial, we are relying on self-assessment of medication adherence for secondary outcomes. Like most clinicians, we were unable to conduct pill counts or calculate medication refill adherence, as participants receive medications from multiple pharmacies.

We did observe some discrepancies in baseline data between the 2 data sources (self-report vs EHR). For example, the race data showed 90.2% agreement between the data sources. For the main trial analysis, self-reported race will be used as the gold standard. The proportions of those reporting having hypertension and taking blood pressure medications (94.5% and 79.8%, respectively) were similar to those found from the EHR data (91.9% and 88.1%, respectively). Differences may be due to a number of factors, including incomplete medical coding, individuals not taking medications that have been prescribed, blood pressure medications that have other indications, and individuals not understanding the indications for all their medications.

The trial is being conducted in a clinic with a population that is largely underserved, without substantial additional resources from the clinic itself. On the baseline survey, we confirmed that the study population is a group with high medication nonadherence, poor self-reported health, low socioeconomic status, and high social needs. Other characteristics such as health literacy, health numeracy, and diet are similar to populations in other safety-net health systems. To put our self-reported medication adherence rate of 36.4% in perspective, Weidenbacher et al found an adherence rate of 63% among US veterans taking antihypertensive medications, using the same adherence scale [41]. Our percent reporting good or better health (46%) can be compared with 2016 Behavioral Risk Factor Surveillance System rates of 78% in New Mexico and 79% in the Albuquerque Metropolitan Area [56].

Our finding that over three-quarters of the sample reported a poor diet score is similar to other studies. National Health and Nutrition Examination Survey (NHANES) 2005-2006 found that 76% of adults reported a poor diet, 24% an intermediate diet, and <0.5% an ideal diet [38]. In the Strong Heart Family study, among a sample of 1639 American Indians without diabetes at the baseline exam, 8.1% reported an intermediate diet score and 91.9% a poor diet score [56]. The health literacy and numeracy scores we found are similar to those from a survey of 3033 American Indian and Alaska Native adults with diabetes who were enrolled in the Special Diabetes Program for Indians Healthy Heart Project, with our population having a slightly higher print literacy and slightly lower health numeracy [37].

Mean perceived health competence was similar to a study based in a Kentucky practice-based research network on individuals with diabetes and suboptimal blood pressure control (3.3 vs 3.2) [57].

We found a baseline level of blood pressure control (blood pressure <140/90) of 61.0%, which compares favorably with the national NHANES 2011 to 2014 estimates of 54.4% [58]. Including individuals with blood pressure at goal at baseline will limit our power to detect a difference between the intervention and usual care groups but reflects the pragmatic design of the trial. Although we focused on designing an intervention that was feasible in the UIHO setting, we enrolled individuals regardless of race and ethnicity. We enrolled a slightly smaller proportion of AI/ANs than in the recruitment pool (22.0% vs 28.3%). This will also limit our ability to detect interactions by race, but again reflects the pragmatic design of the trial and recommendations from the Advisory Council.

Hypertension is the most common chronic disease in the United States, and treatment of hypertension is crucial to CVD prevention. Although the Controlling Blood Pressure Trial is set in a UIHO, it could potentially be adapted to other under-resourced clinical environments. It, therefore, has implications for other populations with low socioeconomic status and high social needs. Results from the trial should be available in early 2019.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Messaging used for the IVR-T intervention.

[PDF File (Adobe PDF File), 70KB - resprot_v8i4e11794_app1.pdf]

Multimedia Appendix 2

Baseline survey.

[PDF File (Adobe PDF File), 81KB - resprot_v8i4e11794_app2.pdf]

Multimedia Appendix 3

Diagnosis codes for hypertension, diabetes, cardiovascular disease, and depression.

[PDF File (Adobe PDF File), 23KB - resprot_v8i4e11794_app3.pdf]

Multimedia Appendix 4

Recruitment Diagram.

[PDF File (Adobe PDF File), 34KB - resprot_v8i4e11794_app4.pdf]

Multimedia Appendix 5

Recruitment plot.

[PDF File (Adobe PDF File), 24KB - resprot_v8i4e11794_app5.pdf]

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Abbreviations

AAAHC: Accreditation Association for Ambulatory Health Care
AI/ANs: American Indians and Alaska Natives
CAIANH: Centers for American Indian and Alaska Native Health
CVD: cardiovascular disease
EHR: electronic health record
FNCH: First Nations Community HealthSource
IHS: Indian Health Service
IVR-T: interactive voice response and text message
KPCO IRB: Kaiser Permanente Colorado Institutional Review Board
MAR: missing at random
NHANES: National Health and Nutrition Examination Survey
NIDDK: National Institute for Diabetes and Digestive and Kidney Diseases
RCTs: randomized controlled trials
REDCap: research electronic data capture

UIHO: Urban Indian Health Organization

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Protocol

Effectiveness of a Web- and Mobile-Guided Psychological Intervention for Depressive Symptoms in Turkey: Protocol for a Randomized Controlled Trial

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Abstract

Background: In Turkey, there are serious deficiencies in mental health care. Although depression is highly prevalent, only a small number of people seek professional help. Innovative solutions are needed to overcome this treatment gap. Web-based problem-solving therapy (PST) is an intervention proven to be effective in the treatment of depression, although little is known about its clinical effects in Turkey.

Objective: This study aims to test the clinical effects of a Web and mobile app of an adapted PST for depressive symptoms among the general population in Turkey.

Methods: Participants will be recruited through announcements in social media and the Middle East Technical University. Adults (18-55 years) with mild to moderate depressive symptoms (Beck Depression Inventory-II [BDI-II] score between 10-29) will be included in the study. Participants with a medium-to-high suicidal risk (according to the Mini-International Neuropsychiatric Interview) will be excluded. A 3-armed randomized controlled trial with a waiting control group will be utilized. A sample size of 444 participants will be randomized across 3 groups. The first experimental group will receive direct access to the Web version of the intervention; the second experimental group will receive direct access to the mobile app of the intervention as well as automated supportive short message service text messages based on PST. The control group consists of a wait-list and will gain access to the intervention 4 months after the baseline. The intervention is based on an existing PST for the Turkish population, *Her Şey Kontrol Altında* (HŞKA), consisting of 5 modules each with a duration of 1 week and is guided by a clinical psychologist. The primary outcome is change in depressive symptoms measured by the BDI-II. Secondary outcomes include symptoms of anxiety, stress, worry, self-efficacy, and quality of life. Furthermore, satisfaction with, usability and acceptability of the intervention are important features that will be evaluated. All outcomes will take place online through self-assessment at posttest (6-8 weeks after baseline) and at follow-up (4 months after baseline).

Results: We will recruit a total of 444 participants with mild to moderate depressive symptoms from March 2018 to February 2019 or until the recruitment is complete. We expect the final trial results to be available by the end of May 2019. This trial is funded by the Scientific and Technological Research Council of Turkey (National Postdoctoral Research Fellowship Programme 2016/1).

Conclusions: Results from this study will reveal more information about the clinical effects of HŞKA as well as its applicability in a Turkish setting through the Web and mobile platforms. On the basis of the results, a guided Web- and mobile-based PST intervention might become an appropriate alternative for treating mild to moderate depressive symptoms.

Trial Registration: ClinicalTrials.gov NCT03754829; https://clinicaltrials.gov/ct2/show/NCT03754829 (Archived by WebCite at http://www.webcitation.org/74HugwLo7).

International Registered Report Identifier (IRRID): DERR1-10.2196/13239

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KEYWORDS

randomized controlled trial; depressive symptoms; mobile app; psychotherapy; telemedicine; depression

Introduction

Background

According to the Human Rights in Mental Health Initiative (RUSIHAK), mental health care in Turkey has serious deficiencies [1]. From 2011 to 2014, RUSIHAK monitored Turkey's largest psychiatric hospitals and reported several problems. Among these are the undertreatment of mentally ill patients, a lack of psychologists, and inadequate psychosocial and rehabilitation options for patients and their relatives [1,2]. In Turkey, limited epidemiological studies are available; however, some studies revealed rates of depressive disorders ranging from 4.4% [3] up to 48.0% in the general population [4]. However, only 18% of these seek professional help during their lifetime [1]. Depression is one of the most common mental disorders worldwide [5].

The World Health Organization states that depression is the leading cause of disability globally [5]. It affects the quality of life considerably [6,7]; it is associated with impaired social relationships [8] and high economic costs [9,10]. Moreover, it is also associated with excess mortality rates [11].

Over the past decennia, several clinically effective treatments have been developed for depressive disorders, including antidepressant medication and psychotherapy such as cognitive behavioral therapy (CBT) [12-15]. However, not everyone who is in need of professional mental help receives adequate therapy in Turkey [1].

Innovative ways to overcome this treatment gap are electronic mental health (e-mental health) apps. E-mental health refers to the use of information and communication technologies for mental health, which are promising in several ways. The internet offers opportunities to target populations that are not sufficiently reached in other ways. Furthermore, self-management by the patient is encouraged, and the cost-effectiveness and delivery of treatments are increased [16]. As Turkey occupies fifth place among countries in Europe using the internet, with a penetration rate of 69.6% [17], and almost 84% of the Turkish population uses a smartphone [18], the internet could offer many benefits.

For approximately two decennia, Web-based treatments built on evidence-based face-to-face protocols, which are highly structured and guided, are being used [19]. These treatments have been found to be effective in the treatment of depression. The treatments include Web-based CBT [20] and problem-solving therapy (PST) [21]. The version of PST that is most examined as an internet-based intervention is based on self-examination therapy [22,23] and is aimed at teaching patients how to cope with solvable, unsolvable, and unimportant problems that cause depressive symptoms and determine the important things in life by a structured step-by-step method. By doing this, patients regain mastery of their problems in daily life, leading to a reduction in their depressive symptoms. However, only limited data on the effects of such interventions (either offered offline or online) in Turkish populations are available [24].

One randomized controlled trial (RCT) was conducted at the Vrije University in Amsterdam to test the clinical effects of a culturally adapted Web-based PST (originally developed by the VU University) *Her Şey Kontrol Altında* (HŞKA) for Turkish migrants with depression in the Netherlands [25]. A total of 287 people applied for the trial, but only 96 participants were included and randomized into 2 groups: 49 in the experimental group and 47 in the control group (wait-list). Results showed that there was no significant difference between the 2 groups concerning depression because of an underpowered sample. However, a high effect size was found at follow-up, suggesting possible effectiveness of the treatment in the longer term [25]. Furthermore, in a recent meta-analysis, it was found that PST is effective with small effect sizes across different populations and settings [21]. In addition, the internet can be also advantageous for several different purposes. To recruit participants, Facebook has been used in a Web-based intervention [25,26]. For example, Facebook has been used as part of the trial to reach Turkish migrants, which led to 3308 Friends on Facebook, of whom about 250 sent a direct message to the researcher [26], implying that the internet may be used to try to lower the stigma for seeking professional help for psychological problems. Electronic learning (e-learning) platforms can also be used for communicating about participants' weekly exercises [24]. Videoconferencing can be applied as an efficient alternative to face-to-face therapy [27].

In 2014, the Vrije University in Amsterdam and Middle East Technical University (METU) in Ankara initiated a European scientific collaboration [28]. In a total of 11 European regions, computerized CBT and videoconferencing were evaluated and implemented in routine mental health care practices, with a minimum of 5230 patients with depression. The Web-based treatment HŞKA designed by the Vrije University, with the enhancement of a behavioral activation module, was used for the Turkey region. Initial results are encouraging regarding the reduction of depressive symptoms [24]. However, this

intervention was provided through the student e-learning platform of the METU. This system was developed for coursework, in which users had to download and upload PDF or Word files to fulfill the exercise requirements of the Web-based therapy modules. For monitoring clients' assessments and evaluations and to provide feedback, separate stand-alone software programs had to be used. Therefore, the overall suitability of an e-learning platform for Web-based PST was evaluated as low.

On another front, mobile health technologies may offer opportunities to boost the effects of psychological interventions [29]. For example, a recent study showed higher adherence in the experimental group who received CBT therapy with daily automated supportive messages on their smartphone compared with the control group who received CBT without these messages [30]. The addition of automated supportive short message service (SMS) text messages to Web-based interventions may be, therefore, potentially effective in monitoring patients and their adherence to treatment [30,31].

Objectives

On the basis of our previous experience with HŞKA, we intend to start a new trial, because previous research has shown that computerized CBT is an effective way to reach and possibly to treat problems associated with mild to moderate depression [25,26]. In this trial, HŞKA as a stand-alone intervention will be used for 2 purposes. First, a compact Web and mobile app of the treatment will be developed and updated with pilot studies that evaluate the acceptance and usability of the intervention. Second, an RCT of the clinical effectiveness of the Web and mobile app will be conducted in the general population in Turkey.

Methods

Intervention Description

HŞKA was previously culturally adapted and tested for clinical effectiveness in Turkish migrants in the Netherlands [25,32]. The cultural adaptation consisted of language, the use of culture-specific cases and problems according to the worldview of the Turkish target group, and culture-specific examples of persons with similar problems. The intervention was translated from Dutch into Turkish, and it was adapted in terms of cultural sensitivity.

Cultural adaptation of psychotherapy has been defined as the modification of intervention protocols according to clients' values, contexts, and worldviews [33]. Culture-specific adaptations in this intervention included several components: first, the participants' native language; second, description of psychological problems in terms of idioms of distress (eg, using symptoms of depression instead of the term depression); third, explicit discussion of migration and culture by using culture-specific cases and problems that are recognizable for the target group concerned; and finally, inclusion of recognizable examples of persons with similar problems (eg, a young woman who migrated 2 years ago and cannot find her way in the Netherlands). For the purpose of this study, migration-related adaptations were removed, and the language was checked again by a native speaker.

HŞKA consists of 5 modules over 5 weeks, consisting of text, photos, videos, and exercises. Briefly, the length of each module is 1 page and the duration of videos 2 to 3 min. First, participants indicate what they think is important in their lives; they make a list of their problems and worries, and they categorize their problems into 3 groups: (1) unimportant problems, which are not related to what they think is important in their lives; (2) important but solvable problems, which are tackled with a systematic, problem-solving approach consisting of 6 steps (which consists of defining the problem, developing alternative solutions, choosing the best solution, making a plan for the solution, implementing the solution, and evaluation); and (3) important but unsolvable problems, such as having lost someone through death or having a chronic physical illness and making a plan for how to live with it. Each session includes about 1.5 A4 pages long text with explanations and examples and short videos about the theory; at the end of each session, exercises can be made. The core of the intervention is the 6-step problem-solving procedure, which teaches users this technique for several of their important but solvable problems. The idea is that by mastering this technique, people will regain mastery of their problems and ultimately their lives. Participants receive feedback on their homework assignments in brief weekly online messages from a clinical psychologist with a PhD degree in Clinical Psychology (first author). Those who have not sent their assignments will receive a reminder within the app once a week. After 3 reminders, participants who still have not sent anything will be considered as dropouts.

This project consists of 3 phases (Figure 1). In the first phase, the content of the existing intervention HŞKA for depressive symptoms will be used to develop a compact Web app. In the second phase, the content of the Web-based intervention will be used to develop a mobile app. In both of these phases, pilot studies will be conducted to optimize the software apps to find and resolve software errors. In this last phase, the final version of the Web and mobile apps will be used to perform an RCT with 3 arms. Screenshots of the interventions are provided in Multimedia Appendices 1-3 [34]. The first experimental group will receive direct access to the Web version of the intervention; the second experimental group will receive direct access to the mobile app of the intervention and will also receive daily automated supportive SMS text messages based on PST once a day for 2 months. The content in the daily notifications is derived from the content of the modules, for example, "Once a week, take a birds-eye view of your life to evaluate it." The rationale behind using notifications in the mobile app is to avoid dropouts as indicated [30,31]. Adding notifications for the Web version does not make it equal to the mobile version because the users who use the Web version only see the notifications if they decide to log in, whereas the users of the mobile version see the notifications when a flag appears on their main screen. The control group consists of a wait-list and will receive the treatment after the study has been finished. A flow chart of the RCT is presented in Figure 2. Ethical approval for the RCT study has been obtained from the Human Subjects Ethics Committee of METU (No. 28620816/21).

Figure 1. Flowchart of the study phases.

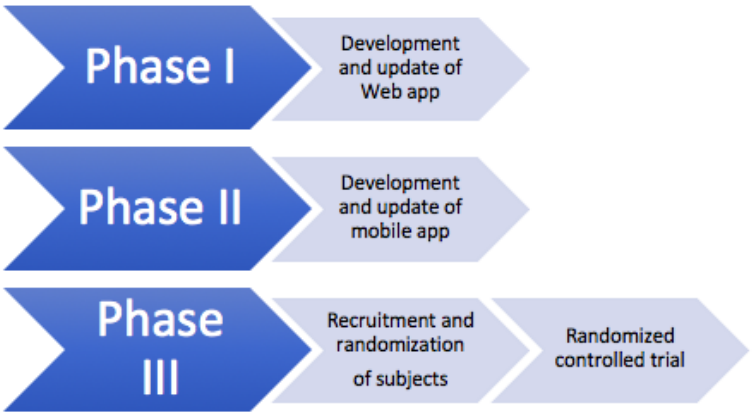
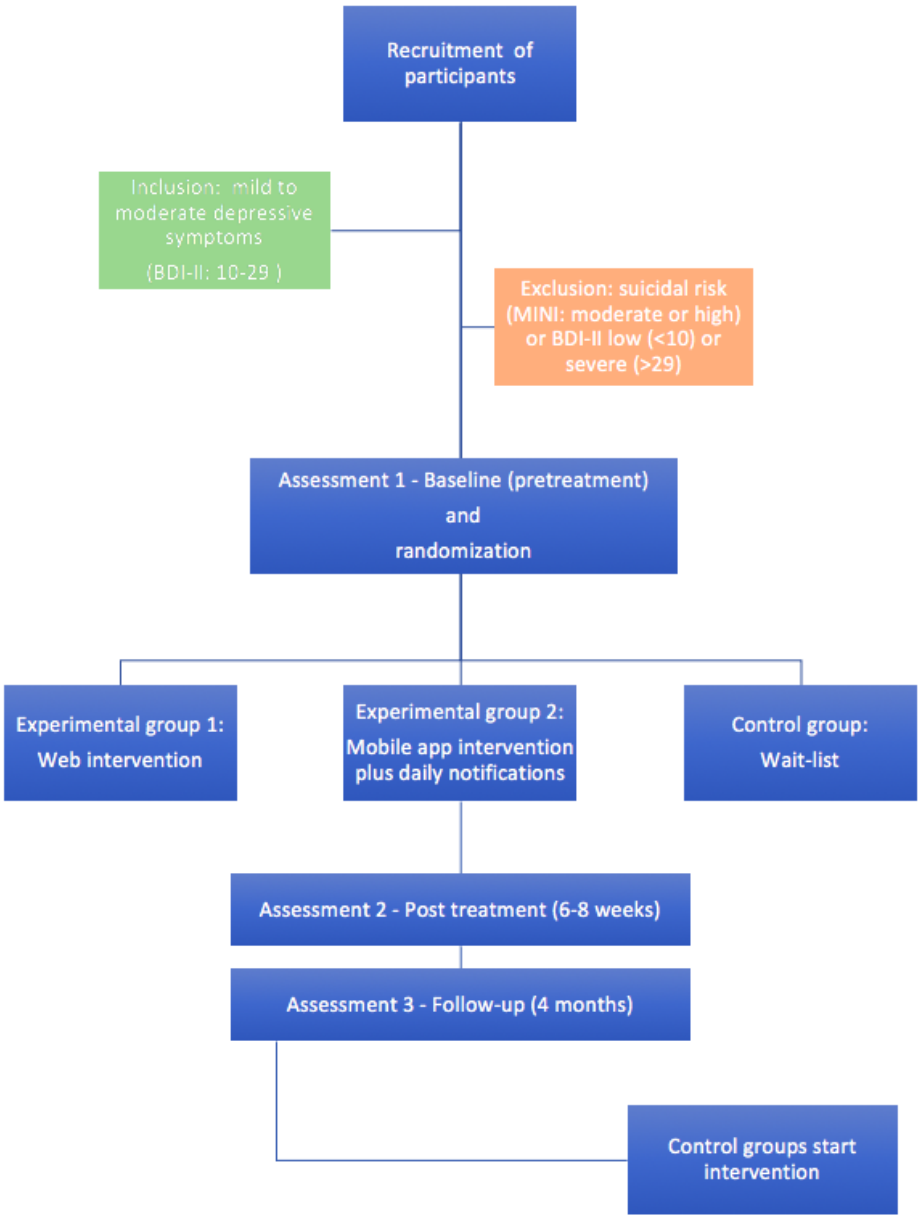


Figure 2. Flowchart of the randomized controlled trial. BDI-II: Beck Depression Inventory-II; MINI: Mini-International Neuropsychiatric Interview.



Inclusion and Exclusion Criteria

Turkish participants living in Turkey are eligible if they are aged between 18 and 55 years, have internet access, have both a personal computer (PC) and a smartphone or tablet, and have mild to moderate depressive symptoms (Beck Depression Inventory-II [BDI-II] score between 10 and 29) [35]. Participants will be excluded if they have a BDI-II score above 29 or a medium-to-high suicidal risk (according to the Mini-International Neuropsychiatric Interview [MINI]), and they are advised to contact a psychiatrist or clinical psychologist by sending them an email [36,37].

Recruitment

Recruitment will take place in the general population in Turkey until the end of the project or earlier if the sample size will be achieved. A total of 2 psychologists will be involved in the recruitment, assessments, and therapy delivery: the clinical psychologist will deliver the therapy messages, follow up with the administration of the assessments, message management for admission to the study, and convince dropouts to continue, whereas the other psychologist (Bachelor's degree) will actively recruit participants for the study. Announcements will be placed online at health-related social media sites and offline at several meeting points at the university. These announcements will contain a link to the research website with detailed information about the study. Respondents who are interested can apply by sending an email to the clinical psychologist. A link to the screening and an informed consent form will be emailed to the respondent. The screening includes the BDI-II and MINI questionnaires; access to a PC and smartphone or tablet; and demographic information of the respondents, such as name, surname, email address, age, and gender. Applicant admission is done by checking the BDI-II and MINI scores of applicants manually.

Measures

Assessments will take place before randomization (baseline), directly after completing the treatment (2 months after baseline), and finally, 4 months after baseline as a follow-up assessment. All outcomes are self-assessed through online questionnaires and can take up to 20 to 30 min to complete. Participants will receive 15 TL (Turkish Lira, the local currency) in total only if completing all 3 assessments. An overview of the measures used per assessment is given in Table 1.

Sociodemographic and Additional Information

At baseline, sociodemographic information about the participant will be collected by asking questions about the following: sex, age, educational level, employment, long-term relationship or partner status, living situation, chronic physical illness, chronic psychological illness, and psychological or psychiatric treatment status.

Primary Outcome: Depressive Symptoms

To measure depressive symptoms as the primary outcome, the Turkish version of the self-report BDI-II will be used at baseline, posttreatment, and follow-up [38]. It has 21 items in total describing depressive symptoms. Each item is scored on a 4-point scale, with a range of 0 (not at all) to 3 (severe). The total score ranges from 0 to 63. The BDI-II has good psychometric properties for online administration [39]. The Turkish version has been proven to have good reliability and validity [38,40]. The cut-off scores are 0 to 9 for minimal, 10 to 29 for moderate, and 30 to 63 for severe depression.

Secondary Outcomes

Anxiety Symptoms

Anxiety will be measured with the State-Trait Anxiety Inventory (STAI), a measure of trait and state anxiety by self-report [41]. The STAI has 40 items in total, of which 20 items are allocated in the state scale (S-Anxiety) and 20 items in the trait scale (T-Anxiety). The S-Anxiety scale is intended to assess the intensity of current feelings of anxiety, whereas the T-Anxiety scale assesses feelings of anxiety in general. All items are rated on a 4-point scale (from almost never to almost always). A higher score indicates greater anxiety levels. The STAI is available in Turkish and has been shown to be a valid and reliable measure [42].

Table 1. Overview of instruments per assessment.

Instruments	Number of items	Baseline	Posttreatment	Follow-up
Sociodemographic and additional information	20	✓[a]	—[b]	—
Depressive symptoms (Beck Depression Inventory-II)	21	✓	✓	✓
Anxiety (State-Trait Anxiety Inventory)	40	✓	✓	✓
Worry (Penn State Worry Questionnaire)	16	✓	✓	✓
Stress (Perceived Stress Scale)	10	✓	✓	✓
General Self-Efficacy	10	✓	✓	✓
Quality of life (EuroQol-5D-5L)	6	✓	✓	✓
Satisfaction and log data	8	—	✓	—
Usability and acceptability	40	—	✓	—

[a]These instruments will be assessed during the trial.

[b]These instruments will only be assessed once during the trial.

Worry

The Penn State Worry Questionnaire (PSWQ) will be used to measure pathological worry [43]. The PSWQ has 16 items in total. Each item can be scored on a 5-point scale from 1 (not at all typical of me) to 5 (very typical of me), with a total score varying from 16 to 80. The PSWQ has good psychometric properties to use in an online format [44]. The PSWQ has been translated into Turkish and shown to be valid and reliable in a Turkish sample [45].

Stress

The Perceived Stress Scale (PSS) will be used to measure the perception of stress [46]. It consists of 14 items originally, but it can also be assessed in a short form of 10, for which the total score range is 0 to 40 [47]. Each item is rated on a 5-point scale, ranging from 0 (never) to 4 (very often). The Turkish version of the PSS has been shown to be valid and reliable [48]. For this study, the short form consisting of 10 items will be used.

Self-Efficacy

The General Self-Efficacy (GSE) scale is a measure to assess self-efficacy beliefs [49]. The GSE scale contains 10 items, which are rated on a 4-point scale from 1 (not at all true) to 5 (exactly true). The total score varies from 10 to 50. The Turkish version will be used, which has been shown to have good reliability and validity [50].

Quality of Life

To measure quality of life, the EuroQol-5D-5L (EQ-5D-5L) will be used [51]. It consists of 5 items each measuring different dimensions of health status (mobility, self-care, usual activities, pain or discomfort, and anxiety/depression). The items are rated on a 5-point scale from level 1 to level 5 (no problems, slight problem, moderate problem, severe problem, and extreme problem). All the answers to each item are combined, resulting in 3125 possible health states, ranging from 11,111 (full health) to 55,555 (worst health). Furthermore, there is an EQ-visual analog scale measuring a global rating of self-perceived health. This is scored by 0 (the worst health you can imagine) to 100 (the best health you can imagine). The EQ-5D-5L is valid and reliable for use in an online format [52]. The Turkish version has good validity and reliability properties [53].

Satisfaction and Log Data

After completion of the intervention, participants will be asked to define their satisfaction with each module in the intervention (ie, “Was this lesson useful to you?”). The answers can be rated on a 5-point Likert scale from 1 (not at all) to 5 (very useful). Finally, log data will be collected by using the following parameters: type of device, last activity, first session, app version, and usage duration, which will be monitored until the follow-up assessment.

Usability and Acceptability

To test the final version of the Web and mobile app of the intervention, the usability and acceptability will be measured. A questionnaire developed by Çetin Kaya [54] about acceptance of the technology will be used. It consists of 3 parts: first, the general use of electronic services (e-services) and second, the acceptance of the e-service concerned, which consists of 40 items (of which 2 have been removed from this study because of irrelevance). The questionnaire has 13 subscales: perceived application mobility, perceived device mobility, expected benefit, informational influence, intention to use e-service, perceived behavioral control, perceived enjoyment, value to personalization, perceived usability, trust in the e-service, perceived ubiquity, value expressiveness, and value to incentive. This questionnaire has good psychometric properties in terms of validity and reliability [54].

Sample Size

In this RCT, 2 experimental groups (receiving the intervention by either the internet or a mobile app) will be compared with a waiting list control group. The sample size is calculated based on an expected difference of Cohen d=0.45 (moderate) between 1 of the experimental groups and the control group as in previous studies [22,25]. “ F tests-analysis of variance repeated measures” will be applied in G-Power Statistical Power Analysis program version 3.1 and used for sample size calculation [55]. To obtain a power of .80 for a 1-tailed test and an alpha of .05, a total of 234 participants for 3 groups is needed. However, high attrition rates at posttest (25.0%) and at follow-up (30.0%) are expected based on previous studies [24,25]. Therefore, the sample size will be increased to 444 participants in total (allowing an attrition of 25.0%*30.0%=52.5%). This means that 148 participants are required at baseline for each group.

Randomization

Participants will be randomly assigned to 1 of the 2 experimental groups or to the control group after the first assessment (at baseline) based on 1:1:1 randomization. The allocation schedule will be generated using an online randomization tool [56], which will be performed and communicated to the patient by an independent researcher. Block randomization will be used with blocks of 9 allocations each. Furthermore, 2 strata will also be used based on age: 1 stratum for 18 to 24 years and another for 25 to 55 years. Participants will be informed about the randomization outcome by email after completing the baseline assessment. Participants in the experimental groups receive a Web link to subscribe free to the intervention with a special code. Afterwards, the participants are required to create an account on the platform with their personal code and self-chosen password. The mobile app will be free to download in the App Store and Google Play Store; however, the intervention will not be open to the general public. Blinding the participants in this RCT will not be possible; however, the statistician is blinded to group assignment.

Statistical Analyses

The study will be reported in accordance with the consolidated standards of reporting trials guidelines [57]. The data obtained from the study will be evaluated and data tables created using the Statistical Package for Social Sciences version 25.0 statistical software program [58]. The significance level will be accepted as 95% CI (P<.05) in all statistical analyses. Quantitative (categorical) variables will be expressed as mean, SD, and upper and lower values in this study, whereas qualitative (continuous) variables will be expressed as numbers (n) and percentage (%). The Kolmogorov-Smirnov Test will be used to examine whether

the quantitative data were distributed normally. To measure the efficacy of the treatment in this study, general linear model repeated measures analysis will be used to investigate the change on the primary outcome (BDI-II) scores in dependent variables for the total sample based on the intention-to-treat principle and for analyzing missing data [59]. McNemar tests will be used to measure categorical change as a version of the Chi-square test of independence in repeated measures of dependent groups. Furthermore, the Fisher exact Chi-square tests will be used if the number of crosstabs data is insufficient and the hypothesis is not achieved. Attrition will be defined as not completing any or 1 of the posttreatment measures. The notification effect will be analyzed by comparing the dropout rates of the Web and mobile versions. Finally, the correlation coefficient and statistical significance between the quantitative variables will be calculated by 2-way Pearson correlation analysis.

Clinically Significant Change

Analyses of clinically significant change on the primary outcome (BDI-II) will be conducted according to the Jacobson and Truax formula [60]. This method evaluates 2 criteria for each participant. The first is whether each participant's BDI-II score has improved such that it is unlikely to be because of chance (Reliable Change Index [RCI]). The RCI is a function of a participant's pretest and posttest scores, the SD of the population before treatment, and the test-retest reliability of the measure [55]. A participant is considered to have experienced reliable change if his or her RCI is greater than 1.96 [61]. The second criterion evaluated for participants shown to have reliable change is whether their posttreatment symptom level places them at a score of 10 or lower on the BI-II. A clinically significant change was determined if the participant had recovered and shown reliable improvement over time.

Per-Protocol Analysis

Secondary per-protocol analyses will be performed for participants who completed all the measurements and all 5 modules of the intervention (if randomized to the experimental conditions).

Results

A total of 444 participants with mild to moderate depressive symptoms will be recruited from March 2018 to February 2019 or until the recruitment is complete. We expect the final trial results to be available by the end of May 2019. This trial is funded by the Scientific and Technological Research Council of Turkey under its National Postdoctoral Research Fellowship Programme 2016/1.

Discussion

Strengths

In an earlier report, RUSIHAK raised alarm concerning mental health care in Turkey [1]. A new mind-set and alternative solutions for this challenging problem are needed. E-mental health could be an inventive solution to reach, treat, and monitor people with psychological problems. The flexibility in time and place and the high levels of anonymity and accessibility could make a positive difference to mental health care.

To our knowledge, this project will be the first trial studying the effects of guided PST in a Web-based and mobile app for depressive symptoms in the general population in Turkey. In addition, the effects of receiving notifications based on PST techniques in the app will be evaluated. Although notifications seem to be a promising solution to increase adherence, the impact of it has earlier been evaluated as disruptive [62]. As Turkey has some major shortcomings in providing mental health care, HŞKA can bridge this gap in several ways, such as providing alternative and evidence-based care besides pharmacotherapy and relatively easily accessible health care for a wider population in need of help. Online guided self-help can be an innovative way to reach and treat populations with limited access to mental health care. The first and second phases of the study will shed light on the general stance of the Turkish population toward mental health and the usability and acceptability of the apps.

Limitations

Although online guided self-help for depressive symptoms is promising, there are some points to consider. First, in a previous study among Turkish migrants with depressive symptoms, the sample size was not large enough to detect a small to moderate effect [25]. Recruitment was difficult, and the suicidal risk was moderate to high in the same study. It is expected that the same difficulties will be encountered during this trial. Second, attrition is generally high in online intervention trials and can be more than 50% [63,64]. In the study of Ünlü Ince et al [25], attrition was even higher, which led to missing data. It is expected that attrition in this study will be comparable with that of online intervention studies; however, the daily automated notifications in the mobile experimental group may counteract such high attrition rates. Finally, this study will only evaluate the severity of depressive symptoms, which means it will not be possible to say anything about recovery from a depressive disorder.

Conclusions

In the event that promising results are obtained from this study, usage of Web and mobile apps in a Turkish setting will be validated. Thereby, guided Web and mobile-based PST intervention might become an appropriate alternative to psychiatric care for mild to moderate depressive symptoms. In the future, the feasibility, economics, and management of online apps for depression will be studied.

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Conflicts of Interest

HŞKA was developed in collaboration with the online counseling center Ruhuna İyi Bak, the IT Enterprise Doksan6, and the project group. The VU University owns the copyrights of HŞKA.

Multimedia Appendix 1

Screenshot of the main page of the Web version.

[PNG File, 104KB - resprot_v8i4e13239_app1.png]

Multimedia Appendix 2

Screenshot of module 1 of the mobile version.

[PNG File, 4MB - resprot_v8i4e13239_app2.PNG]

Multimedia Appendix 3

Screenshot of the exercise mobile version.

[PNG File, 4MB - resprot_v8i4e13239_app3.PNG]

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Abbreviations

BDI-II: Beck Depression Inventory-II
CBT: cognitive behavioral therapy
EQ-5D-5L: EuroQol-5D-5L
GSE: General Self-Efficacy
HŞKA: Her Şey Kontrol Altında
METU: Middle East Technical University
PC: personal computer
PSS: Perceived Stress Scale
PST: problem-solving therapy
PSWQ: Penn State Worry Questionnaire
RCI: Reliable Change Index
RCT: randomized controlled trial
RUSIHAK: Human Rights in Mental Health Initiative
SMS: short message service
STAI: State-Trait Anxiety Inventory

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Protocol

Person-Centered Interactive Self-Management Support in Primary Health Care for People with Type 2 Diabetes: Protocol for a Randomized Controlled Trial

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Abstract

Background: Type 2 diabetes (T2D) is increasing as the population ages. The development of new medical treatments is promising and important, but the basic treatment remains self-management, even if adherence to lifestyle advice is low. Electronic health (eHealth) or mHealth interventions can increase empowerment among people living with T2D and may compensate for the lack of professional resources and geographical distances. The interactive self-management support (iSMS) project aims at including digital tools to support people living with T2D in their self-management and facilitating their interaction with diabetes specialist nurses (DSNs). This protocol outlines a study with the purpose of developing and evaluating an intervention where people living with T2D can increase self-efficacy and empowerment through digital self-monitoring and interaction with DSNs.

Objective: To develop and evaluate a person-centered iSMS intervention in primary health care for people with T2D in addition to their usual diabetes care.

Methods: This study is a 12-month, 3-armed, nonblinded randomized controlled trial (RCT), which will be conducted in 6 primary health care centers (HCCs) in northern Sweden. Eligible participants will be randomized to either an intervention group (n=46), a control group (n=46), or an external group (n=46) for comparison. The intervention group will receive the mobile app, and the control group will receive a minimal intervention (diabetes brochure) and the usual standard of care. Changes in glycated hemoglobin (HbA_{1c}) will be the primary outcome measure.

Results: This trial is currently open for recruitment. The first results are expected to be submitted for publication in Autumn 2019.

Conclusions: This study, with its focus on iSMS, will provide insights regarding suitable ways to promote and develop a person-centered intervention. If successful, the intervention has the potential to become a model for the provision of self-management support to people with T2D.

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KEYWORDS

type 2 diabetes; eHealth; internet; mobile apps; nurse specialists; primary health care; self-management; randomized controlled trial

Introduction

Background

Type 2 diabetes (T2D) occurs in up to 20% of people aged ≥70 years. T2D is a progressive disease with an increased risk of cardiovascular disease, cancer, and dementia. Physical inactivity and being overweight owing to an unhealthy lifestyle, such as that involving the use of tobacco and alcohol consumption, are key factors in the progression of T2D [1,2]. T2D requires both active self-management of people living with the disease and advanced medical treatment over time [1,2,3]. About 350,000 people living in Sweden are diagnosed with T2D [3], and the risk increases with age, regardless of gender [2,3]. Education levels relate to diabetes development, the higher the education, the lower the incidence. The incidence also varies by country (of birth) with higher prevalence among people born in the Nordic countries than in Europe outside Scandinavia [3].

Caring for people with T2D is a challenge for society, especially in rural areas that suffer from a shortage of general practitioners in primary health care [4]. In Sweden, primary health care nurses with responsibility for diabetes clinics (diabetes specialist nurses, DSNs) have a heavy workload and are often responsible for a large number of T2D patients regarding self-management support (SMS) and follow-ups. SMS includes motivating T2D patients to quit smoking, increase physical activity, change diet, initiate weight loss, and adhere to medication and blood sugar testing [5], all examples of frequent work tasks that fall on DSNs. The medical treatment is multifactorial and includes monitoring of blood sugar targets, blood pressure (BP), blood lipids, and other medical measures [6]. Furthermore, preventive measures such as retinal scans [7] and annual foot examinations are of great importance for delaying complications [8].

T2D is a complex disease with complex treatment, in which self-management is the basic treatment [9-11]. In recent years, SMS in groups and culturally appropriate education have been recommended, led by staff with both subject expertise and pedagogical training [3]. Findings in studies [10,12] show that SMS or patient education in groups and directed to individuals are equally effective among people with T2D and result in similar improvements in learning, behavioral, and clinical outcomes. In diabetes care, there have to be various individual options and scope for those who do not want to participate in or fit into groups. Additionally, person-centered care (PCC) that enables custom solutions and person-centered approaches that strengthen self-efficacy and patient empowerment are beneficial [10,13-14]. Electronic health (eHealth) interventions for chronically ill patients, instead of or in addition to usual care, can lead to positive effects on primary health outcomes [15]. eHealth interventions are also requested today and are motivated not only by the problems of geographical distance [16] and lack of health care staff [17] but also by the opportunities offered by the approach, namely, strengthened power and ownership as well as increased person-centeredness. Therefore, we believe that it is important to develop SMS using an eHealth intervention.

Recent research suggests that patients view the use of smartphone apps for self-monitoring and channels aimed at social support and interaction with the caregiver via computers and smartphones [18] as a good and important complement to traditional care. Some patients, however, express doubt about the technological issues that may arise [19]. A challenge may also be health care staff's hesitation to use eHealth and mobile health in patient care. A recent interview study [20] among nurses in primary health care indicates that they viewed the trend toward eHealth approaches in patient care as unavoidable. However, the transition from traditional face-to-face visits to eHealth support could lead to a lack of control in their daily work, and they expressed a need to protect both themselves and the patients in the digital chaos created [20,21]. They preferred to meet patients face-to-face and saw a risk in the ongoing role change that may lead to losing their expert role in providing practical advice to patients. The solution could be to involve patients with T2D and DSNs in working together to develop an intervention with both obstacles and opportunities within their respective perspectives in mind. Several researchers recommend this kind of co-design and participatory design [22-24] since the implementation of new ideas is facilitated; these become accepted by users and are thereby longer-term solutions.

The purpose of the interactive self-management support (iSMS) project is to include digital tools by offering the use of a smartphone or tablet app to support people living with T2D in self-management and to facilitate interaction with DSNs. This study protocol outlines a randomized controlled trial (RCT) to evaluate the effectiveness of person-centered iSMS in primary health care. This study puts a particular focus on how digital technology is used as a tool for self-management in daily life, wherein patients with T2D manage their illness in closer collaboration with DSNs through self-monitoring and self-care activities. The objectives of this project are to develop and evaluate a person-centered iSMS intervention in primary health care for people with T2D in addition to their usual diabetes care. The hypotheses are that an iSMS program will decrease glycated hemoglobin (HbA_{1c}) and improve metabolic measurements, such as BP (mm HG), body mass index, waist circumference (cm), and total and high-density lipoprotein cholesterol (mmol/L). Furthermore, we hypothesize that an iSMS program will improve lifestyle habits such as physical activity, diet, and smoking; decrease the need for SMS and changes in medical treatment; increase diabetes empowerment; increase diabetes-dependent quality of life (QoL); improve illness perception; and improve eHealth literacy in the intervention group compared with an internal (intervention and control) and external control group at 4 and 12 months' follow-up.

Theoretical Framework

This randomized intervention study is grounded on the theoretical perspectives of PCC, which is a care model that supports the person's views about their life situation and condition as being indisputable and is always at the center of care. According to PCC, patients are persons who are more than their illness. PCC is based on the patient's experience of the situation and the individual's circumstances, resources, and obstacles. PCC has been described as the gold standard of care that will help individuals to develop the knowledge, skills, and confidence they need to more effectively manage and make informed decisions about their health or illness and health care

and thus become partners in care. It also means that the patient should always be treated with respect. PCC is a partnership between patients or relatives and professional caregivers. It requires that health care professionals and patients together lay the ground for a relationship or partnership. The starting point for PCC is the patient's story, which should be written in a structured way into a health plan that includes the goals and strategies for implementation and short- and long-term follow-up [25,26]. By shifting from an illness focus to a strengths-based, person-centered one, this intervention may change the usual care for people with T2D in primary health care. The process is intended to develop and implement an actionable plan to assist people with T2D in achieving their personal goals in the "illness process". This RCT is intended to address the specific barriers that interfere with the person's personal goal achievement; the aims are to transform and offer the participants a process for sustainable behavior change to fulfill their personal goals.

Methods

Trial Design

This protocol describes a 3-armed, nonblinded RCT to evaluate the effectiveness of person-centered iSMS in primary health care on metabolic balance, as measured by HbA_{1c}. Within this project, interactive SMS (iSMS) is defined as person-centered and interactive self-management support. The person-centered part lies in an assessment of individual needs for SMS through a quantitative measurement and by listening to patients' stories. The interactive part lies in the patients' use of a smartphone or tablet app for self-monitoring and also interaction with the nurse and other participants through a patient forum when needed. Furthermore, other digital sources, such as a website with information about T2D, self-care, and so forth, will be included in the intervention. This protocol was prepared according to the Consolidated Standards of Reporting Trials [27], the Consolidated Standards of Reporting Trials extension for Electronic and mobile Health Applications and onLine TeleHealth interventions [28], and the Standard Protocol Items: Recommendations for Intervention Trials guidelines [29,30].

Framework of Activities

Assessment of Patients' Perceived Needs for Self-Management Support

A 10-item questionnaire, the Self-management Assessment Scale (SMASc), assessing patients' needs for SMS, has been developed within the project, and its validity and reliability have been tested and found acceptable (manuscript, Öberg et al, 2018, unpublished data). The questionnaire is a person-centered measure of the type of iSMS that is needed for each person. The questionnaire includes subscales knowledge, routines, goals, emotional support, and social support and is generated from the literature on patient perspectives on chronic illness or T2D and self-management challenges.

Co-Designed Workshop

Several activities to prepare for the co-design and participatory workshop have been completed. Individual interviews among persons with T2D treated in Swedish primary health care centers (HCCs) were conducted to gain an understanding of their perceptions about and experiences of using eHealth services for self-management [19]. Furthermore, focus group interviews have been conducted with primary health care nurses about their perceptions of working with digital resources and iSMS in the care of people with chronic conditions, including T2D [20]. These earlier studies have been the basis for the development of the intervention.

A multistakeholder workshop was held on 16 September, 2016, which 27 invited participants attended, (5 were academic representatives, 6 were living with T2D, 2 were relatives of persons living with T2D, and 1 was a medical doctor and also the head of primary health care in the County Council). Furthermore, 10 were DSNs, 1 worked with information technology development in the County Council health care service and lastly, 2 were representatives of a Swedish company that develops apps for people living with diabetes.

The purpose of the workshop was to involve various participants in ideas about the design of the app, thereby influencing and developing the intervention and choice of app. During the workshop, the potentials and limitations of SMS with digital technology were explored and how SMS could be designed to motivate self-management in everyday life, at work and in the patients' daily life with diabetes, was considered. The workshop used both focus group discussions with mixed groups of representatives and mentometers to answer questions. During the workshop, it was revealed that the most important needs were related to person-centeredness, accessibility, and effectiveness. The summary of the results from the workshop suggested guidelines for setting up the intervention (manuscript, Schimmer et al, 2018, unpublished data) and provided guidance in planning the 1-year intervention, expected to start in autumn, 2018.

Intervention

DSNs will be trained in using the SMASc questionnaire to score the SMS needs. They will also be trained in using and instructing participants how to use the app. Furthermore, they will be taught how to use the Web page, with diabetes facts and illness integration support, included in the project. All recommendations to patients will be based on patients' stories and expressed needs as well as patients' scores on the SMASc questionnaire to make the individual plans person-centered.

Both the intervention and control groups will continue with their usual diabetes care, including all medical visits, tests, and diabetes support programs. The starting point for the 4-months' intervention is the baseline scoring on the SMASc questionnaire, resulting in a tailored person-centered plan for self-management through monitoring and interaction with DSN. The intervention group will receive the app, including instructions on how to use it, and the Web page with diabetes facts, as described above. DSNs will also assist in installing the app on the participants' smartphone or tablet. The software can be personally tailored according to the participant's needs to provide a personal overview of how food, exercise, medicine, blood sugar, and BP interact. The participants can evaluate food intake, blood glucose levels, insulin, medicine intake, exercise (physical activity),

and weight over time and receive reminders if they would like them. Participants may, if they wish, choose whether their DSN should have access to their data or not. The system will maintain logs of all outgoing and incoming messages, and incoming blood glucose values will be graphed by the system, which individuals can view.

Diabetes Management App

The diabetes management app, mySugr, offers data tracking and coaching services for people living with type 1 or type 2 diabetes. The mySugr App is a registered certified medical device, and carries the CE marking (Medical Devices Directive 93/42/EEC). Furthermore, the app is registered with the Food and Drug Administration, and per se, it is required to meet the highest of data security and reliability standards. The app is available for iOS and Android operating systems for mobile access. There is easy manual input of data, which may be synchronized with selected glucose meters via Bluetooth, and one can easily log in and maintain a record of diabetes clinical data. The app uses these data to provide analysis and trending results. Currently, the app offers features for self-monitoring of diet, exercise, blood sugar, smoking, weight, and medication as well as gamification to support improved self-management. Reminders and self-reflection are linked to these areas, as are statistics and visualization [31-33].

Website

The website (www.t2d.se-in Swedish) is a complement to the app with opportunities for social support, factual information, and links for interaction with other patients through discussion forums as well as opportunities for interaction and support from the diabetes nurse via a messaging feature.

Power Calculation and Sample Size

A power calculation showed that with a sample of 46 participants per group, a power of 80% with an alpha<.05 will demonstrate significant HbA_{1c} difference of 6 mmol/mol between the groups and a within-group SD assumed to be 9 [10]. This means that there is an 80% likelihood that the study will yield a statistically significant effect and allow us to conclude that the mean HbA_{1c} differs between the intervention group versus the control group. To compensate for dropouts, the study needs to enroll 46 participants per group for a total of at least 120 participants.

Randomization and Blinding

Eligible participants will be randomized to either the intervention or the control groups in a 1:1 ratio. Owing to the nature of the intervention, participants will be aware of their treatment allocation. Therefore, the blinding of participants will not be possible. However, DSNs in charge at HCCs will not be involved in the randomization, preparation of the envelopes with study information, or statistical analyses.

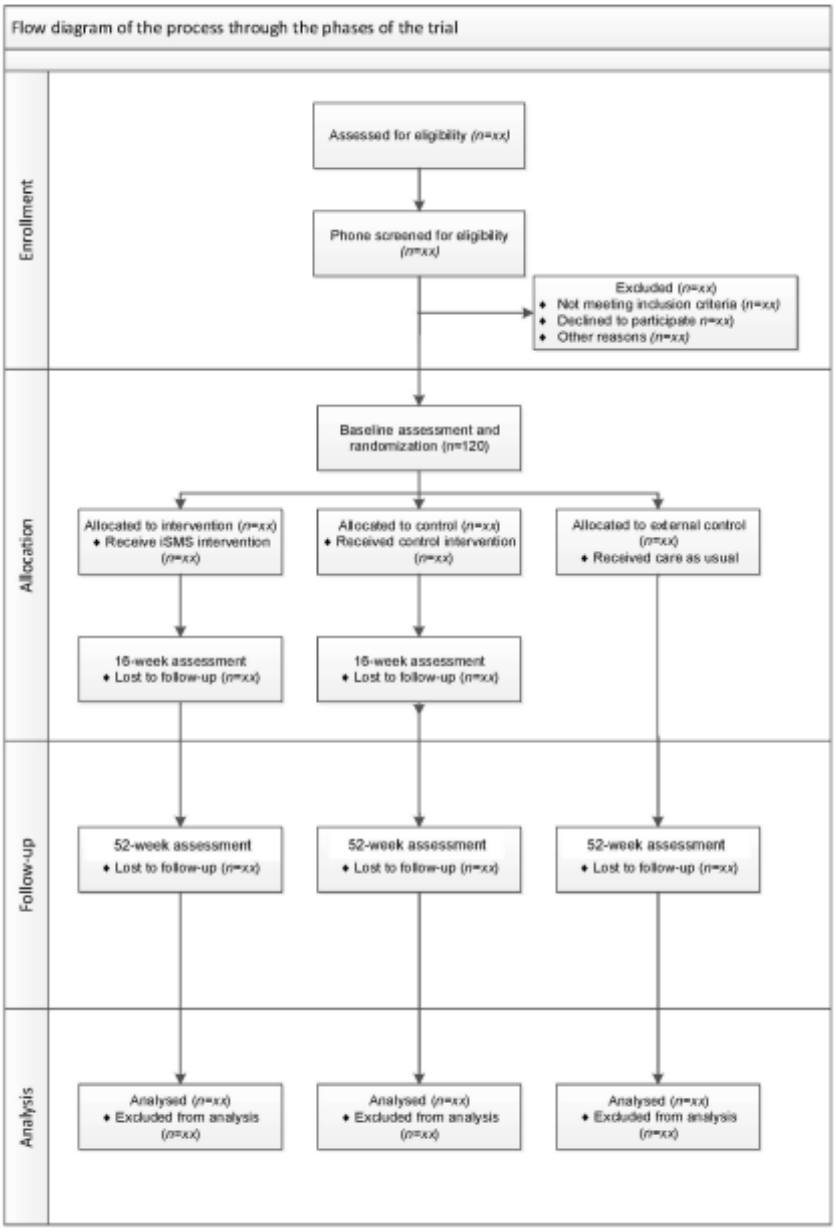
Study Population and Sampling

Sampling will be conducted both at the organizational HCC level and at the patient level. First, primary health care managers at HCCs in a county in northern Sweden have previously received verbal and written information on the purpose of the study and the implementation process as well as inclusion criteria, and all have accepted participation. After receiving consent from primary health care managers, DSNs at 6 HCCs accepted participation, got verbal and written information about the study, and were invited to participate in the co-design and participatory workshop and the RCT study and were further asked to collaborate in patient recruitment using a clustered RCT design.

Inclusion Criteria

Eligible participants are adult, aged ≥18 years, patients with T2D diagnosed within the last 5 years, Swedish-speaking, noninsulin-treated at inclusion, and own a smartphone. They will be randomized to either an intervention group (n=46) or a control group (n=46). An external comparison group (n=46) will be recruited from 2 different HCCs to analyze for a possible Hawthorne effect. The recruitment process will start in September 2018. The study flow chart is presented in Figure 1.

Figure 1. Flow diagram of trial design.



Exclusion Criteria

The exclusion criteria are planned (within 2 years) or current pregnancy, life-threatening physical illness (eg, cancer), and cognitive impairment. Furthermore, patients not responsible for their care and those not residing in their home environment (eg, those in nursing homes and in-patient hospital wards) will be excluded. The recruitment process will build on patients identified in the electronic medical record system at each HCC cared for by DSNs. Participants will be contacted via phone by the research team to discuss the study and gain informed consent about the randomization process. Informed consent will be obtained from all participants before they are enrolled in the study.

Control Groups

The control groups will be included in the data collection of laboratory values as well as questionnaires, similar to the

intervention group. In addition to this, they will receive the usual care and take part in a minimal intervention in the form of a brochure about self-management of diabetes.

Diabetes Specialist Nurses

The study includes DSNs (n=6-10) from the 6 HCCs. DSNs are fundamental to this RCT study because they will take part in introducing and training patients to use the app and recommend individualized self-care support from a website. The training of the nurses will involve learning to use the SMASc questionnaire, to develop the person-centered plan for SMS, and how to train the patients in using a medical software product.

Outcome Assessments

At baseline and 4 and 12 months' evaluation, assessments will be conducted. Baseline assessments will involve the collection of demographic data regarding age, gender, marital or family relationships, housing, education, and employment; self-reported outcome measures via questionnaires; and collection of laboratory tests and physical measurements via participants' medical records. Finally, information regarding diabetes duration, tobacco use, prescribed medication, diet, and exercise habits will be collected. For the follow-up assessments, completion of self-reported outcome measures via questionnaires and collection of laboratory tests and physical measurements via participants' medical records will be performed.

Outcome Measures

Primary Outcomes

The primary outcome among patients is a change in glycemic control, measured as HbA_{1c} (in mmol/mol) by registered laboratories at baseline and 4 and 12 months' follow-up. This data will be obtained from patient records. HbA_{1c} levels have been associated with an increased risk of diabetes-related complications. Therefore, the primary outcome in this RCT is the change in HbA_{1c}. The main goals of glucose-lowering therapy in T2D are to reduce the risk of diabetes complications while minimizing harms associated with therapy, thus increasing both longevity and health-related QoL.

Secondary Outcomes

Secondary outcomes include metabolic measurements, BP, body mass index, waist circumference, and total and high-density lipoprotein cholesterol. Furthermore, lifestyle habits, physical activity, diet, smoking, changes in medical treatment, SMS, diabetes empowerment, diabetes-dependent QoL, improved illness perception, and improved eHealth literacy in the intervention group will be evaluated.

Instruments

Self-Management Assessment Scale

SMS needs will be measured by SMASc. This 10-item questionnaire has been developed within the research group and measures 5 domains, namely, knowledge, routines, goals, emotional support, and social support, rated on a 6-point Likert scale. Validity and reliability have been tested and found acceptable (manuscript, Öberg et al, 2018, unpublished data).

Audit of Diabetes-Dependent Quality of Life

Diabetes disease-specific QoL will be measured by the Audit of Diabetes-Dependent Quality of Life (ADDQoL) [34] at baseline and follow-up. This questionnaire measures patients' perspectives on the impact of diabetes on their QoL in the following 19 domains: leisure activities, working life, journeys, holidays, physical health, family life, friendship and social life, personal relationship, sex life, physical appearance, self-confidence, motivation, people's reactions, feelings about future, financial situation, living conditions, dependence on others, freedom to eat, and freedom to drink. It consists of 2 overview items, 1 assessing general overall QoL and the other the specific impact of diabetes on QoL [35,36]. Audit of Diabetes-Dependent Quality of Life has been shown to have good validity and reliability in research and practice [35,37]. In this RCT, the Swedish version, SE-ADDQoL, will be used.

Brief Illness Perception Questionnaire

Illness perception, measuring cognitive and emotional representations of diabetes, will be assessed using the Brief Illness Perception Questionnaire (IPQ) [38] at baseline and at follow-up. The instrument consists of a 9-item self-reported measure designed to assess cognitive and emotional representations of illness. The Brief IPQ measures concerns, consequences, emotions, identity, illness comprehensibility, personal and treatment control, and the timeline and causes of diabetes. In the Brief IPQ questionnaire, each item is rated using an 11-point Likert scale wherein higher scores indicate greater agreement with the item. The Brief IPQ has been shown to have good reliability and validity in research and practice [38]. In this RCT, the Swedish version, SE-B-IPQ, will be used.

European Health Literacy Survey Questionnaire

eHealth literacy will be measured by the shorter Swedish version of the European Health Literacy Survey Questionnaire. The Swedish version of European Health Literacy Survey Questionnaire will be used at baseline and follow-up [39,40]. The instrument consists of 16 items focusing on the following 4 dimensions of health literacy: the ability to access and obtain health information, ability to understand health information (not only in written form), ability to process and appraise health information, and ability to apply and use health information.

Electronic Health Literacy Scale

eHealth Literacy will also be measured by the eHealth Literacy Scale (eHEALS) [41]. The 8-item eHEALS scale will be tested and validated to assess consumers' combined knowledge, comfort, and perceived skills at finding, evaluating, and applying electronic health information to health problems. In this study, a Swedish translated version of the eHEALS will be developed, and its psychometric properties will be tested.

Diabetes Empowerment Scale

Diabetes empowerment will be measured by the Diabetes Empowerment Scale (DES) [42]. The short-form Diabetes Empowerment Scale-Short Form, Swedish version will be used at baseline and follow-up. It includes 4 empowerment subscales: goal achievement, self-awareness, stress management, and readiness to change. A 5-point Likert scale is used. Originally, this questionnaire was based on SWE-DES-23, which is

considered a valid and reliable tool to assess empowerment in diabetes and rheumatic disease [43,44]. SWE-DES-23 was tested and shortened to become Diabetes Empowerment Scale-Short Form, Swedish version, which was found to be valid and reliable in relation to the original version [43].

Intuitive Eating Scale

Eating behaviors will be measured by the Intuitive Eating Scale (IES) [45]. This 21-item scale measures the tendency to follow physical hunger and satiety cues when determining when, what, and how much to eat. In this RCT, the Swedish version, SWE-IES, will be used.

Health-related Quality of Life and Cost and Health Economic Evaluation

Health-related QoL and cost and health economic evaluation of the intervention will be measured by the EuroQol 5-Dimensional 5-Level Questionnaire (EQ-5D-5L) at baseline and follow-up. EQ-5D is a generic health-related QoL instrument and a standardized instrument for use as a measure of health outcome [46] from which a single-index value of the respondent's health status can be derived. EQ-5D is commonly used to estimate the QoL components. Furthermore, it is possible to calculate quality-adjusted life years and thereby perform an economic evaluation of the intervention by means of quality-adjusted life years. It is also used as a health care performance indicator and in the measurement of population health in surveys [47,48]. EQ-5D-5L is a further development of EQ-5D and is based on a health profile consisting of a descriptive system and the EQ visual analog scale. The descriptive system consists of the following 5 dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension has the following 5 severity levels: no problems, slight problems, moderate problems, severe problems, and extreme problems [49]. In this RCT, the Swedish version, SE-EQ-5D-5L, will be used.

Data Analyses

All analyses to evaluate change over time with regard to intervention outcomes will be made with the intention-to-treat principle, which means that all participants are analyzed according to the group they were randomized into [50]. Appropriate imputation methods will be applied to the missing data.

Baseline and sociodemographic characteristics will be summarized using descriptive statistics. Continuous variables will be summarized as numbers of observed values and mean (SD) or median and quartiles when appropriate. Categorical variables will be described using central tendencies and variability. Differences between groups will be analyzed using inferential statistics.

Ethical Considerations

This study will conform to the principles of the declaration of Helsinki [51]. Ethical approval for this trial was granted by the Regional Ethical Review Board at Umeå University (Dnr 2014-179-31M). The major ethical considerations for this study concern the data collection, which might be experienced as tiresome for the participants. However, this risk for the participants is judged as relatively small in comparison with the benefits of receiving person-centered SMS.

Results

This trial is currently open for recruitment. The anticipated completion date for the study is September 2019.

Discussion

Intervention Design

This study protocol describes a planned project aiming to develop and implement an intervention consisting of person-centered, iSMS in primary health care for people with T2D and to evaluate its effectiveness. An intervention like this, in which patients and health care providers are involved in the developmental phase, can lead to more effective SMS and sustainable longer-term effects on health among patients.

The design for this intervention is based on experiences in the research group from previously conducted focus group interviews with primary health care nurses, individual interviews with patients with T2D, a multistakeholder workshop, and results from other studies [19,20,52,53]. Merging current research is beneficial to develop clinically useful interventions based on theory, which could be tailored more specifically for the participants through a cocreative design [54].

Any modifications to the study protocol will be discussed and agreed upon by consensus between the research group before implementing them, and all changes will be documented in a memorandum.

Conclusions

This study, with its focus on iSMS, will provide insights regarding suitable ways to promote and develop a person-centered intervention regarding the usage of mobile tools. If successful, the intervention has the potential to become a model for the provision of SMS to people with T2D.

Acknowledgments

The study is part of a collaborative program between interdisciplinary research representatives of research in nursing and informatics at Umeå University, Sweden, and is supported by the head manager of primary health care services in Umeå, Sweden. Overall, the research team has good experience of research in the area of self-management and SMS support, informatics, and use of technology as well as good methodological experience in both qualitative and quantitative methods, including RCT design and psychometric testing. Additionally, the study has strong involvement of representatives from primary health care services in the Västerbotten County Council. The Swedish Diabetes Foundation funded this study. The funders were not involved in any way

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Authors' Contributions

ÅH, who initiated the study, is the principal investigator and is responsible for the research design and implementation of the intervention and furthermore, the grant holder. All authors (UÖ, UI, LJ, CJO, and ÅH) contributed to the study concept, design, and procedures from different perspectives. UÖ drafted the manuscript. UÖ and CJO planned the workshop. UI created the statistical analysis plan. All authors contributed to the refinements of the study protocol and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ADDQoL: Audit of Diabetes-Dependent Quality of Life
BP: blood pressure
DES: Diabetes Empowerment Scale
DSN: diabetes specialist nurse
eHealth: electronic health
eHEALS: eHealth Literacy Scale
EQ-5D-5L: EuroQol 5-Dimensional 5-Level Questionnaire
HbA_{1c}: glycated hemoglobin
HCC: health care center
IES: Intuitive Eating Scale
IPQ: Illness Perception Questionnaire
iSMS: interactive self-management support
PCC: person-centered care
QoL: quality of life
RCT: randomized controlled trial
SMASc: Self-Management Assessment Scale
SMS: self-management support
T2D: type 2 diabetes

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Protocol

Protocol for the Inroads Study: A Randomized Controlled Trial of an Internet-Delivered, Cognitive Behavioral Therapy–Based Early Intervention to Reduce Anxiety and Hazardous Alcohol Use Among Young People

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Abstract

Background: The transition to adulthood is a unique developmental period characterized by numerous personal and social role changes and increased opportunities for alcohol consumption. Using alcohol to cope with anxiety symptoms is commonly reported, and young people with anxiety are at a greater risk of hazardous alcohol use and progression to alcohol use disorder. Anxiety and alcohol use tend to fuel each other in an exacerbating feed-forward cycle, leading to difficult-to-treat chronic problems. The peak in onset of anxiety and alcohol disorders suggests this developmental window represents a promising opportunity for early intervention before these problems become entrenched.

Objective: This study aims to evaluate the efficacy of the *Inroads* program, a therapist-supported, internet-delivered early intervention for young adults that targets alcohol use, anxiety symptoms, and the interconnections between these problems.

Methods: A randomized controlled trial will be conducted nationally among young Australians (aged 17-24 years) who experience anxiety symptoms and drink alcohol at hazardous or harmful levels. Participants will be individually randomized on a 1:1 basis to receive the *Inroads* intervention or assessment plus alcohol guidelines. Participants randomized to the *Inroads* intervention will receive access to 5 Web-based cognitive behavioral therapy (CBT) modules and weekly therapist support via email and/or phone. The primary outcome assessment will be 8 weeks post baseline, with follow-up assessment 6 months post baseline to determine the sustainability of the intervention effects. Primary outcomes will be the total number of standard drinks consumed in the past month (assessed by the Timeline Follow-Back procedure), severity of alcohol-related harms (assessed by the Brief Young Adult Alcohol Consequences Questionnaire), and anxiety symptoms across multiple disorders (assessed by the Generalized Anxiety Disorder-7). Secondary outcomes will include alcohol outcome expectancies; functional impairment and quality of life; and symptoms of social anxiety, anxious arousal, and depression. Results will be analyzed by intention-to-treat using multilevel mixed effects analysis for repeated measures.

Results: The study is funded from 2017 to 2020 by Australian Rotary Health. Recruitment is expected to be complete by late-2018, with the 6-month follow-ups to be completed by mid-2019. Results are expected to be published in 2020.

Conclusions: The study will be the first to evaluate the benefits of a youth-focused early intervention that simultaneously targets anxiety and hazardous alcohol use. By explicitly addressing the interconnections between anxiety and alcohol use and enhancing

CBT coping skills, the *Inroads* program has the potential to interrupt the trajectory toward co-occurring anxiety and alcohol use disorders. The Web-based format of the program combined with minimal therapist support means that if effective, the program could be widely disseminated to reach young people who are not currently able or willing to access face-to-face treatment.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12617001609347; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=372748&isReview=true (Archived by WebCite at http://www.webcitation.org/77Au19jmf)

International Registered Report Identifier (IRRID): DERR1-10.2196/12370

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KEYWORDS

alcohol abuse; alcohol-related disorders; anxiety; comorbidity; early medical intervention; cognitive behavioral therapy; young adult

Introduction

Background

The transition from adolescence to early adulthood is a unique and important developmental period characterized by numerous personal and social role changes, including new relationships and living arrangements, increased independence, and pursuit of employment and/or higher education [1]. Young adulthood also marks a period of increased vulnerability for the onset of both anxiety and alcohol use disorders [2-5]. Up to 1 in 5 young people aged between 16 and 29 years report an anxiety disorder in the preceding 12 months (12.2%-22.3%) [6-9]. Experiencing anxiety symptoms at this important developmental stage affects the way a young person adjusts to changing life circumstances and can make it more difficult to form new friendships and navigate the challenges, increasing life demands and stressors that emerge [10]. Young adulthood is also characterized by increased availability and opportunities for alcohol use, coinciding with a change to the legal of drinking at age 18 years in many countries including Australia. Within a 12-month period, nearly 1 in 2 (42.0%) young adults aged 18 to 24 years report consuming alcohol at high-risk levels (ie, 5 or more standard drinks on a single occasion at least once a month) and approximately 1 in 6 (15.3%) at very high–risk levels (ie, 11 or more standard drinks on a single occasion at least once per year) [11]. Intoxication, particularly at this age, can have significant health, legal, social, and financial consequences, including progression to alcohol use disorder [1]. Patterns of alcohol use established at this age are linked to outcomes later in adulthood, including risk of chronic alcohol use problems and a range of physical, social, and mental health consequences [12]. Despite the profound potential impact, less than 1 in 4 young people with a mental health or substance use disorder will seek help for these problems [2,13]. For young people, common barriers to seeking treatment include fear of judgment or stigma and practical constraints including difficulty accessing treatment at a convenient time or location [14].

Interrelationship Between Anxiety and Alcohol Use

Anxiety has been consistently associated with increased risk of hazardous alcohol use and alcohol use disorder [15,16]. In view of evidence that the onset of anxiety symptoms typically precedes that of hazardous alcohol use [15], the co-occurrence of anxiety and alcohol use is often explained by the self-medication model [17,18], whereby alcohol is consumed in an attempt to reduce or cope with anxiety symptoms. Over time, this can lead to progressively greater alcohol intake, related psychosocial problems, functional impairment, and heightened stress and anxiety [19,20]. Among young people, overly positive expectancies about the tension-reducing and social lubricant effects of alcohol are common, and anxious young people may be particularly susceptible to the use of alcohol to cope with symptoms of anxiety and nervousness as they navigate new social and occupational challenges [21,22]. Indeed, coping-motivated drinking has been linked to the development of alcohol-related problems [23-25], and anxiety disorders are associated with an earlier first use of alcohol [26] and increased risk of progression from first alcohol use to regular use and from regular use to alcohol use disorder [27]. If left untreated, anxiety and hazardous alcohol use tend to fuel each other in an exacerbating feed-forward cycle that interferes with recovery from either condition [28-31].

Integrating Anxiety and Alcohol Use Interventions Improves Outcomes

People with co-occurring anxiety and hazardous alcohol use tend to respond poorly to standard, single-disorder interventions [32-34]. Increasingly, the co-occurrence of anxiety symptoms and hazardous alcohol use is understood as a clinically important relationship involving mutually reinforcing connections that are likely to require integrated interventions [16,35]. Evidence from adult samples [30,36,37] suggests integrating treatment for co-occurring anxiety and alcohol use disorders is a promising approach that is intuitively appealing to patients. Our research group has developed an integrated cognitive behavioral therapy (CBT) for co-occurring social anxiety and alcohol use disorders [28], which has demonstrated greater improvements in anxiety symptoms, depression, and overall functioning compared with standard treatment approaches [37]. Furthermore, our work with young adolescents (aged 13-14 years) has demonstrated that early intervention implemented in secondary schools to improve coping with high-risk personality traits, including anxiety sensitivity, effectively reduces alcohol misuse and alcohol-related harms over a 3-year period [38]. Most recently, a randomized controlled trial (RCT) of a youth-focused, internet-delivered, early intervention targeting co-occurring depression and harmful alcohol use has demonstrated clinically significant short-term symptom improvements compared with an attention control among young adults [39]. These findings

demonstrate the clear clinical benefits of integrated approaches and demonstrate that age-appropriate early intervention has the potential to prevent or halt the escalation of anxiety and drinking into disorder-level problems.

The Inroads Program: Providing Accessible, Age-Appropriate, Early Intervention for Young Adults

The increased availability and opportunities for drinking during early adulthood, combined with the peak in onset of anxiety disorders, suggests this is a critical developmental window for interrupting the trajectory into chronic anxiety and alcohol use disorders. Despite the associative links between anxiety and hazardous alcohol use, there are no existing youth-focused interventions that target anxiety symptoms, hazardous alcohol use, and the interconnections between them. The internet presents a promising delivery method for this age group as it reduces barriers to seeking treatment such as fear of judgment or stigma, cost, and difficulties accessing treatment [14]. Reviews suggest young people prefer internet-delivered over face-to-face treatments [40], and limitations relating to engagement and retention can be ameliorated through the provision of therapist support via phone, chat, or email [41]. To meet this need for an age-appropriate, internet-delivered, integrated intervention targeting anxiety and hazardous alcohol use, the *Inroads* program was developed. The program was designed in consultation with the target age group to ensure the content and features (ie, case vignettes, skill-based videos, language, illustrations, and layout) were deemed relevant, acceptable, and appealing and would maximize engagement of anxious young people at risk of hazardous alcohol use. This brief, 5-session intervention combines therapist phone and email support with internet-delivered CBT content via contemporary Web design, youth-focused illustrations, videos, and vignettes. The active intervention components draw from our integrated CBT program for adults with social anxiety and alcohol use disorder [28] and our Web-based youth program for alcohol use and depression treatment [39]. The *Inroads* program and development process are described in full elsewhere [42].

Aims

This study will evaluate the efficacy of the *Inroads* program—a brief, Web-based CBT intervention that combines 5 online skills-based modules with minimal psychologist support for young adults (aged 17-24 years) who experience both anxiety symptoms and hazardous or harmful alcohol use. The study will be an RCT comparing the *Inroads* program with a control condition who will receive assessment plus alcohol guidelines and information. The study will be the first to evaluate the benefits of an early intervention for young adults targeting hazardous alcohol use, anxiety symptoms, and the interconnections between these problems.

It is hypothesized that compared with the control condition, the *Inroads* intervention will achieve greater reductions in (1) alcohol use, including drinks per drinking day and frequency of binge drinking; (2) alcohol-related harms; and (3) anxiety symptoms at 8 weeks post baseline. To assess the sustainability of these effects, outcomes for both groups will be assessed again at 6 months post baseline. Furthermore, it is hypothesized that participants allocated to receive the *Inroads* program will report decreased coping-motivated drinking and positive alcohol expectancies and greater improvements from baseline to post intervention on secondary outcomes of stress, social anxiety and depression symptoms, overall functioning, and quality of life.

Methods

Study Setting and Design

The study will be conducted nationally across Australia and involves a parallel RCT in which eligible participants will be individually randomized into either (1) the intervention condition (*Inroads* program) or (2) the control condition (assessment plus alcohol guidelines and information). The primary end point will be the posttreatment assessment, conducted at 8 weeks following baseline, with a secondary end point at 6 months after baseline. Figure 1 depicts the study design.

Ethics Approval and Registration

The study has been prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617001609347) and received ethical approval from the University of New South Wales Human Research Ethics Committee (HC17185). Informed consent will be obtained electronically from all participants and confidentially assured via rigorous data encryption.

Participants

A total of 122 participants (male and female) aged between 17 and 24 years who report anxiety symptoms and hazardous or harmful alcohol consumption will be recruited into the study in 2018. This age range captures the transition from late adolescence at 17 years into the unique developmental stage of young adulthood [43].

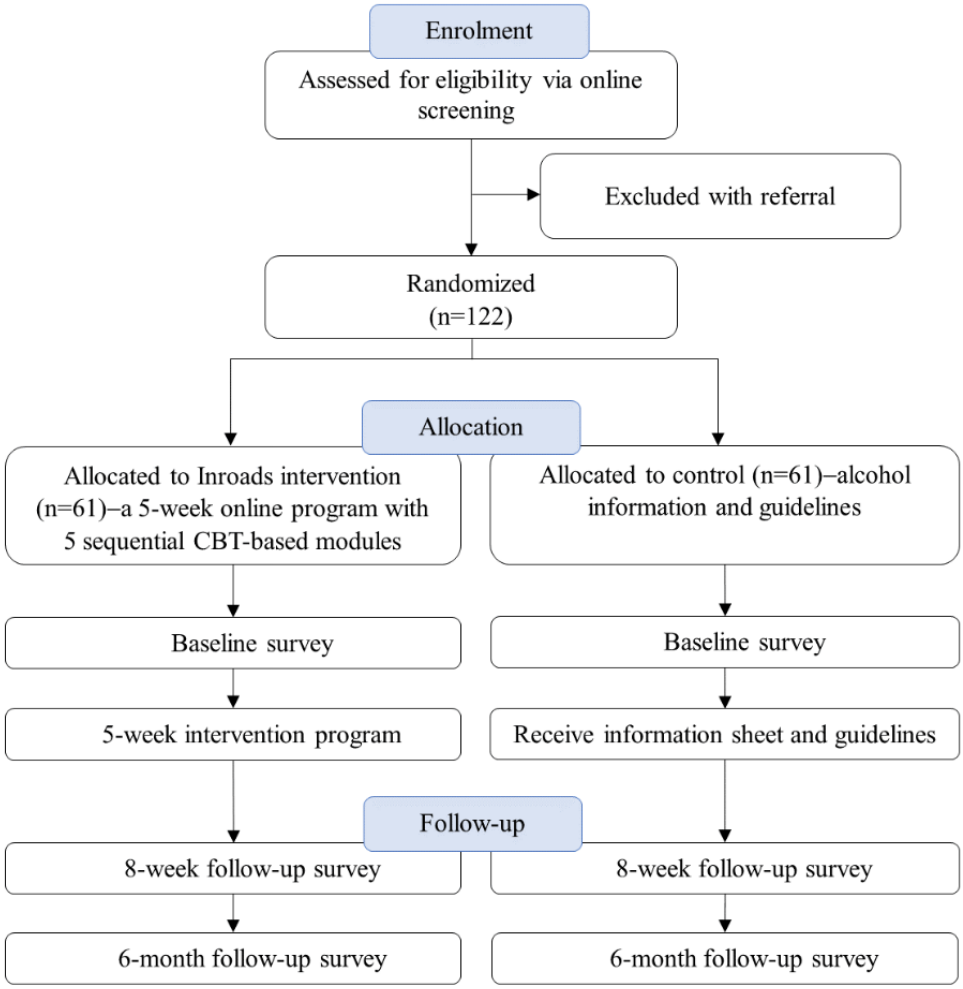
Recruitment

Participants will be recruited through a variety of advertising methods including media coverage (TV and radio), social media posts, paid online advertising via social media and search engines (eg, Facebook, Twitter, Instagram, YouTube, and Google search), distribution of posters and flyers at universities, technical and further education institutes and youth-focused institutions, and referral from youth mental health services. Potential participants will be referred to the study website [44], which provides a description of the study. To be assessed for the study, interested participants will click a link to provide informed consent before proceeding to the online eligibility assessment.

Eligibility Criteria

Individuals who consent to participate will be directed to complete a 15-min online eligibility assessment. Inclusion and exclusion criteria are shown in Textboxes 1 and 2, respectively. Eligible participants will be invited to complete an online baseline assessment before proceeding with the trial. Participants who do not meet eligibility criteria will be provided with a list of referral options.

Figure 1. Inroads study design. CBT: cognitive behavioral therapy.



Textbox 1. Inclusion criteria.

- Aged between 17 and 24 years.
- Living in Australia.
- Currently reporting hazardous or harmful levels of alcohol use, as indicated by an Alcohol Use Disorders Identification Test score ≥8 [45].
- Experiencing at least mild symptoms of an anxiety disorder, as indicated by a score ≥5 on the Generalized Anxiety Disorder-7 (GAD-7) Questionnaire [46] or a score ≥6 on the Mini-Social Phobia Inventory (Mini-SPIN) [47]. Although the Mini-SPIN focusses on anxiety symptoms consistent with social anxiety disorder, the GAD-7 has been found to index symptoms across multiple disorders and is sensitive to GAD, panic, and social anxiety disorder, facilitating screening of young people presenting with a range of anxiety presentations [48].

Textbox 2. Exclusion criteria.

- Inability or unwillingness to provide contact information.
- Insufficient English literacy.
- Inability to access the internet to participate in the program.
- Daily use of cannabis or benzodiazepines or weekly use of psychostimulants (assessed by the National Institute on Drug Abuse quick screen questions [49]).
- Primary current concern as identified by the participant is related to trauma symptoms or substance use other than alcohol.
- Significant risk of complicated alcohol withdrawal (indicated by past experience of severe alcohol withdrawal symptoms such as seizures, hallucinations, or high fever).
- Active suicidal ideation (indicated by a single item assessing experience of suicidal thoughts and intent in the past 2 weeks).
- Active symptoms of psychosis (score ≥3 on the Psychosis Screening Questionnaire [50]) or currently accessing ongoing psychological treatment for mental health or drug or alcohol problems.

Allocation

To avoid bias, participants will be individually randomized to either the intervention or control condition via the trial website using a computer-generated randomization sequence, which is concealed from the investigators. Automatic randomization within the Web-based program removes the potential for researcher involvement. Randomization will occur directly after completion of the online baseline assessment. Following randomization, the study psychologists (LS, EK, and AB) and project coordinator (KP) will be informed of group allocation to deliver the intervention (phone or chat sessions and motivational emails) to participants allocated to the intervention condition, whereas the research assistant (BL) who is responsible for reminding participants to complete follow-up assessments will remain blind to allocation status.

Assessments

All assessments are well-validated instruments commonly used in mental health and alcohol research and will be administered online via the trial website hosted by a secure, dedicated server in Australia. Participants will complete an online eligibility screening and baseline assessment before random allocation. Automatic email prompts to complete follow-up assessments will be sent to participants at 8 weeks (primary end point) and 6 months (secondary end point) after baseline. The following evidence-based strategies will minimize data attrition [51,52]: (1) monetary incentives (Aus $30 gift voucher) for each follow-up assessment completed, (2) collection of multiple sources of contact information at baseline (eg, email, mobile number, and postal address), (3) user-friendly electronic survey design that can be completed via multiple devices (eg, via mobile phone), (4) personalized reminder messages (short message service [SMS] text message and email) to complete survey, and (5) follow-up letter with photo of the research team and telephone call from the research assistant (blind to allocation status) to those participants who do not respond. Self-report assessment, use of standardized reminder templates, and blinding of the research assistants administering follow-up calls removes the potential for researcher influence over study results. The timing of assessments is detailed in the *Inroads* study schedule in Table 1.

Measures

Primary and secondary outcomes of the study were assessed at baseline, 8-weeks post baseline, and 6-months post baseline using validated psychometric instruments.

Primary Outcomes

Due to the focus of the study on co-occurring anxiety and hazardous alcohol use, primary outcomes encompass measurement across both anxiety symptoms and alcohol-related problems. Primary outcomes for alcohol are consumption per drinking day, calculated from the total number of Australian standard drinks (10 g of alcohol) consumed in the past month and assessed by a computerized version of the Timeline Follow-Back (TLFB; [53,54]) procedure and alcohol-related harm as assessed by the Brief-Young Adult Alcohol Consequences Questionnaire (B-YAACQ; [55]). The TLFB is a widely used procedure that has been validated across a number of countries and among a variety of subpopulations, including young adults, and the self-report computerized version has demonstrated good reliability with test-retest correlations exceeding 0.85 (see review by Deady [56]). The B-YAACQ assesses 24 age-appropriate consequences of alcohol consumption in the past 30 days using a dichotomous (0 “no” or 1 “yes”) response format. Scores range from 0 to 24, with higher scores indicating more problems and negative consequences from drinking. Primary outcomes for anxiety will be assessed by the Generalized Anxiety Disorder-7 (GAD-7) [48], which is sensitive to symptoms across anxiety disorders and has been previously used to assess outcomes in trials of internet-delivered treatment for mixed anxiety samples [57]. The GAD-7 contains 7 items, ranging from 0 “not at all” to 3 “nearly every day.” Total scores range from 0 to 21, with scores of 5, 10, and 15 representing cut points for mild, moderate, and severe anxiety, respectively.

Table 1. *Inroads* study timeline.

Assessments	Study period				
	Enrollment	Pre-allocation	Allocation	Post-allocation	
		t_1 (baseline)		t_2 (8 weeks)	t_3 (6 months)
Enrollment					
Eligibility screen	✓[a]	_[b]	–	–	–
Informed consent	✓	–	–	–	–
Allocation	–	–	✓	–	–
Intervention					
Inroads [c]	–	–	✓	✓	–
Control	–	–	✓	✓	–
Assessments					
Alcohol Use Disorder Identification Test	✓	–	–	✓	✓
Generalized Anxiety Disorder-7	✓	–	–	✓	✓
Mini-Social Phobia Inventory	✓	–	–	–	–
National Institute on Drug Abuse quick screen	✓	–	–	–	–
Psychosis Screening Questionnaire	✓	–	–	–	–
Alcohol Outcome Expectancies tension-reduction scale	–	✓	–	✓	✓
Brief Young Adult Alcohol Consequences Questionnaire	–	✓	–	✓	✓
Depression and Anxiety Stress Scale	–	✓	–	✓	✓
Drinking Motives Questionnaire-Revised	–	✓	–	✓	✓
Emotion Regulation Questionnaire	–	✓	–	✓	✓
Life Events Checklist for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)	–	✓	–	✓	✓
Post-Traumatic Stress Disorder symptom checklist for DSM-5	–	✓	–	✓	✓
Self-Compassion Scale-Short Form	–	✓	–	✓	✓
Sheehan Disability Scale	–	✓	–	✓	✓
Social Phobia Scale and Social Interaction Anxiety Scale-Short forms	–	✓	–	✓	✓
Substance Use Risk Profile Scale	–	✓	–	✓	✓
Treatment Acceptability Questionnaire	–	–	–	✓	–
Timeline Follow-Back	–	✓	–	✓	✓
Working Alliance Inventory-Short Form	–	–	–	✓	–

[a]Indicates that enrollment, intervention delivery and/or assessments occurred at these time points.

[b]Indicates that enrollment, intervention delivery and assessments were not relevant at these time points.

[c]*Inroads* intervention includes 5 modules which are delivered over 5 weeks, with flexibility in module completion provided up until t_2 (8-week post-baseline assessment).

Secondary Outcomes

Module completion, time spent, rate of completion, and number and duration of therapist contacts via email, chat, and phone will be recorded to measure treatment retention and dose. Frequency of binge drinking (past month consumption of ≥5 standard drinks on 1 occasion) will be calculated from alcohol consumption data collected using the TLFB procedure [53,54]. Symptoms specific to social anxiety will be assessed using the 12-item Social Phobia Scale and Social Interaction Anxiety Scale-short forms [58]. Items are scored on a 5-point Likert-type scale from 0 “Not at all characteristic or true of me” to 4 “Extremely characteristic or true of me.” Total scores range from 0 to 48, with higher scores indicating higher levels of social anxiety. Symptoms of anxious arousal and depression will be assessed using the 21-item anxiety and depression subscales of the Depression and Anxiety Stress Scale [59]. Items are rated on a 4-point scale (0-3), summed and doubled for each

subscale. Subscale scores range from 0 to 42, with higher scores indicating greater severity of emotional symptoms. Overall, functional impairment and quality of life will be assessed by the Sheehan Disability Scale [60] . Participants rate the extent to which their work, social life/leisure activities, and home life/family responsibilities are impaired by their symptoms on a 10-point visual analog scale. Higher numbers indicate greater impairment. The 3 items may be summed into a single dimension of global functioning impairment that ranges from 0 “unimpaired” to 30 “highly impaired.” The 28-item Drinking Motives Questionnaire-Revised [61] will be used to assess alcohol use motives across 5 subscales: social, coping-anxiety, coping-depression, enhancement, or conformity. Each item is rated on a 5-point Likert scale ranging from 1 “almost never/never” to 5 “almost always/always.” Subscales are scored as the average across the items within a scale, which allows a direct comparison across subscales. Positive alcohol expectancies will be assessed by the 17-item alcohol tension-reduction expectancies scale [62]. Each item is scored from 0 “not at all important” to 3” very important,” with total scores ranging from 0 to 51. Higher scores indicate greater expectancies regarding the tension-reducing effects of alcohol.

Additional measures will be included to explore secondary research questions, namely (1) Emotion Regulation Questionnaire [63] to assess emotional regulation difficulties; (2) Self-Compassion Scale-Short Form to assess self-compassion [64]; (3) Life Events Checklist for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [65], adapted to assess lifetime exposure to potentially traumatic events; (4) Post-Traumatic Stress Disorder (PTSD) symptom checklist [66] to assess severity of past-month PTSD symptoms according to DSM-5; (5) Working Alliance Inventory-Short Form-revised [67] to assess therapeutic alliance; (6) Treatment Acceptability Questionnaire [68]; and (7) Substance Use Risk Profile Scale [69] to assess personality risk factors. Demographic information including age, sex, education, employment, country of birth, sexuality, geographical location, and treatment use (ie, medication and treatment from health professionals such as psychologists, psychiatrists, counselors, and general practitioners) will also be collected.

Inroads Anxiety and Alcohol Use Intervention

The *Inroads* program is a therapist-supported, internet-delivered CBT program aimed at reducing symptoms of anxiety, hazardous alcohol consumption, and alcohol-related harms. It involves 5 sequential modules over a 5-week period that focus on enhancing motivation to change and developing CBT strategies to manage anxiety and hazardous alcohol use. Each module should take approximately 30 min to 45 min to complete, and to allow time for skill practice and consolidation, new modules will become available at a rate of 1 module each week, irrespective of whether the previous module has been completed. Automated email and SMS text message reminders to complete program modules will be provided weekly. Goal setting, planning, and review are completed each module, with new skills being introduced in each module (Table 2).

The content for each module is delivered via written text, images, infographics, and interactive forms, whereby participants are guided to identify their goals recognize their cognitive and/or behavioral responses, and practice CBT skills by working through personal examples. Additional online forms are provided for homework practice. In modules 2, 3, and 4, a brief 3-min animated video illustrates the key skills introduced in the module (module 2: realistic thinking, module 3: strategies to reduce or avoid drinking, module 4: facing fears to overcome anxiety). In addition, as participants work through the program, they follow the stories of 2 characters. This narrative is presented via audio segments (with accompanying text) to illustrate case examples aligned with the key concepts or skills in each module. A 5-item quiz at the end of each module provides the opportunity for participants to test and reinforce their knowledge of the key points.

Therapist support will be provided by a team of trained psychologists, ranging from recent graduates to experienced clinicians, who will receive supervision from experienced clinicians. At the completion of each module, participants will receive an email providing feedback, troubleshooting, and personalized suggestions aligned to module content. In addition, telephone and/or chat sessions following modules 1 (30 min) and 4 (30 min) will focus on motivational enhancement, developing a shared anxiety-drinking problem formulation, troubleshooting, and tailoring behavioral experiments and cognitive therapy exercises. The 5 modules are intended to be completed weekly; however, to allow some flexibility in the rate of completion, postintervention surveys will be administered to all participants 8 weeks after baseline. Participants in the intervention will also be asked to complete another follow-up survey 6 months post baseline.

Table 2. New skills introduced in each module of the *Inroads* program.

Modules	Skills learned
Module 1	Normative feedback about alcohol use; understanding motives for change and the interrelationship between anxiety and alcohol use; psychoeducation regarding the cognitive, physiological, and behavioral aspects of anxiety and alcohol use; goal setting and drinking limits; and emotion surfing to ride out cravings and uncomfortable feelings
Module 2	Understanding the ABC[a] model and cognitive therapy targeting anxious thoughts
Module 3	Cognitive behavioral therapy strategies for sticking to drinking limits, cognitive therapy targeting positive alcohol expectancies (ie. ‘drinking thinking’), assertiveness, and handling group dynamics
Module 4	Understanding avoidance and anxiety and graded behavioral experiments
Module 5	Enhancing social support, longer-term goal setting, and relapse prevention

[a]ABC: Refers to activating event or objective situation, belief, and consequences.

Assessment and Alcohol Information Control

Participants in control condition will receive assessment followed by an online information pamphlet outlining the effects of alcohol and risks of overuse, the Australian National Health and Medical Research council's recommended guidelines for alcohol consumption, and a list of links to national telephone helplines and alcohol information websites. The information pamphlet will be available for immediate download and will also be emailed to them. Past research demonstrates that answering detailed questions about drinking alters subsequent self-reported behavior, particularly among young adult samples [70-72], and thus, it is expected that the assessment procedures in combination with information provision will lead to a modest decrease in alcohol consumption in the control group. By using an alcohol-only control condition, the *Inroads* integrated intervention can be compared with current recommendations for comorbidity management, which state that alcohol use problems should be addressed before co-occurring conditions such as anxiety [73]. Participants in the control group will be informed that they will be recontacted in 8 weeks and 6 months for follow-up surveys, and after completion of the final survey, they will be offered the *Inroads* program.

Safety Protocol

Before consenting to the study, the information statement will provide all participants with a list of crisis and support services. At entry to the study, participants will be screened for risk of complicated alcohol withdrawal and active suicidal ideation in the past 2 weeks, and those who screen positive will be referred to appropriate support services. For participants allocated to the *Inroads* program, the project psychologists will monitor symptoms during phone, email, and/or chat contact and via review of content submitted online. The Web-based program will provide links for participants to request additional support from the project psychologists via phone or chat room. Psychologists will provide up to a maximum of 2 hours of additional phone and/or chat support where required, and in cases where a severe deterioration or safety risk is indicated, participants will be referred to appropriate services for more intensive support. Participants in both conditions will complete assessments 8 weeks and 6 months after baseline, which provides an opportunity for symptom monitoring, and all participants will be provided with a list of support services that can be accessed should they require additional help. In addition, the trial website will automatically detect any English words or phrases entered in the program modules or assessment surveys that are consistent with the vernacular of suicidal ideation [74]. If any words indicative of suicidality are detected, a notification will be sent to the project psychologists, who will manually examine the relevant content. When manual review suggests suicidal ideation, the psychologist will contact the participant to conduct a risk assessment and provide referral to appropriate support services.

Sample Size

Previous evaluations of brief, multisession, internet-delivered interventions for young adults have indicated an effect size at post intervention of between 0.68 and 0.99 for reduction in the number of drinks consumed [39,75], 0.56 for reduction in alcohol-related consequences [75], and 0.59 for reduction in anxiety symptoms [76]. Optimal Design software [77] was used to calculate the required sample size, taking into account the multilevel analysis with a nested repeated measures design. Using a conservative approach with intraclass correlation coefficient of .55 estimated based on our adult comorbidity trial [37], power calculations indicated a sample size of 90 (45 each group) would be required to detect a moderate effect size of 0.50 between the intervention and control group with power=0.8 and alpha=.05. To allow for data attrition at post assessment, estimated at 35% (n=32/90) [78], a total sample of 122 individuals will be recruited to the study.

Statistical Analysis

Primary analyses will use multilevel mixed effects analysis for repeated measures [79,80], which is a flexible analytic approach for modeling change over time that has emerged as a flexible and rigorous method for analyzing RCT results. The approach has a number of advantages over traditional approaches, including better treatment of missing data and flexible modeling of variance at the individual level, time effects, and the within-subject covariance structure [79,80]. Models will include a random intercept, and preliminary models will be estimated and model fit statistics examined to determine the most appropriate model and covariance structure. All models will use baseline measurements as the reference point to estimate participant-specific starting points and change over time. Intervention condition will be represented by a dummy-coded variable, and the condition by time interaction will be examined to assess between-group differences in treatment response over time. Treatment dose (hours of therapist contact and module completion) will be entered as an independent variable in secondary analyses to examine moderation of treatment effects. For outcomes with evidence of significant intervention effects, Cohen *d* will be calculated from model estimated marginal means and standard errors to determine the size of effect between conditions at the relevant end point. All analyses will be carried out on an intention-to-treat basis, retaining and analyzing all participants in the intervention groups they were originally allocated to. Missing data will be accounted for in all analyses using maximum likelihood estimation, and the impact of missing data on study conclusions will be examined using recommended methods [81]. Data analyses will be conducted using Stata, version 15 [82], with significance levels set at $P<.05$ (95% CI).

Results

The study is funded from 2017 to 2020 by Australian Rotary Health. Recruitment is expected to be complete by late 2018, with the 6-month follow-ups to be completed by mid-2019. Results are expected to be submitted for publication in 2020.

Discussion

Potential Findings

There is a need for evidence to guide policy and practice to address hazardous alcohol use occurring in the context of anxiety symptoms. We describe the protocol for the first trial of a

youth-focused, Web-based, early intervention that targets anxiety, hazardous alcohol use, and the mutually reinforcing connections between these problems. Given the transition into early adulthood is a key risk period for the onset of anxiety and alcohol use disorders [2-5], evidence of improved outcomes would provide a scalable intervention strategy to reduce the substantial burden, social costs, and disability associated with these disorders.

Strengths and Limitations

The study will address an important knowledge gap by examining for the first time the benefits of an integrated, Web-based, early intervention approach that targets the interrelationship between anxiety and alcohol use. An additional strength of this study is the intervention delivery in a brief format that has been adapted and designed specifically for young adults, featuring engaging and interactive content delivery, visually appealing illustrations and videos, and age-appropriate case vignettes. Delivery via the internet is a further strength, given that young people report a preference for internet-delivered over face-to-face treatments [40], and this format circumvents some of the barriers to youth seeking treatment, including fear of judgment or stigma, and difficulties accessing treatment at a convenient time or location [14].

A challenge for this study is treatment retention and data attrition. Motivation to change alcohol consumption is known to fluctuate over time [83], and treatment dropout is relatively high, with a recent meta-analysis estimating dropout from substance use treatment at 36.4% [78]. Lower attrition is typically observed for anxiety disorders (19.6%; [78]); however, higher treatment dropout is typical in samples with comorbid problems [84-86]. Although internet-delivered mental health interventions offer a number of advantages, particularly for young people, they are also associated with higher dropout rates (34.2%) compared with face-to-face treatment delivery (24.6% and 25.1% for individual and group treatment dropout rates, respectively; [78]). To address this potential limitation, the *Inroads* program was developed to combine internet-delivered content with psychologist support via email and phone. In a systematic review, supplementing internet-delivered interventions with support was associated with improved outcomes and greater treatment retention [41]. Furthermore, therapeutic components of the *Inroads* program are consolidated within a brief, 5-session intervention, in view of evidence that time pressure is a common barrier to treatment [87] and young people are less likely to commit to longer treatment duration [88]. To minimize data attrition, we will implement a comprehensive follow-up protocol incorporating multiple evidence-based strategies [51,52], including monetary incentives and multiple reminder messages, that we have used to good effect in previous trials involving young people [38,39]. Moreover, missing data will be accounted for in all analyses using maximum likelihood estimation, and the impact of missing data on study conclusions will be examined using recommended methods [81]. A second limitation of the study is that the control condition is not matched to the *Inroads* program in terms of length of intervention content or access to therapist support. Nonetheless, the comparison condition involves comprehensive alcohol assessment and information provision, which has been found to alter subsequent self-reported drinking, particularly among young adults [70-72], and thus provides a suitable benchmark to assess the additive benefits of the *Inroads* program. We consider the comparison between this integrated approach and single-disorder interventions of equivalent length an important next step should the program prove efficacious in this trial.

Conclusions and Implications

The link between anxiety and hazardous alcohol use is well established, and when these conditions do co-occur, the presentation tends to be more severe and difficult to treat; indeed, psychiatric comorbidity represents one of the most significant challenges to effective treatment provision and an urgent global priority for health research. The increased availability and opportunities for drinking during early adulthood, combined with the peak in onset of anxiety disorders, suggests this developmental window represents a promising opportunity for early intervention to interrupt the trajectory toward co-occurring anxiety and alcohol use disorders. By explicitly addressing the expectancies and behavioral links between anxiety and alcohol use as well as enhancing CBT coping skills specifically tailored to the unique stressors and drinking contexts of young adulthood, the *Inroads* program has the potential to improve anxiety symptoms and reduce alcohol consumption before these problems become entrenched. The Web-based format of the program combined with minimal therapist support via phone or email means that if effective, the program could be widely disseminated, with potential to maximize impact by reaching young people who are not currently able or willing to access face-to-face treatment.

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Authors' Contributions

LAS, NCN, MT, and AJB designed the study and obtained funding support. LAS prepared the first draft of the manuscript. All authors reviewed and contributed to the final manuscript.

Conflicts of Interest

The authors are developers of the *Inroads* Web-based program.

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Abbreviations

B-YAACQ: Brief-Young Adult Alcohol Consequences Questionnaire
CBT: cognitive behavioral therapy
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
GAD-7: Generalized Anxiety Disorder-7
PTSD: Post-Traumatic Stress Disorder
RCT: randomized controlled trial
SMS: short message service

TLFB: Timeline Follow-Back

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Protocol

Reducing Alcohol Consumption Among Risky Drinkers in the General Population of Sweden Using an Interactive Mobile Health Intervention: Protocol for a Randomized Controlled Trial

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Abstract

Background: Harmful use of alcohol continues to be a leading contributor to premature deaths globally. Not only does harmful drinking have consequences for the individuals consuming at increased levels, but it may also result in a range of negative consequences for their family members and friends. Interventions delivered via mobile phones (mobile health [mHealth] interventions) could potentially support risky drinkers seeking help to reduce their alcohol consumption.

Objective: This protocol describes a randomized controlled trial that aims to validly estimate the effect of a novel mHealth intervention targeting risky drinkers in the general population of Sweden. Nested within the trial are 3 substudies that focus on methodological and user satisfaction research questions.

Methods: A 2-arm parallel group randomized controlled trial will be employed to estimate the effect of the novel intervention. Participants will be recruited through Web advertisements and social media. The inclusion criteria are as follows: 18 years or older, ownership of a mobile phone, and being classified as a risky drinker according to Swedish guidelines. Participants allocated to the intervention group will receive a novel mHealth intervention. The intervention consists of weekly screening, personalized feedback on current consumption, functions allowing for planning of future consumption, as well as a series of messages delivered throughout the week. Participants allocated to the control group will receive a short message regarding negative consequences of alcohol consumption and a hyperlink that offers more information. Following 2 and 4 months after randomization, both groups will be asked to complete follow-up questionnaires (2-month interval being primary). Primary outcomes are weekly alcohol consumption and heavy episodic drinking. Participants in the control group will be given access to the novel intervention after completing the 4-month follow-up. The trial includes 3 substudies: We will explore whether the mode of presenting information before participants giving informed consent affects participation rates and recall of trial parameters, investigate if the content of the short message received by the control group affects study outcomes and requests for more information, and explore user satisfaction with the intervention and reactions of the control group.

Results: Participant recruitment is planned to begin in April 2019 and to last for a maximum of 24 months. The first dataset will be available approximately 2 months after the final participant has been recruited, and the final dataset will be available approximately 2 months later. No participants had been recruited at the time of submitting this protocol.

Conclusions: If found effective, the intervention has the potential to reduce negative consequences of alcohol consumption for individuals. The technology has been designed to have potential for extensive reach among those who may benefit.

Trial Registration: ISRCTN Registry ISRCTN48317451; http://www.isrctn.com/ISRCTN48317451 (Archived by WebCite at http://www.webcitation.org/779tKLsu3)

International Registered Report Identifier (IRRID): PRR1-10.2196/13119

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KEYWORDS

telemedicine; alcohol drinking; randomized controlled trial

Introduction

Background

Harmful use of alcohol contributes to approximately 4.5% of deaths globally, as well as having a causal relationship with a range of mental and behavioral disorders [1]. Premature death is not the only negative consequence from harmful alcohol use but it may also lead to injuries, road traffic accidents, violence, and social and economic burdens [2]. Not only does harmful drinking have consequences for the individuals consuming at increased levels but it may also result in a range of negative consequences for their family members and friends.

In Sweden, risky drinking is defined as either drinking more than 9 (female) or 14 (male) standard units of alcohol per week (weekly consumption) or drinking more than 4 (female) or 5 (male) standard units of alcohol on a single occasion at least once a month (heavy episodic drinking). A standard unit is defined as 12 g of alcohol in Sweden. These criteria vary among countries, where for instance the National Institute on Alcohol Abuse and Alcoholism in the United States uses the same thresholds except for a 7-unit threshold per week for women, but at the same time also defines 1 standard unit as 14 g of alcohol. A recent report showed that, in 2016, approximately 31% of the adult Swedish population were risky drinkers according to the Swedish criteria [3].

Electronic Health and Mobile Health Interventions

Early initiatives to use electronic health interventions to support change of alcohol consumption behavior investigated the use of electronic screening and brief interventions (eSBIs) [4-8]. Commonly, individuals engaging with this type of intervention respond to a series of questions, after which a summary of their drinking habits is presented, and feedback is given with regard to recommended drinking levels, alongside some advice on behavior change.

In a trial including university students in Sweden [7], there were 3.7 percentage points fewer risky drinkers among those who had been invited to complete an eSBI (n=4969) compared with those who had not been invited (n=4972), measured 3 months after initial invitation (odds ratio [OR] 0.91, 95% CI 0.82 to 1.02; *P*=.08). In addition, meta-analyses suggest that there exists a small positive effect of eSBIs on the amount of alcohol consumed weekly in the short term: Cohen *d*=−0.17, 95% CI −0.27 to −0.18 [9]; Cohen *d*=−0.14, 95% CI −0.24 to −0.03 [10]; and weighted mean difference of alcohol in grams=−16.59, 95% CI −23.70 to −9.48 [11]. Although long-term effects have not been measurable, these brief interventions are nevertheless useful for reaching a large number of individuals at a relatively low cost.

Interventions that have attempted to increase effect sizes and make benefits more persistent by requiring participants to revisit a website several times have had problematically low retention [12,13]. However, with the advent of mobile technology, it is now easier to deliver interventions to individuals over time, allowing interventions to become a part of individuals' everyday life. For instance, it is possible to remind participants of their decisions to reduce their alcohol consumption just before the weekend or ask them to reflect on their consumption on a Sunday evening. Such approaches appear promising from studies of mobile health (mHealth) interventions for behavior change more widely [14-20].

Short Message Service–Based Interventions

Interventions that use short message service (SMS) messages to deliver textual content to individuals trying to quit smoking have been widely successful, and the evidence is strong in favor of such interventions [21,22]. However, for alcohol use, the evidence for this type of intervention is less well-developed.

One study invited university students in Sweden to a 2-arm randomized trial comparing a novel SMS-based intervention against treatment as usual (eSBI) [23,24]. The novel intervention consisted of a series of supportive messages sent over 8 weeks. Of the 896 randomized participants, 91.1% (816/896) responded to the 3-month follow-up; however, no significant difference was found between the 2 arms.

Another study investigated the efficacy of a combined Web- and SMS-based intervention to reduce risky drinking among vocational and upper secondary school students in Switzerland (n=1041) [25]. The intervention consisted of a single session eSBI followed by 3 months of SMS messages. Despite losing only 7.01% (73/1041) to follow-up at 6 months after randomization, there were statistically significant differences between those who did and did not respond (education level and estimate of peer's consumption). Analyses with imputed values did show in favor of the intervention with regard to heavy episodic drinking (OR 0.62, 95% CI 0.44 to 0.87; *P* <.01) but not when complete case analyses were used (OR 0.79, no CI reported; *P*=.24). Therefore, although the evidence may be suggestive of a positive effective, no conclusive evidence was found in favor of the intervention.

Young adults were also randomized in a third study of an SMS-based intervention, drawing its study population (n=765) from emergency department patients at 4 hospitals in Pittsburgh (United States) [26]. One group was given an intervention, which asked them to respond to drinking-related questions and receive feedback through SMS each Thursday and Sunday; another group was asked to respond to drinking-related questions on Sundays only and without feedback; and a control group was not sent any SMS. At 3-month follow-up, 78.0% (597/765) of randomized participants responded, and those who were lost-to-follow-up were more likely to be African American, not currently enrolled in college, and with a baseline higher number of episodes of heavy drinking. Thus, although the trial did identify a significant difference between the participants that received an SMS on Thursdays and Sundays compared with the control who received nothing (drinks per drinking day: incidence rate ratio=0.86, 95% CI 0.79 to 0.94; no *P* value reported), these results should be viewed with some skepticism given the systematic loss to follow-up.

Finally, a pilot study conducted among risky drinkers seeking treatment on the Web suggested that delivering motivational SMS messages daily rather than weekly reduced consumption [27]. Although the study was a pilot, the recruitment of 661 eligible participants over an 8-month period was encouraging.

Mobile Phone Apps

The efficacy of alcohol consumption interventions delivered via mobile phone apps has also been investigated in randomized trials. The nature of such apps vary, from simple calculators of estimated blood alcohol concentration to intervention programs that are richer in content.

In Sweden, 2 apps were tested against each other as well as against a control [28]. Participants were university students who screened as risky drinkers (n=1932). Loss to follow-up at 7 weeks was high (from 22.7% [147/649] to 39.1% [250/640] in the different groups), and there were significant signs of systematic attrition, further made problematic by the choice to use per-protocol analyses. The report did not suggest that the apps were effective in reducing alcohol consumption but did, however, suggest that the use of one of the apps might have increased the alcohol consumption of male participants.

Another trial aimed to identify effective components of a mobile phone app [29] and recruited participants (n=672) who were looking for an app (rather than recruiting and then offering an app). A factorial design allowed testing of several variations of the mobile phone app, including both basic and enhanced versions of components. Although the factorial design allowed for important questions to be answered with regard to effective content, a low follow-up rate of 26.6% (179/672) questions any findings from the trial, and the report did not suggest any effect of the intervention on alcohol consumption.

Finally, 1 trial aimed to determine the efficacy of a mobile phone app offering continued support to patients leaving alcohol use disorder treatment [30]. A total of 349 participants were recruited from the Midwestern and Northeastern United States and subsequently randomized to an intervention and control group. The app contained both static content (frequently asked questions, Web links, and daily thoughts) and interactive features (discussion groups, ask an expert, and a weekly brief survey). Follow-up at 4 months identified a significant difference between the control and intervention group with regard to the number of days with heavy episodic drinking (mean difference 1.37; 95% CI 0.46 to 2.27; *P*=.003). No attrition analysis was supplied, but sensitivity analyses only reversed the outcome when missing outcome data (12.3% [43/349]) were set to the maximum possible value.

Mobile Health and Alcohol

The development of mHealth interventions targeting harmful alcohol consumption is still in its infancy [31], and there is much that we do not know with regard to increasing effect sizes. A recent meta-analysis determined that the evidence for the effect of mobile phone–based interventions on alcohol consumption reduction was inconclusive [32].

The novel intervention that we are proposing draws from the evidence of eSBIs and leverages technological advancements and the ubiquitousness of mobile phones. Using SMS, we schedule weekly screening of current consumption patterns and offer personal and interactive feedback and advice. In addition, the intervention offers means to plan and set goals for behavior change. Messages are sent via SMS throughout the week to further support a change of alcohol consumption behavior. A more detailed description of the intervention can be found in the section Intervention Content.

Control Conditions

The estimated effect of an intervention measured in a randomized controlled trial is always to be understood as being relative to the control condition. Attention to the design of control conditions in trials is underdeveloped [33-35]. Being denied immediate access to an intervention, where that has been the motivation for study participation, may have effects on control group participants, which are highly relevant to the interpretation of any apparent intervention effect [36].

It is common to use basic health information (in the form of a leaflet or referring to a website) as a control condition in behavioral intervention trials. Study participants are likely to have previously searched, or in the future search, for alcohol information on the Web. Much information is available of variable quality, and there is a paucity of evaluation studies of the actual effects, if any, of such material [37,38]. Nonetheless, alcohol and health information is commonly used as a control condition in trials, and the design of such control conditions is rarely studied.

General Data Protection Regulation and Recall of Trial Procedure

With the introduction of the General Data Protection Regulation (GDPR) in the European Union, greater emphasis has been placed on individuals' rights to their personal data. In layperson's terms, GDPR says that each individual owns their own personal data, and those who collect it for scientific purposes only borrow it. Individuals have the right to know how the data are going to be used; thus, it is timely to consider issues associated with standard consent practices to develop stronger methods.

Although it may appear easy to obtain consent in internet-based studies, the extent to which typical consent procedures are ethically satisfactory can be questioned. Challenges include conveying that the intervention being evaluated has yet to be shown to be effective, potentially also the concept of placebos or other aspects of the design of control conditions, and allocation to different groups by means of randomization [39,40]. Trial participants' legal and ethical rights to be offered full disclosure of trial procedures before freely accepting or declining participation is an important aspect of trials involving human subjects; however, poor recall of these trial procedures is troubling [39-42].

Aims

The overall aim of this study is to evaluate a novel intervention for help-seeking risky drinkers among the general adult population of Sweden in a rigorously designed randomized controlled trial. Nested within the study are 3 substudies. The

first substudy aims to investigate participants' recall of the trial procedure, which they were given information about before confirming their consent. We shall explore two different modes of presenting information regarding the trial procedure. The second substudy will investigate the nature of the control condition. The control group will be given brief health information and have access to further information and then wait for access to the intervention, and we will explore 2 contrasting approaches to the presentation of basic health information. The third substudy will investigate intervention group participants' experiences of using the novel intervention and control group participants' reactions to being allocated to the control setting.

The key objectives of the study are to:

1. Validly estimate the effect of the novel intervention on alcohol consumption among risky drinkers in the general population of Sweden in comparison with a health information control condition.
2. Estimate to which degree the total effect is mediated through motivation, importance, and know-how.
3. Explore participants' recall of trial procedures and if these differ between 2 modes of presenting information.
4. Explore the scope for effects of the 2 contrasting approaches to the presentation of basic health information.
5. Investigate usability and acceptability of the novel intervention in terms of users' experiences.

Methods

Intervention Content

There is no clear picture of which components have the strongest evidence base for inclusion in an alcohol intervention of the kind envisaged. Changing any behavior is a complex process in which many factors interact. Health behavior, from around 30 years ago, has been understood through social cognitive theories of behavior, such as the Health Belief Model and Theory of Planned Behavior. Common to many such theories is the importance of an individuals' own motivation and self-efficacy, including the skills that the individual possesses and environmental constraints on these intraindividual phenomena [43]. Improving motivation and self-efficacy, as well as teaching new skills and addressing environmental constraints, is understood to improve the likelihood of successful behavior change, including for changing one's drinking.

The novel intervention that we are proposing aims to target the 4 aforementioned components through the use of several interactive modules contained within a dashboard that individual's access through their mobile phone. Although the evidence is not yet strong, promising components include those that focus on behavior substitution, problem solving, goal setting, review of behavioral goals, self-monitoring, and normative feedback [44,45]. Thus, modules included in the proposed intervention will revolve around these particular activities. Furthermore, the intervention will include content that aims to increase the understanding of the consequences of alcohol consumption and simulation possibilities that aim to help individuals visualize the outcome of changing their consumption levels.

Each week, participants will receive an SMS that will contain a hyperlink to a dashboard made available on the participant's mobile phone. The dashboard will allow participants to explore their current consumption, set goals and monitor progress, create plans, learn skills, and learn about the risks involved with alcohol consumption. The dashboard will also work as a simulation device, allowing participants to enter different levels of consumption and interactively seeing health risks change, for example, reducing the number of heavy drinking episodes leads to fewer injuries and reduced risk of premature death. As additional support, participants will receive SMS messages throughout the week that contain motivational and reinforcing information to help them reduce their consumption.

In the following description of the intervention content, we will use behavior change technique (BCT) codes defined in the BCT Taxonomy v1 [46]. This allows us to highlight which techniques are included in the intervention while also creating a link between content and theory.

Weekly SMS messages sent on Sunday evenings will remind participants to access the dashboard and at the same time assess their current consumption. Participants will be asked questions concerning their total weekly consumption and their frequency of heavy drinking over the past week. A screenshot of this is shown to the left in Figure 1. On Wednesdays, Fridays, and Saturdays, participants will receive SMS messages with content aimed to increase motivation and skills. The message set is a refinement of a previously developed set that was created through formative development, and a BCT analysis of these messages has been conducted and reported previously [47].

Apart from the SMS messages and weekly assessments, the dashboard will have 6 modules, which can be accessed by participants in any order and any number of times:

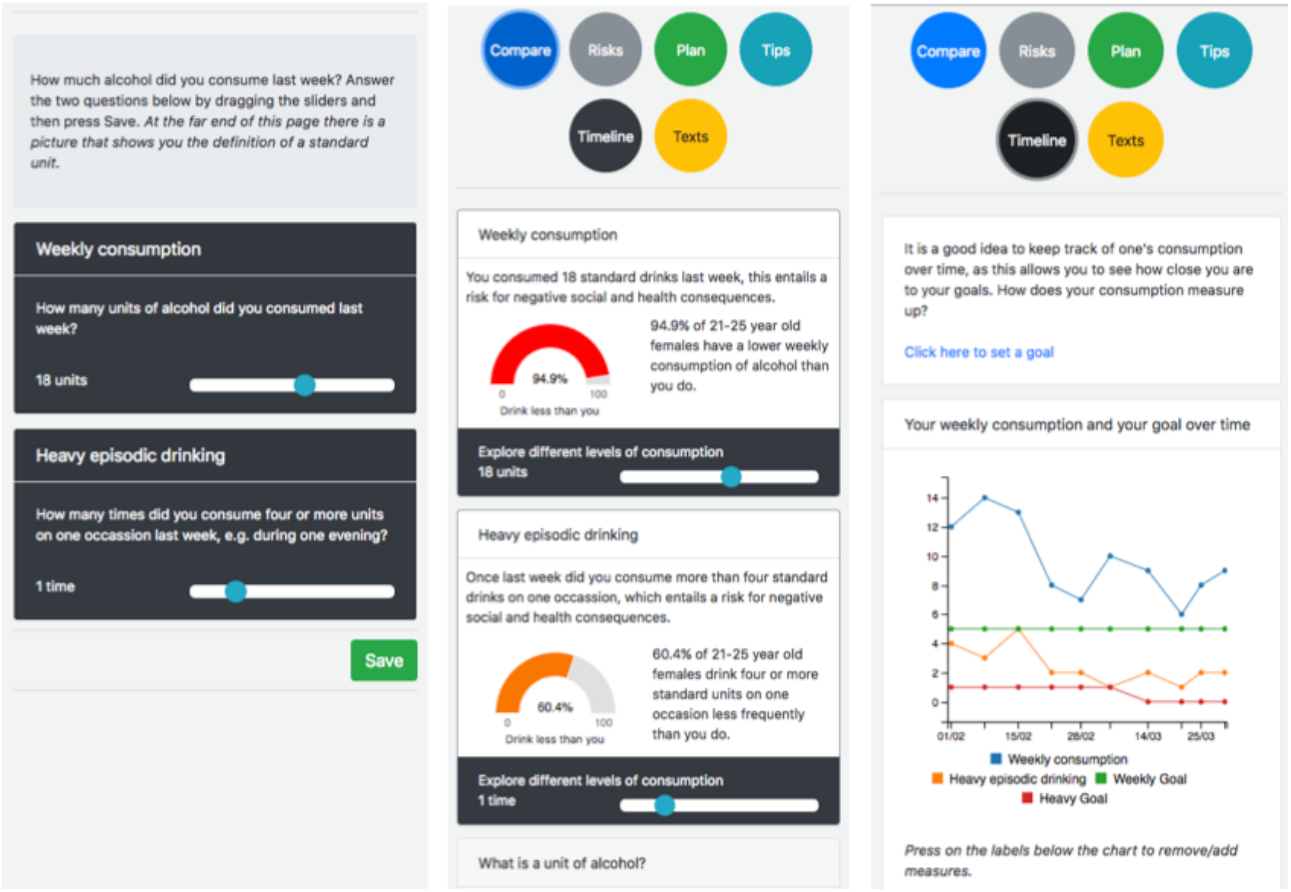
- Normative comparison of the participants' current consumption compared with others of the same age group and gender (based on data from Sweden). A screenshot of this module can be found in the middle of Figure 1. At the bottom of the module, participants can change consumption levels, which changes the normative feedback interactively, effectively allowing participants to explore how different levels of consumption lead to different outcomes. This module will leverage BCT6.2 and BCT9.3, which concerns social comparison (normative feedback) and comparing future outcomes.
- One module will give information about general risks and risk of disease connected to different levels of alcohol consumption. This module will also allow participants to simulate different levels of consumption and interactively see how risks change. This module is connected to BCT9.3 (comparing future outcomes) as well as BCT5.1 and BCT5.3, which addresses information about both social and health consequences of excessive alcohol consumption.
- One module will allow participants to create a plan that they can use when subjected to a behavioral trigger (eg, going to the pub). This module will ask participants to write an SMS message to themselves and pick a time and date

for when they want to receive this message in the coming week (up to 3 times). This module leverages BCT1.2 (problem solving).

- General tips to strengthen participants' know-how on how to reduce their consumption will be given in 1 module. The tips will leverage BCT7.2, which suggests that participants should create prompts or cues, for example, putting a ribbon around their wrist as a reminder that they have committed to reduce their drinking, as well as BCT8.1 and BCT8.2, which suggest that participants practice a new behavior and substitute their current behavior with a different one (eg, replacing at least 2 alcoholic beverages with nonalcoholic beverages each week). The tips will also concern identification of relapse triggers and barriers, avoiding social cues for drinking, and environmental restructuring (eg, avoid keeping alcohol at home).
- One module will show the participants' consumption over time. A screenshot of this module can be found to the right in Figure 1. The data come from the weekly assessments. This module leverages BCT2.2 and BCT2.3, which concerns recording and feedback of performance over time. Optionally, participants can decide to set a goal for their consumption, which would then show up graphically in the chart. This will allow participants to set and review their own goals while also visualizing the discrepancy between their current consumption and their goals (BCT1.1, BCT1.5, and BCT1.6).
- The final module will allow participants to sign up for additional SMS messages sent to their mobile phones throughout the week (ie, until the next assessment). This will add SMS messages on top of the messages already received on Wednesdays, Fridays, and Saturdays.

At any time, participants can send an SMS message with the word STOP to the phone number from which they receive messages. At this point, there will be no more SMS messages sent to the participant, including weekly assessments and links to the dashboard. Participants will, however, receive 1 more message where it says that we have acknowledged that they no longer wish to receive the intervention, unless they respond with START in an SMS, and that we will contact them solely with follow-up questionnaires, as previously agreed. The 4-month period of study for this trial is for research purposes only as, in principle, there is no finite end point to the intervention, and in a real-world setting, participants could engage with the intervention as long as they prefer. Therefore, we do not strictly interpret a STOP message from a participant as noncompliance but rather that the individual has decided that they no longer need the support. In an exploratory analysis, we will investigate if there is a relationship between alcohol outcomes and those who decide to stop the intervention before the 4-month mark.

Figure 1. Three screenshots from the interactive dashboard. Left: Each week participants are asked to assess their current consumption. Middle: One of the modules explores normative comparison of consumption levels. Right: Participants can see their consumption over time, allowing them to compare with their own goals.



Design

To study the effect of the intervention, a 2-arm parallel group randomized controlled trial will be employed. Nested within this trial will be the 3 substudies.

Recruitment and Eligibility

Using Web search engine advertisements (Google, Yahoo, and Bing) and social media (Facebook), we will target individuals in the general population of Sweden seeking help to reduce their alcohol consumption (advertisements are shown in Figure 2). Participants will initially be recruited over a 6-month period. Additional 6-month periods will be added if not enough participants have been recruited according to the initial power calculation. If 20.03% (426/2126) or less of the required population has been recruited at 12 months, then recruitment will stop at this time and data will be analyzed to inform future trial design. Recruitment will stop after 24 months if not before.

Individuals interested in participating in the study will be asked to send an SMS message with a specific code to a dedicated phone number. Within 10 min, participants will receive an SMS with a hyperlink that takes them to a Web page asking for informed consent. Individuals will be randomized to 1 of 2 different means of presenting the trial procedure when asking for informed consent (Consent-1 and Consent-2). Please see Multimedia Appendix 1 for more details.

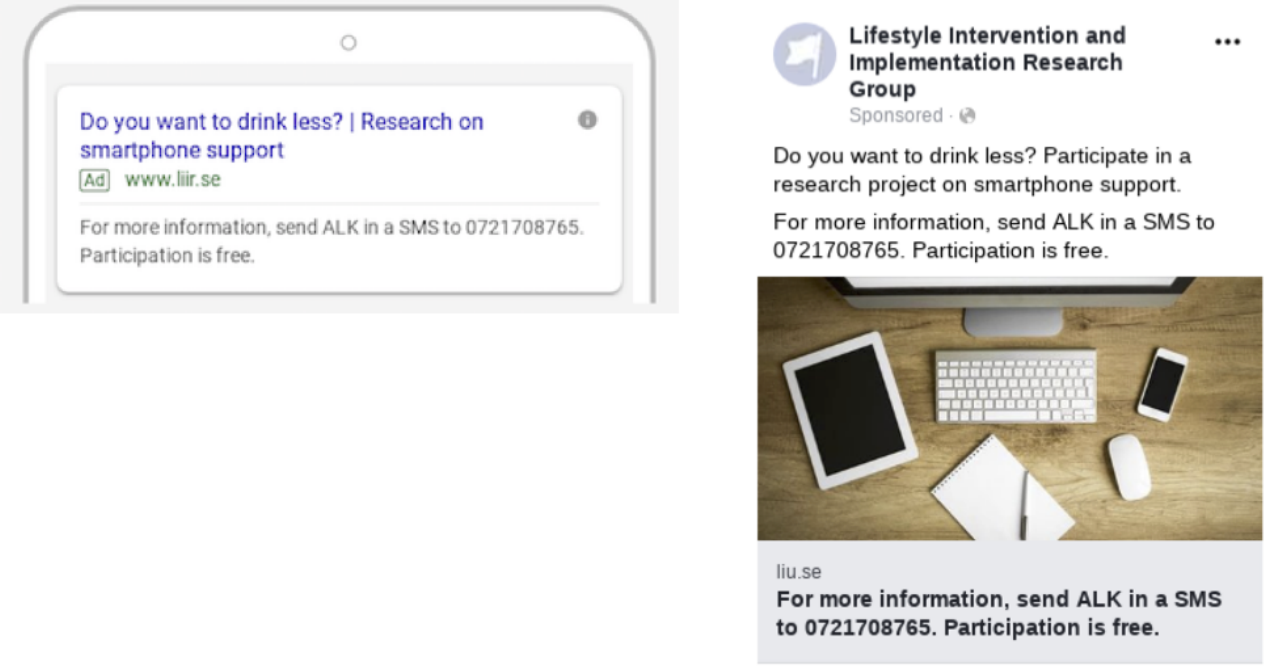
All individuals giving informed consent will be asked to complete a baseline questionnaire, which will also assess eligibility for the trial. The inclusion criteria will include the following: aged 18 years or older, ownership of a mobile phone, and being classified as a risky drinker according to Swedish guidelines.

Note that there is no upper limit to alcohol consumption as an exclusion criterion, meaning the study population is anticipated to comprise both harmful (ie, individuals who have experienced harm from any level of consumption [48]) and hazardous drinkers (ie, individuals with a consumption pattern that suggests increased risk to health [48]). No additional support will be offered to individuals who have a very high-consuming behavior.

Intervention and Control Conditions

Eligible individuals will be randomized to either an intervention group or a control group (intervention and control). The intervention group will receive the novel intervention for 4 months and will also be recommended to read about alcohol, health, and society on the same website as the control group (see Multimedia Appendix 2). Participants allocated to the control group will be advised that they will go through an initial phase of 4 months during which they are to receive information to increase their motivation and reduce their consumption, after which they will be given access to the new support tool. Thus, individuals allocated to the control setting will be given access to the novel intervention after completion of the final follow-up (4 months after randomization); no further data will be collected from individuals in the control setting.

Figure 2. Advertisements shown in search and on Facebook.



The control group will be randomized further into 2 groups (Info-1 and Info-2). Both Info-1 and Info-2 will receive a single SMS message with basic health information regarding short- and long-term effects of alcohol consumption. In this substudy, we incorporate a contrast between 2 very brief types of information; one which emphasizes possible complexities associated with the short- and long-term effects of alcohol (such as is widely available from alcohol industry sources [49], Info-1) and another which provides a clear and straightforward public health messaging style (while being appropriately evidence informed, Info-2). Each is delivered in a single SMS and includes the same link to a Swedish website with information about alcohol and society (IQ). As individuals who have enrolled are looking for help to change their alcohol consumption, we anticipate that most participants will be motivated to click on the link. It is plausible that either type of message could encourage trial participants more than the other to click on the link. This exploratory substudy concerned with the direct behavioral effects on accessing health information will assist further consideration of the design of control conditions and be relevant to alcohol health promotion more broadly. As there is some health information provided, including to participants who do not click on the link, we refer to the control condition as alcohol information. Please see Multimedia Appendix 2 for more details.

Mediation

To further understand the potential effects of the proposed intervention, we will measure psychosocial factors believed to be important for behavior change. We will use these measures to estimate how the effects of the intervention are mediated through these factors. Specifically, we will measure perceived confidence, importance, and know-how.

Confidence is closely linked to self-efficacy, a cornerstone of modern theoretical models of behavior change, prominently in social cognitive theory [50]. Importance is an aspect of both motivation and intention, 2 key factors in modern theory, for example, protection motivation theory [51], social cognitive theory [50], and theory of planned behavior [52] (and has been retrospectively added to the health belief model [53]). Know-how, alternatively expertise or skills, connects with several factors in theoretical models, for example, to behavioral control in the theory of planned behavior, and has been proposed as a specific necessary factor for behavior change [43,54]. Measuring if, and to what degree, these factors mediate the effect of the proposed intervention will help us better understand which factors are affected by the intervention and thus, why the intervention (potentially) works.

Randomization

In all cases, randomization will be fully computerized, will not employ any strata or blocks, and will not be possible to subvert as this and all subsequent study processes are fully automated. The main study will be single-blind as participants will be aware that 2 settings exist, and they will know which one of them they have been allocated to (intervention or control). The substudies involving Consent-1, Consent-2, Info-1, and Info-2 will be double-blind as participants will not be aware of the existence of the substudy or that they have been randomized. It is not possible to blind the individual responsible for data analysis, as this individual will also be responsible for data collection and involved in the monitoring of the technical platform.

Follow-Up

At 1 month after randomization, an SMS message will be sent to both intervention and control with a hyperlink to a questionnaire exploring mediators. At 2 and 4 months after randomization, an SMS message will be sent to both intervention and control with a hyperlink to a questionnaire exploring alcohol consumption. At 2 months after randomization, the questionnaire exploring recall of trial procedures will be added for both groups. At 4 months after randomization, the intervention group will receive questions regarding the usability and their experiences of the intervention, and the control group will receive questions regarding their experiences of being allocated to the control condition.

Figures 3 and 4 offer an overview of the design in the form of a Standard Protocol Items: Recommendations for Interventional Trials figure and Consolidated Standards of Reporting Trials flowchart.

Hypotheses

There are 5 main and 2 exploratory hypotheses mentioned in Textbox 1.

Apart from the hypotheses tested here, we will also do both a quantitative and qualitative analysis of users' experiences of engaging with the intervention and being allocated to the control group.

Measures

All questions asked at baseline and subsequent follow-ups can be found in Multimedia Appendix 3.

For hypotheses 1, 6, and 7:

- Primary outcome measures: Total weekly alcohol consumption and frequency of heavy episodic drinking.
- Secondary outcome measures: Classification as risky drinker according to Swedish guidelines.

For hypothesis 2:

- Mediation measures: Confidence in one's ability to reduce consumption, importance of reducing, and knowledge of how to reduce consumption.

For hypotheses 3 and 4:

- Primary outcome measures: Enrollment rates from each study condition
- Secondary outcome measures: Recall of trial procedures measured through a series of questions.

For hypothesis 5:

- Primary outcome measures: Rates of additional information being requested by pressing on the supplied hyperlink.

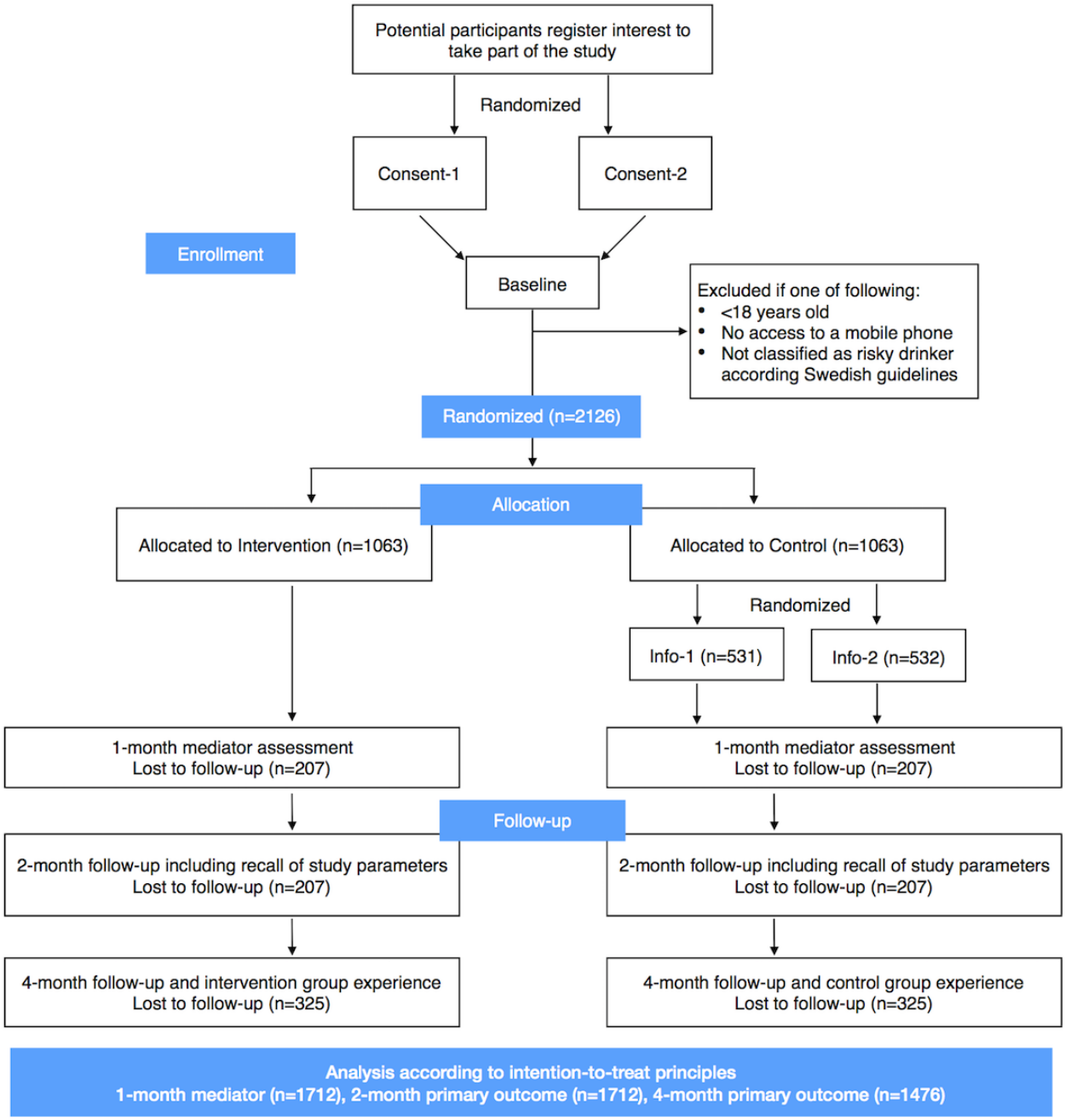
Figure 3. Standard Protocol Items: Recommendations for Interventional Trials figure.

	STUDY PERIOD					
	Enrollment	Allocation	Post allocation			Close-out
TIMEPOINT	$-t_1$	0	t_1	t_2	t_3	t_x
ENROLLMENT:						
Randomization to Consent-1 and Consent-2	X					
Informed consent	X					
Eligibility screen	X					
Allocation		X				
ALLOCATIONS:						
Intervention		X	←	—	—	→
Info-1		X	←	—	—	→
Info-2		X	←	—	—	→
ASSESSMENTS:						
Baseline questionnaire	X					
Mediator questionnaire				X		
Alcohol outcome measures					X	X
Recall of trial procedure					X	
Intervention group experience						X
Control group experience						X

Total weekly alcohol consumption will be assessed by asking participants the number of standard units of alcohol they consumed last week, that is, a short-term recall method [55]. Using a summary measure, rather than asking day-by-day, will allow for the same question to be asked, regardless if responses are collected via Web questionnaires, SMS, or by phone interviews (see Follow-up Attempts). In addition, 1 study suggests that when considering short-time spans, summary measures do not imply any noteworthy bias compared with asking for consumption day-by-day [56]. The frequency of heavy episodic drinking will be assessed by asking participants how many times they have consumed more than 4 (females) or 5 (males) standard units of alcohol on 1 occasion the past month, again asking for a summary measure over a concrete time period. An individual is classified as a risky drinker if either total weekly consumption or heavy episodic drinking exceeds recommendations.

Confidence, importance, and know-how will be measured at baseline and at 1-month follow-up by asking “How confident are you that you will be able to reduce your alcohol consumption?,” “How important do you think it is to reduce your alcohol consumption?,” and “How well do you know how to reduce your alcohol consumption?,” all 3 with response options on a 10-point scale (see Multimedia Appendix 3). The wording of the questions at 2- and 4-month follow-up will change to include those who have reduced their consumption: “How confident are you that you will be able to reduce or keep a lower level of alcohol consumption?,” “How important do you think it is to reduce or keep a lower level of alcohol consumption?,” and “How well do you know how to reduce or keep a lower level of alcohol consumption?.”

Figure 4. Consolidated Standards of Reporting Trials flow diagram (see power calculation section for details of n).



Textbox 1. Hypotheses.

Main Hypotheses

1. Alcohol consumption will differ between intervention and control groups, with the intervention group drinking less than control at 2 and 4 months after randomization. The 2-month interval will be primary.

2. Confidence, importance, and know-how at 1-month follow-up will mediate the effects of the intervention on drinking outcomes at 2-month follow-up. The same measures at 2-month follow-up will mediate the effect on drinking outcomes at 4-month follow-up.

3. Enrollment rates will differ between groups Consent-1 and Consent-2.

4. Accurate recall of study parameters will differ between groups Consent-1 and Consent-2.

5. Rates of accessing further information will differ between groups Info-1 and Info-2.

Exploratory Hypotheses

6. Alcohol consumption will differ between groups Consent-1 and Consent-2 at 2 and 4 months after randomization. The 2-month interval will be primary.

7. Alcohol consumption will differ between groups Info-1 and Info-2 at 2 and 4 months after randomization. The 2-month interval will be primary.

With regard to recall of trial procedures, there are 3 parameters that are of interest. First, participants will be asked if they recall receiving information about allocation to 2 different groups. As information regarding group allocation was presented identically for Consent-1 and Consent-2, this question will both work as a check that randomization succeeded and as a general baseline for recall regardless of group allocation. Second, participants will be asked if they recall how personal data will be handled in the study and their rights to these data. Finally, participants will be asked if they remember how the data would be analyzed and results communicated (see Multimedia Appendix 3).

We wish to measure if participants access further health-related information after reading a short SMS with basic information about short-term and long-term consequences of alcohol consumption. A proximal outcome of this is to measure whether or not participants in Info-1 and Info-2 request more information by following the included hyperlink. In addition, a short questionnaire at 4-month follow-up will investigate the control group participants, which will be used to investigate further differences between Info-1 and Info-2 (see Multimedia Appendix 3).

The acceptability and usability of the intervention will be measured through a questionnaire and the system usability scale [57] at 4-month follow-up (see Multimedia Appendix 3). The system usability scale comprises 10 Likert items exploring users' perception on usability of a product or service.

Follow-Up Attempts

There are 3 follow-up stages: 1, 2, and 4 months after randomization. All follow-ups will be initiated by sending SMS messages to participants with hyperlinks to questionnaires. In all cases, the following attempts will be made to collect data from nonresponders:

1. A total of 2 reminders will be sent 2 days apart to those who have not responded.
2. If no response is given to (1), then we will send questions directly in an SMS message, asking participants to respond directly with an SMS (no hyperlink).
    - At 1 month, we will ask all 3 mediator questions.
    - At 2 and 4 months, we will only ask for primary alcohol outcome measures.
3. If there is no response given to (2), we will attempt to call participants to collect responses to the same questions as in (2). A maximum of 5 attempts will be made.

Statistical Analysis Methods

All analyses will be done under the intention-to-treat principle, where all randomized individuals will be included. Missing outcome data will initially be handled by a complete-case analysis, which assumes that data are missing at random (MAR). If data are systematically missing, then it may be the case that early responders differ from late responders and, in extension, that late responders are more similar to nonresponders. We will, therefore, explore the plausibility of the MAR assumption by regressing the primary outcomes on the number of follow-up attempts needed before a response was recorded. To further explore the MAR assumption, attrition will be investigated among study groups by comparing baseline characteristics between those who did and did not respond at follow-up. A sensitivity analysis that includes imputed values for missing outcome data (using multiple imputation by chained equations [58]) will also be performed. Data will be graphically examined for outliers or data input errors, and sensitivity analyses will be performed excluding any erroneous data points.

For all models, coefficients of interest will be assessed for statistical significance using a null hypothesis testing approach, where tests will be 2-tailed at the .05 significance level. Alongside the null hypothesis tests, posterior distributions using a Bayesian approach will be calculated for each coefficient. Both significance tests and posterior distributions will create a basis for scientific inference [59].

Baseline

Baseline characteristics will be compared among the different groups using chi-square tests or Fisher exact tests for comparison of proportions and Mann-Whitney *U* tests for comparison of means.

Hypotheses 1, 6, and 7

Total weekly alcohol consumption and frequency of heavy episodic drinking are likely to be skewed and overdispersed, and we will, therefore, analyze both using negative binomial regression. Classification as a risky drinker will be analyzed using logistic regression. Both unadjusted and adjusted regression models will be created. Adjusted models will include baseline values of the respective outcome measures and responses to the baseline questions regarding sex, civil status, age, motivation, importance, and know-how. As alcohol consumption differs significantly among age groups, and possibly also the effect of the intervention, multilevel models will also be created in which slopes are allowed to vary among age groups. Effect modification tests will be performed in all models to assess if any of the baseline characteristics moderate the effect of the intervention. The adjusted models will be the primary models.

Hypothesis 2

Mediators will be explored using a causal inference framework [60], where Monte Carlo methods are relied upon for inference. This allows for any type of model (linear and nonlinear) to be used to represent the relationships between the group allocation, mediating variable, and outcome. A total of 4 models will be created for each outcome measure, 3 that investigate the mediating factors on their own and a fourth that incorporates all mediators at once. If any baseline characteristics were found to moderate the effect in the primary analysis, then additional mediator models will be created to include these as moderators.

Hypotheses 3 and 4

Whether or not individuals decided to give informed consent will be regressed against group allocation (Consent-1 and Consent-2) using logistic regression. Adjusted regression models will be explored that include baseline characteristics (including only participants who gave informed consent). Differences among the 2 groups on responses to the recall questionnaire

will be investigated using chi-square tests or Fisher exact tests for comparison of proportions.

Hypothesis 5

Whether or not individuals requested more information by pressing the hyperlinks will be regressed against both group allocation (Info-1 and Info-2) and fixed responses to the control group experience questionnaire using logistic regression. Adjusted models will be explored that include baseline characteristics. Differences among the 2 groups on responses to the control group experience questionnaire will be investigated using chi-square tests or Fisher exact tests for comparison of proportions.

Acceptability and Usability of Intervention

Responses to the Likert items of the system usability scale are processed so that the total score ranges from 0 to 100. Empirical and validation studies suggest that systems scoring above 68 should be considered to have an above average usability [61]. We will calculate mean total scores and compare against this general guideline of 68.

To further investigate how different individuals perceive the usability of the intervention, linear regression models will be used to regress system usability scores against baseline characteristics and alcohol- and mediator-related outcome measures, as well as usage statistics of the intervention (collected as participants engage with the intervention).

Exploratory Analysis

The weekly assessments of the intervention group are primarily an aid for the individual to his or her behavior change. The data cannot be used in the primary analysis as they will quite certainly contain a lot of missing data (we do not expect participants to zealously report each week) and there are no data from controls. However, the data collected may nevertheless be useful to identify trends in potential reduction of alcohol consumption over time, thus, exploratory time series models will be created to see if there are patterns that are informative about intervention effects (such as reduction plateaus). Similarly, we will regress alcohol consumption outcomes on usage statistics in the intervention group, including frequency of use of different modules and whether or not the participant decided to stop the intervention before the end of the trial, possibly identifying a dose-effect relationship.

As part of the primary investigator's precision health initiative, we aim to include predictive modelling of the intervention. Traditionally, trials contrast the mean difference between 2 groups; however, they do not address individual variability. Intuitively, we know that some individuals will respond well to an intervention, whereas others might not, and some might further be harmed by it. We wish to predict how individuals will respond to an intervention using only individuals' baseline characteristics. We do this by measuring characteristics at baseline related to the behavior change theory, in this particular case self-efficacy, importance, and know-how, as well as alcohol consumption levels and conventional baseline characteristics (age and gender). These characteristics are then used to learn statistical models that predict individual outcomes.

Predictive analysis requires a radically different approach of assessing a model's performance, as explaining and predicting are 2 different tasks [62]. We utilize a Bayesian approach using shrinkage priors [63,64], which allows us to include all characteristics measured at baseline and then learn which ones should be included in the predictive model from the data. The result is a model that can tell individuals how likely it is that the intervention has a positive effect on them specifically, rather than always quoting the group mean difference.

Power Calculation

We conducted a Monte Carlo simulation study to determine the necessary number of individuals to randomize (N). We deliberately focused on the total weekly consumption outcome, as the analysis of this outcome in general requires more individuals than does the analysis of heavy episodic drinking (because of higher variance). We will begin by describing the initial distributional assumptions that we made and then the result of the simulations. We aimed to achieve 0.8 power at the .05 significance threshold.

- The effect (γ) of the intervention, that is, the percentage reduction in mean total weekly alcohol consumption in the intervention group, is assumed to follow a beta distribution with mean 0.15 and SD 0.025.
- The mean number of standard units consumed in the control group (μ_C) at follow-up is assumed to follow a normal distribution with mean 10 and SD of 0.5. The population under analysis are risky drinkers, thus, a mean consumption of 10 standard units is appropriate, and the analysis is quite robust to moderate changes in this assumption.
- The mean number of standard units consumed in the intervention group (μ_I) at follow-up is assumed to follow a normal distribution with mean $(1-\gamma)_C$ and SD of 0.5.
- The distribution over the number of standard units consumed at follow-up for both the intervention and control group is assumed to follow a negative binomial distribution. The means of these distributions are given by μ_C and μ_I, respectively, and have a dispersion parameter θ sampled from a normal distribution centered at 1 with an SD of 0.05.
- The number of individuals allocated to the intervention group follows a binomial distribution, with a 0.5 probability of success over N trials.

The Monte Carlo simulation explored different values of N (number of individuals randomized). For each N explored, the following simulations were done:

1. Draw 1 sample each for γ, μ_C, μ_I, and θ
    - Allocate a random number of individuals to the intervention
    - Give each individual a number of standard units consumed following the negative binomial distribution appropriate for their respective groups
    - Analyze the data using negative binomial regression
    - Note if the 0.05 threshold has been broken for the group allocation coefficient in the regression model
    - Repeat 100 times from (a) and then calculate power as the percentage of times that the threshold was broken

2. Repeat 1000 times from (1) and calculate the average power from (e)

We found that for N=1800; we have an expected average power of 0.79.

In previous studies similar to this [24,65], we have been able to achieve more than 90% response rate at follow-up using the scheme described in the section Follow-up Attempts. Assuming that the response rate is lowest at 4 months and that it follows a beta distribution with mean 85% and an SD of 5% (giving a 95% credible interval between 75% and 94%), then we will expect to lose 326 individuals to follow-up (interquartile range: 231,398). This implies that we need to randomize approximately 2126 individuals (interquartile range: 2031, 2198).

Results

Participant recruitment is planned to begin in April 2019 and last for a maximum of 24 months. The first dataset will be available approximately 2 months after the final participant has been recruited, and the final dataset will be available approximately 2 months later. No participants had been recruited at the time of submitting this protocol.

Discussion

Principal Findings

In Sweden, the student health care centers routinely administer eSBIs (via email) to the university students that they serve [7,8], and the general public have access to eSBIs via websites (eg, livsstilsanalys.alexit.se). However, beyond this single session intervention, there are no evidence-based digital interventions available for those who need continued support, despite the ubiquitousness of mobile phones in Sweden. The advice for individuals who need support beyond the eSBI is generally to search for advice on health websites or to seek help at a primary health care center.

This study is an evaluation of whether or not access to the novel intervention has any effect on alcohol consumption outcomes compared with providing information including referring individuals on to an alcohol and health website. If found effective, this type of intervention has the potential to reduce the burden from negative consequences of excessive alcohol consumption for individuals who need support beyond a single session eSBI and has been designed to have potential for extensive reach among those who may benefit. It has also been designed so that individuals can choose how long they use it for, meaning that intervention exposure can potentially extend for many years.

Previous trials of mHealth interventions targeting alcohol consumption have been aimed toward specific subgroups of a population, quite often young adults or individuals in alcohol use disorder treatment programs. Many of the studies have had issues with trial design or execution, and therefore, the collective evidence for mHealth interventions' effect on alcohol consumption is not well-developed. The novelty of targeting the adult population of Sweden by means of a broader recruitment than in previous trials, in the ways proposed, allows for both primary prevention: helping individuals prevent negative consequences, and secondary prevention: helping individuals to reduce negative consequences already experienced. By using a scheme that we have previously found successful in achieving high follow-up rates, we aim to avoid the attrition issues that have manifested in previous studies.

Substudies

Apart from the main outcome, this trial will also investigate methodological and ethical issues in randomized controlled trials. Although informing participants about trial procedures before asking for informed consent has been required for some time, the introduction of GDPR has increased the focus on data privacy and handling of personal information. Participants should be made aware of their rights, and the findings from the substudy regarding recall of trial procedures will give insights into how well participants read, and later recall, the information given before informed consent. If individuals cannot recall that randomization was to occur, the ethical implications deserve fuller consideration.

Similarly, we will explore the nature of the alcohol information control condition and the extent to which introductory text has implications for accessing further information via a link. This study is informative about the inter-related issues of the possible effects of contrasting types of information and the nature of control conditions, which commonly employ informational content.

Ethical Concerns

The conduct of the substudies raise ethical issues, as they do not themselves involve informed consent. The possible importance of each substudy provides 1 possible justification for not seeking consent, as seeking consent would interfere with the substudy itself. The consent study also involves data collection from those who choose not to participate in the trial. A key consideration in such a situation is the possibility of harm to participants [66]. In this instance, not obtaining informed consent is regarded as being unlikely to produce harm in each substudy.

A further ethical risk lies in the nature of the control condition and its appropriateness for those who have been targeted for recruitment because they wish to drink less. Ethical considerations led us to construct the control condition, and the information contained within each arm, to resemble content that is available on the Web that study participants may encounter. The control condition is thus similar to usual care. Note, however, that this is not a population that is defined by the existence of problems or has been identified as seeking help to reduce problems, beyond responding to Web advertisements. For those participants who are drinking harmfully or seeking further help, the control condition refers on to the national Swedish Web resource.

Limitations

The trial is designed to recruit enough participants to power the main alcohol-related outcomes; thus, the included substudies are not powered to detect significant differences. Rather, the substudies included herein are supposed to be seen as

preliminary and exploratory work laying a basis for future trials of these phenomena.

The power calculation considers a range of follow-up rates (beta distribution with a mean of 85% and an SD of 5%), and the number of individuals (n=2126) found to be necessary to randomize may have to increase toward the upper quartile (n=2198) if follow-up rates are found to be lower than the mean of 85%. Our previous trials [24,65] have been able to collect data from more than 90% of participants using the same follow-up scheme used in this trial; thus, despite not using incentives to sustain high levels of follow-up rates, we believe our expectation of 85% follow-up rate to be warranted.

Acknowledgments

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Authors' Contributions

MB had the original idea for the study, which was expanded on by JM. MB led on the statistical analysis plan and the authoring of this trial protocol. MB undertook all computer programming and is responsible for all steps in the data collection. JM added to the trial protocol, and both authors read and approved the final manuscript.

Conflicts of Interest

MB owns a private company that develops and distributes lifestyle interventions to be used in health care settings. If the proposed intervention is found effective, then it will be made available for free to the general public through MB's private company.

Multimedia Appendix 1

Information regarding trial procedures.

[PDF File (Adobe PDF File), 157KB - resprot_v8i4e13119_app1.pdf]

Multimedia Appendix 2

Group information.

[PDF File (Adobe PDF File), 135KB - resprot_v8i4e13119_app2.pdf]

Multimedia Appendix 3

Questionnaires.

[PDF File (Adobe PDF File), 232KB - resprot_v8i4e13119_app3.pdf]

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Abbreviations

BCT: behavior change technique
eHealth: electronic health
eSBI: electronic screening and brief intervention
GDPR: General Data Protection Regulation
MAR: missing at random
mHealth: mobile health
OR: odds ratio
SMS: short message service

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Protocol

Expanding Access to Depression Treatment in Kenya Through Automated Psychological Support: Protocol for a Single-Case Experimental Design Pilot Study

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Abstract

Background: Depression during pregnancy and in the postpartum period is associated with a number of poor outcomes for women and their children. Although effective interventions exist for common mental disorders that occur during pregnancy and the postpartum period, most cases in low- and middle-income countries go untreated because of a lack of trained professionals. *Task-sharing* models such as the *Thinking Healthy Program* have shown great potential in feasibility and efficacy trials as a strategy for expanding access to treatment in low-resource settings, but there are significant barriers to scale-up. We are addressing this gap by adapting *Thinking Healthy* for automated delivery via a mobile phone. This new intervention, *Healthy Moms*, uses an existing artificial intelligence system called *Tess* (*Zuri* in Kenya) to drive conversations with users.

Objective: The objective of this pilot study is to test the *Healthy Moms* perinatal depression intervention using a single-case experimental design with pregnant women and new mothers recruited from public hospitals outside of Nairobi, Kenya.

Methods: We will invite patients to complete a brief, automated screening delivered via text messages to determine their eligibility. Enrolled participants will be randomized to a 1- or 2-week baseline period and then invited to begin using Zuri. Participants will be prompted to rate their mood via short message service every 3 days during the baseline and intervention periods. We will review system logs and conduct in-depth interviews with participants to study engagement with the intervention, feasibility, and acceptability. We will use visual inspection, in-depth interviews, and Bayesian estimation to generate preliminary data about the potential response to treatment.

Results: Our team adapted the intervention content in April and May 2018 and completed an initial prepilot round of formative testing with 10 women from a private maternity hospital in May and June. In preparation for this pilot study, we used feedback from these users to revise the structure and content of the intervention. Recruitment for this protocol began in early 2019. Results are expected toward the end of 2019.

Conclusions: The main limitation of this pilot study is that we will recruit women who live in urban and periurban centers in one part of Kenya. The results of this study may not generalize to the broader population of Kenyan women, but that is not an objective of this phase of work. Our primary objective is to gather preliminary data to know how to build and test a more robust service. We are working toward a larger study with a more diverse population.

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KEYWORDS

telemedicine; mental health; depression; artificial intelligence; Kenya; text messaging; chatbot; conversational agent

Introduction

Background

Depression is a leading cause of disability worldwide. Women suffering from perinatal depression are a particularly underserved population. Depression during pregnancy and in the postpartum period (perinatal depression) affects as many as 20% of women in high-income countries [1] and maybe more in low-income countries [2]. The condition is associated with a number of poor outcomes for women and their children, including increased maternal morbidity and mortality [3,4], poor infant health [5-9], and poor developmental outcomes [10-12].

Although effective interventions exist for common mental disorders that occur during pregnancy and the postpartum period [13], most cases in low- and middle-income countries (LMICs) go untreated. In these settings, more than 7 out of 10 people who need treatment cannot access care because of a lack of trained professionals [14]. In Kenya, for example, there are only 180 psychiatric nurses outside of the capital city, a ratio of 1 provider per 200,000 people. To close this gap, the World Health Organization developed the Mental Health Gap Action Programme intervention guide outlining how to deliver mental health services in primary health care settings through nonspecialist providers. This *task-sharing* approach has proven efficacious, particularly for maternal mental health [15].

A prime example is the 15-session *Thinking Healthy Program*, a cognitive behavior therapy–based intervention for treating perinatal depression that is intentionally nonstigmatizing [16]. Community health workers—typically women educated through secondary school with no specific background in mental health—are trained over 5 to 10 days to help pregnant women learn 3 skills: (1) to identify unhealthy thinking, (2) to replace unhealthy thinking with helpful thinking, and (3) to practice thinking and acting healthy. In a trial in Pakistan with 900 pregnant women, Rahman et al found that the intervention halved the prevalence of major depression [17], and a 7-year follow-up study reported some spontaneous recovery among the control group but also a persistent effect of treatment [18].

Despite this impressive evidence of feasibility and efficacy, however, there are significant barriers to scale-up [19], and there is evidence that intervention effects might not extend to children of depressed mothers without additional engagement [20]. Common implementation challenges of task-sharing models such as *Thinking Healthy* include a lack of funding and infrastructure for training and service delivery, workforce retention in the absence of compensation or incentives for nonspecialists, high workloads, transportation costs, appointment scheduling logistics, and inadequate clinical supervision [21]. Although it is critical to study how to optimize and scale these task-sharing approaches—and a peer-delivered version of *Thinking Healthy* offers a potential cost-effective first-line strategy for treating perinatal depression [22]—the fact remains that, today, most women in LMICs who need treatment still have no access to care. It can also be argued that there are substantial service gaps in high-income countries such as the United States where it was recently recommended that all women at increased risk for perinatal depression be referred for *preventive* counseling [22].

Given this demand and barriers to scale-up, our idea is to make it possible for anyone with a basic phone to receive high-quality, evidence-based psychological support anytime, anywhere. We will do this in the context of perinatal depression by adapting *Thinking Healthy* to an existing artificial intelligence (AI) system for automated psychological support called *Tess* (which we have named *Zuri* in Kenya). This idea is innovative because it introduces an entirely new delivery channel that has the potential for a step change in expanding access to care, while also potentially augmenting and strengthening existing task-sharing models.

Zuri works by engaging a patient in conversation via a variety of trusted channels, including text messaging (short message service [SMS]). Either Zuri or the patient can start a conversation, and Zuri can be programmed to walk a patient through a structured curriculum such as *Thinking Healthy*. As a safety measure, conversations with patients in need of additional support can be handed over to live counselors as needed. Benefits of this approach include on-demand 24/7 access for an unlimited number of patients, no scheduling of appointments, no travel costs to appointments, enhanced sense of privacy and avoidance of social stigma, and high fidelity to treatment.

Scientific Objectives and Significance

Our long-term goal is to expand access to high-quality, on-demand treatment services to people in emerging markets who suffer from common mental disorders such as perinatal depression but cannot receive care from mental health professionals because of cost and human resource constraints. The main objectives of this proposed work are to adapt *Thinking Healthy* for dissemination in Kenya through the Zuri AI system; develop and test study procedures; and generate preliminary evidence of feasibility, acceptability, and response to treatment. If successful in future full-scale trials, we will create an opportunity to expand access to evidence-based treatments on an order of magnitude that has proven difficult to achieve through traditional approaches that rely on expanding the lay and professional mental health workforce.

Expected Outcomes

The expected outcomes of this proposed work include the following: (1) experience recruiting, screening, and enrolling women from this population; (2) evidence on feasibility and acceptability of the intervention in this setting; (3) preliminary evidence on response to treatment; and (4) a set of open source resources for automated delivery of the intervention that can be adapted for new contexts. We plan to use the preliminary evidence generated by this project to inform the design of a randomized controlled trial.

Methods

Research Design

We propose to adapt *Thinking Healthy* for the Zuri AI system and evaluate the combined perinatal depression intervention (which we are calling *Healthy Moms*) with a cohort of pregnant women and new mothers recruited from 2 large public hospitals in Kenya. We will use a single-case experimental design (partially nonconcurrent multiple baseline [23], open label) and qualitative interviews to generate preliminary data on feasibility, acceptability, and response to treatment.

Participants and Recruitment

We will recruit pregnant women and new mothers from 2 large public hospitals in Kiambu County, Kenya. Both hospitals are part of a county-wide partnership offering patients innovative SMS programs that promote healthy motherhood [24]. When a woman signs up for the county SMS service, we will send her an invitation via SMS to complete an automated SMS screening (in English) to see if she is eligible for *Healthy Moms*. The screening will include questions about age, maternity status, expected or actual delivery date, 9 questions about symptoms of depression from the Patient Health Questionnaire-9 (PHQ-9) [25], and a question about her current mood.

We will inform all women who complete the screening that a study team member will call them within 1 business day. During this follow-up call, women who endorsed having thoughts of self-harm in the past 2 weeks (Question 9 on the PHQ-9) will be offered a referral for counseling but will not be eligible to enroll in *Healthy Moms* given the early stage of intervention development. All other women will be eligible to enroll as long as they confirm that they are at least 20 weeks pregnant or no more than 6 months postpartum. The study representative—a Kenyan woman fluent in English and Swahili—will assess each woman's English-speaking ability on the call and ask women to rate their ability to read and understand English. We will allow women to enroll regardless of language ability to examine the relationship between ability and engagement, but we will inform low (English) literacy women that they might not find value in the current version of the program if they are not comfortable reading and writing in English.

If a woman chooses to continue the enrollment process, the study representative will read the informed consent form, answer her questions, and obtain verbal informed consent to enroll. Enrollees will be asked to share information about the type of phone they use, schooling, number of dependents, marital status, and employment status. There is no cap on enrollment.

Eligibility

To be eligible to participate, women must meet the following criteria: (1) pregnant (>20 weeks) or less than 6 months postpartum; (2) receiving antenatal or postnatal health care services from a participating hospital in Kiambu County; (3) enrolled in the county SMS program; and (4) at least 18 years of age. English language proficiency is not a requirement but will be assessed for later subgroup analysis. Likewise, endorsement of depression symptoms is not a requirement, but depression severity and mood will be assessed for later subgroup analysis. Women who endorse suicidal ideation at the time of recruitment will be ineligible to enroll in the study and will be informed about potential resources for treatment.

Randomization to Baseline Length

As each woman enrolls in the study, she will be matched to another new enrollee of similar maternity status and randomly assigned (using a random number generator) to have a 1-week or 2-week baseline period. This will ensure that every participant has a concurrent baseline period with at least one other person.

Outcomes and Data Collection

Outcomes will include intervention use, feasibility, acceptability, depression severity, and current mood.

We will assess intervention use by reviewing Zuri system logs to document (1) completion of *Healthy Moms* sessions and (2) patient-initiated engagement with Zuri outside of scheduled sessions.

The Zuri system logs will also inform our assessment of feasibility and acceptability; low engagement will be considered a marker of potential barriers to feasibility or a lack of acceptability. We will explore these issues by inviting users to participate in up to 3 individual interviews during the evaluation period. During these interviews, we will examine barriers to access and use that may limit the feasibility of offering this intervention at scale if not addressed. We will also examine whether there are aspects of Zuri's *personality* and style that limit acceptability and participants' desire to engage with the intervention. To further explore feasibility issues, we will document all contact the research team has with participants outside of the Zuri AI system and log all adverse events. We are interested in determining how much assistance or encouragement users need from the team to understand and use the automated intervention.

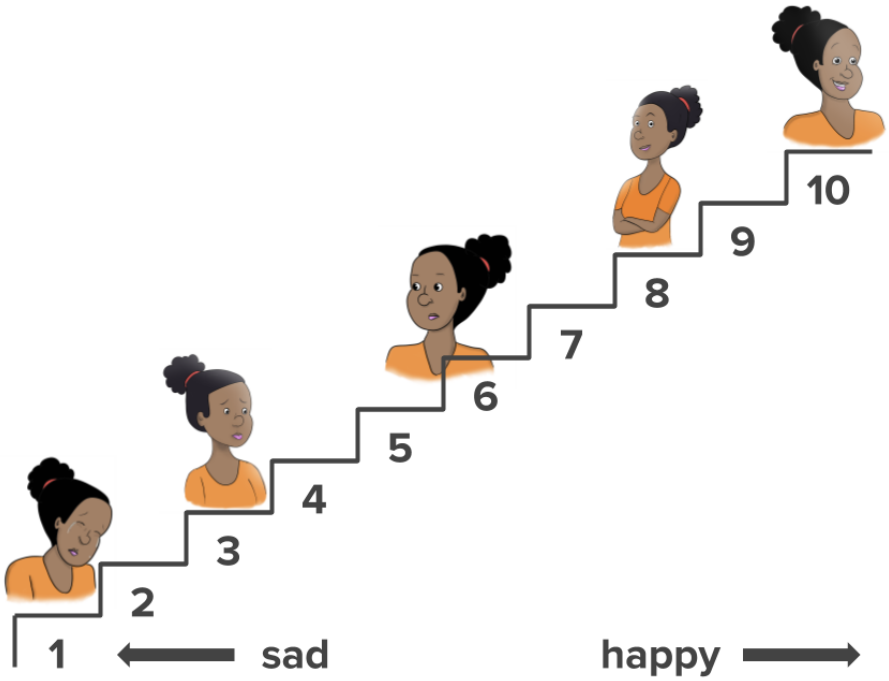
We will assess depression severity during the enrollment screening and throughout the intervention period via SMS. An aim of the study is to determine the frequency of assessment that is useful and acceptable to participants. At a minimum, we will attempt to have at least 2 self-ratings of depression severity representing pre and posttreatment.

To measure mood, we will ask participants to rate their feelings on a 10-point scale we created and tested with users (see Table 1).

Table 1. Mood rating scale.

Message	Text
1	Imagine a 10-step staircase where 1 means very sad and 10 means very happy.
2	Which step best shows how you are feeling today? Very SAD 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10 Very HAPPY

Figure 1. 10-Step staircase visual reference for mood ratings.



We will invite women to rate their current mood via SMS during the enrollment screening and then every 3 days throughout the baseline and intervention periods. Each rating invitation will remind women of their previous rating. We will also encourage women to track and reflect on their mood and behaviors on a daily basis using the *Healthy Moms* journal we will provide as part of the intervention (not analyzed). The journal will include the 10-step illustration shown in Figure 1.

Intervention

We will invite women to participate in up to 15 phone sessions of the *Healthy Moms* intervention depending on their maternity status at enrollment. We modeled these automated SMS sessions after the original *Thinking Healthy* manual that was developed to guide community health workers to deliver the intervention in-person over 15 sessions [16]. We also created a companion *Healthy Moms* journal that we will print and deliver to enrolled participants [26]. The journal includes modified *health calendars* from the original *Thinking Healthy* intervention along with short session summaries and writing prompts. This pilot study is an opportunity to get feedback on the journal to inform how we might adapt the content into text, audio, and video for electronic delivery (and ultimately discontinue print versions in future trials). We conducted an initial round of user testing to develop the SMS intervention journal content [27].

During each *Healthy Moms* session, women will interact with the automated system via SMS. In between sessions, women will be encouraged to start a conversation with Zuri by sending a free SMS. Zuri will attempt to discern the user's request and respond automatically with answers or replies that employ *active listening* techniques such as restatement and reflection. If a woman discusses self-harm or other crisis topics, Zuri will alert a live study support member who can take over the chat session or call the participant directly and facilitate a referral to traditional in-person treatment if indicated. Women will be informed that the response may not be immediate at this stage of testing, so they should seek help at an emergency room if in a crisis. Participants will also be informed that they may seek concomitant care and interventions at any point during the pilot study.

Just as mental health specialists and nonspecialists trained to deliver psychotherapy improve over time with practice and experience, AI-enhanced systems such as Zuri also change, albeit in more subtle ways, given the current state of the technology. For instance, Zuri's emotion recognition algorithms will update automatically each time it correctly or incorrectly interprets the emotional valence of a user's input, but the didactic intervention content will not change dynamically. Modifications to the intervention content are possible but will be manual; we will review conversation transcripts and may make changes to the wording or sequence of messages if we notice that users are confused or not engaging. Any changes are expected to be minor with more substantial changes following the completion of the pilot study.

Analysis Plan

Our analysis will seek to summarize the preliminary evidence on feasibility, acceptability, and response to treatment.

Describe Participant Engagement With the Intervention

We will use the system logs to summarize how frequently each participant engages with the intervention by (1) participating in a *Healthy Moms* session (in response to a scheduled invite) or (2) initiating a chat with Zuri in between scheduled sessions. Figure 2 displays a mock waffle plot that demonstrates one way we might seek to visualize these data.

As part of describing patterns of engagement, we will also calculate and summarize (1) the delay between our invitations to begin a *Healthy Moms* session and participants' start times, (2) the proportion of *Healthy Moms* sessions started and completed, and (3) the duration of participant-initiated chats with Zuri. To further investigate the nature of participant-initiated chats, we will complete a content analysis of conversation transcripts and summarize themes.

Identify Potential Barriers to Intervention Feasibility and Acceptability

As a hypothesis-generating exercise, we will search for possible associations between participant characteristics measured at baseline (eg, age, education, literacy, and symptom severity) and intervention engagement. We will further explore barriers to engagement during in-depth interviews with participants and reviews of chat transcripts. Our search for barriers will include human and system factors that (1) make it challenging for participants to engage with the intervention (usability and feasibility) or (2) lower participants' desire to engage with the intervention (acceptability).

Generate Evidence About the Variability in Participant Response to Treatment

We will use visual inspection, in-depth interviews, and Bayesian estimation to generate preliminary data about the potential response to treatment. First, 2 raters will visually examine time series plots of self-ratings for within-subject changes in trends, as shown in Figure 3.

Second, during in-depth interviews with participants, we will explore potential links women see between engagement with the intervention and their mood, health, and relationships. For women who do not seem to respond, we will examine the possibility that (1) future changes to the intervention may generate a response or (2) there are clinical subtypes that may not benefit much from an intervention like *Healthy Moms*.

Third, we will attempt to aggregate the individual N-of-1 studies and estimate the magnitude of response and quantify uncertainty by fitting a Bayesian linear mixed-effects model [28-30]. The model will include a random effect for observations nested within participants and the following fixed effects: (1) an intercept, (2) a dummy indicator for the treatment phase, (3) a time-within-baseline variable centered around the first observation (equal to 0 for observations outside of the baseline period), and (4) a time-within-treatment variable centered around the last observation (equal to 0 for observations outside of the treatment period). We will apply a first-order autoregressive structure on the covariance matrix for the within-person residuals to account for autocorrelation. With these fixed effects—and with this centering—the intercept weeks will represent the mean value of the outcome at the first baseline assessment, the treatment indicator will be a contrast between the first baseline assessment and last observation in the treatment period, and the time-within-period variables will estimate linear change during the baseline and treatment periods.

Research Ethics

We have obtained approvals to conduct this study from the Institutional Review Boards at Duke University (US, 2018-0396) and Strathmore University (Kenya, SU-IRB 0210/18) as well as from the National Commission for Science and Technology in Kenya.

A trained research assistant (female, Kenyan) will explain the study to prospective participants via telephone and administer informed consent procedures. All eligible participants must provide oral informed consent before enrollment.

Figure 2. Mock waffle plot showing a hypothetical pattern of engagement for 1 participant.

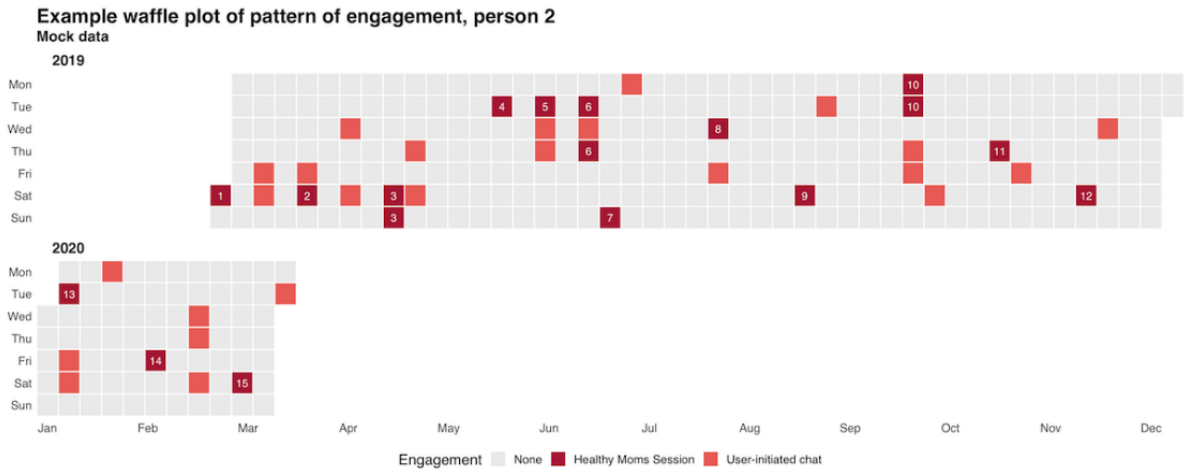
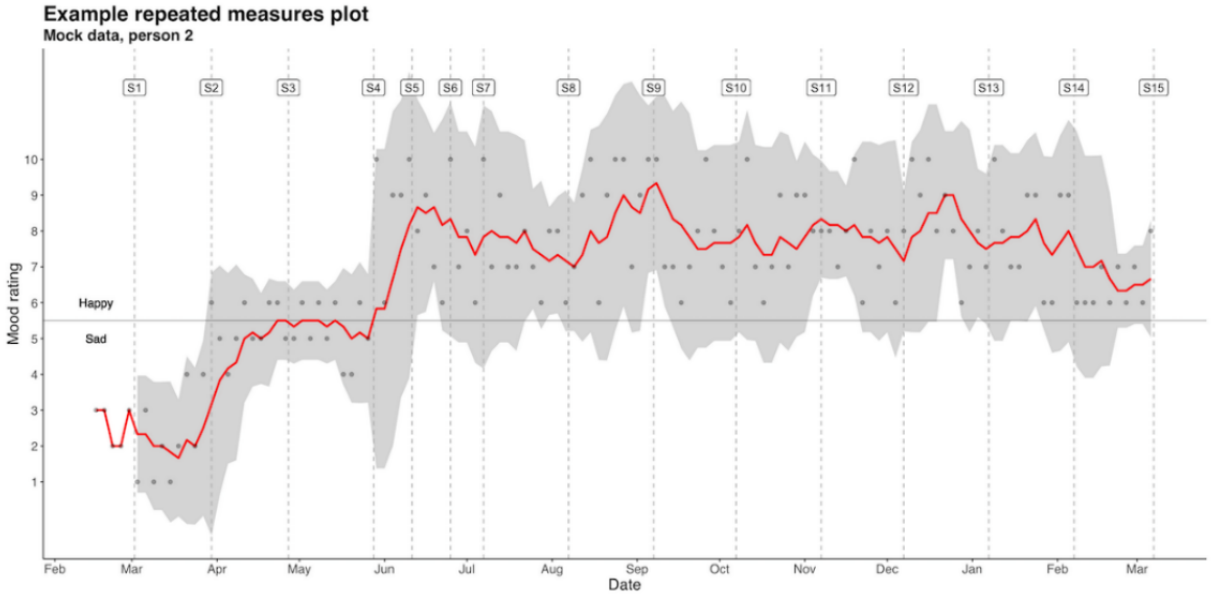


Figure 3. Mock plot of hypothetical mood self-ratings over time for 1 participant session completion dates. The points represent each daily mood rating, the solid red line in the postbaseline period represents a rolling mean of daily ratings (window 6), and the gray band represents the 95% CI of this rolling mean. S#: session number.



Study participants will be provided with an honorarium of Ksh 1500 (roughly US $15) delivered in 3 installments via mobile money transfer (after completing sessions 1, 5, and 10) to recognize time spent completing study assessments. Women who withdraw from the study will receive a prorated honorarium.

Data will be transferred from X2AI, the creators of the AI system that we will use to deliver *Healthy Moms*, to the research team in accordance with X2AI's data security policies [31]. The first author will store identifiable study data on Duke's Box.com servers. At the conclusion of the study, the first author will deidentify the data for analysis using the Safe Harbor method. Quantitative data will be fully anonymized for external sharing. Participant names will never be used in study reporting.

Results

In April and May 2018, we adapted the *Thinking Healthy* curriculum for the Kenyan context and created new content to support automated delivery via SMS text message. In May and June 2018, we conducted an initial round of user testing with 10 nondepressed women recruited from a private maternity hospital outside of Nairobi. We documented our early testing process and learnings in a series of articles on *Medium* [27,32]. From August to December 2018, we attempted to follow a face-to-face enrollment protocol, but we found it to be too slow and potentially subject to underreporting of symptoms given the stigma attached to mental health issues in this setting. Approvals for the revised protocol described here were granted in early 2019. Results are expected toward the end of 2019.

Discussion

The main limitation of this pilot study is that we will recruit women who live in urban and periurban centers outside of Nairobi, Kenya. The results of this study may not generalize to the broader population of Kenyan women, but that is not an objective of this phase of work. Our primary objective is to gather preliminary data to know how to build and test a more robust service. We are working toward a larger study with a more diverse population.

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Authors' Contributions

EPG, NP, SR, MR, and AJ led the design of the study. All authors provided input on the design and planning and will contribute to study implementation.

Conflicts of Interest

MR is the CEO and Founder of X2AI and created Tess. AJ is an employee of X2AI. EPG is an unpaid advisor to the X2AI Ethical Advisory Board and has no financial stake in the company.

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Abbreviations

AI: artificial intelligence
LMIC: low- and middle-income countries
PHQ-9: Patient Health Questionnaire-9
SMS: short message service

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Protocol

Coaching and Education for Diabetes Distress (CEDD): Protocol for a Randomized Controlled Trial

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Abstract

Background: Diabetes distress (DD), a type of psychological distress specific to people with diabetes, is strongly associated with difficulties in performing self-care and inability to meet glycemic targets. Despite increased recognition of the need to manage DD, interventions that are both feasible and effective for reducing DD in routine care settings are not yet known. A pilot study showed that health coaching (HC) has some efficacy in addressing DD, but no adequately powered study has implemented a pragmatic research design capable of assessing the real-world effectiveness of HC in reducing DD.

Objective: The aim of this study is to describe the rationale and design of an ongoing clinical trial, Coaching and Education for Diabetes Distress trial, that seeks to assess whether HC effectively reduces DD among primary care patients with diabetes and whether HC is more effective than an educational program targeting DD.

Methods: The 2-arm randomized controlled trial is taking place at an academic family medicine practice in Houston, Texas. Both arms will receive usual care, which includes education about DD. In addition, the intervention arm will receive 8 HC sessions over a 5-month period. The primary outcome measure is reduction in DD over a 6-month period. Additional outcome measures include changes in hemoglobin A_{1c} and self-care practices (medication-taking, dietary, and physical activity behaviors).

Results: As of March 2019, screening and recruitment are ongoing, and the results are expected by July 2020.

Conclusions: HC is feasible in primary care and has been successfully applied to improving chronic disease self-management and outcomes. This study will provide evidence as to whether it has significant value in addressing important unmet psychological and behavioral needs of patients with diabetes.

Trial Registration: ClinicalTrials.gov NCT03617146; https://clinicaltrials.gov/ct2/show/NCT03617146 (Archived by WebCite at http://www.webcitation.org/76Va37dbO)

International Registered Report Identifier (IRRID): DERR1-10.2196/12166

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KEYWORDS

diabetes mellitus, type 2; diabetes distress; coaching; health coaching; counselling; self care; behavioral medicine; health psychology; health education; primary care

Introduction

Diabetes distress (DD) is a negative emotional reaction to diagnosis of diabetes and concerns about treatment demands, risk of complications, and inadequate support [1]. DD, along with major depressive disorder (MDD) and other depressive symptomatology, constitutes significant emotional and psychological burden to people with diabetes [1,2]. Among these distinct conditions, DD is most strongly associated with difficulties in performing self-care and inability to meet glycemic targets [2-4], and it is more common than MDD [5], leading to calls for DD management to become an essential component of diabetes care [1,6].

A review by Sturt et al [7] identified 6 approaches to address types of DD that have been studied; namely, *psychological* (eg, psychotherapy), *educational* (purely informational), *educational with some behavioral component*, *psychoeducational* (education plus a psychological intervention targeting motivation or affect), *medications and devices*, and *care management or case management* [7]. Of these, psychoeducational approaches were the only approaches found to significantly reduce DD compared with controls. Similarly, a subsequent review [8] found that DD showed improvement following interventions that target both emotion (motivational strategies) and cognition (enlightenment or education).

Psychoeducational interventions that target emotion and cognition are a broad category that includes strategies such as health coaching (HC) and psychotherapy plus education; therefore, it is necessary to identify emotion-cognition interventions that are both feasible and effective for reducing DD in routine care settings. HC is an evolving profession that helps individuals achieve sustainable behavioral change through a growth-promoting relationship that elicits autonomous motivation and improves knowledge, self-efficacy, and self-regulation [9]. HC is particularly important to diabetes care as it has the potential to address both DD and self-care.

The American Diabetes Association (ADA) recommends that providers "routinely monitor people with diabetes for DD, particularly when treatment targets are not met..." [10]. However, ADA's recommendations for dealing with DD (ie, education, referral to a behavioral health provider, or referral to a mental health specialist) are varied and confusing [10]. On the other hand, the Canadian Diabetes Association [11] recommends an approach that is consistent with HC as defined by Olsen [12] and Wolever et al [13]. Even though some interventions have incorporated elements of coaching [7,8], only 1 study has explicitly sought to address DD as a primary outcome using HC [14]. This study found HC to be effective in addressing DD, but the finding has limited generalizability because of methodological limitations such as a small sample size and restriction to a single gender [14]. A recent trial that combined diabetes self-management education with some elements of HC and additional support was successful in addressing DD, but the intervention was too intensive to be feasible and scalable in routine primary care [15]. We proposed to conduct a randomized controlled trial (RCT) to fill the void in the available evidence on the real-world effectiveness of HC on DD. The primary aims of the study are to assess whether education alone is sufficient to address DD and whether HC has additional benefits in addressing DD beyond the effects of education. As coaching services are not typically reimbursed by insurance, cost has been a barrier to greater integration of HC in chronic illness care [16]. Therefore, one of the secondary aims of the study is to assess the willingness of patients with DD to pay for HC. The other secondary aim is to find out whether HC has additional impact on diabetes self-care and hemoglobin A_{1c} (HbA_{1c}), beyond any effects observed in the group that receives only an educational program targeting DD.

Methods

Study Design and Setting

A 2-arm, parallel RCT is being conducted among adults with diabetes who are not meeting glycemic targets (defined as HbA_{1c} ≥8.0), at an academic family medicine clinic in Houston, Texas. The overarching goal of the study is to use a pragmatic approach to assess the effectiveness of HC in addressing DD in real-world primary care settings, in which most diabetes care is coordinated and monitored. Therefore, participants randomized to the control group will receive the current standard of care for patients not meeting glycemic targets at the study clinic as summarized in Textbox 1.

Both arms of the study (control and intervention) will receive the standard of care detailed in Textbox 1. In addition, the intervention arm will receive 8 HC sessions to address DD. The HC sessions will be held biweekly in the first 3 months (6 sessions), followed by monthly sessions in the fourth and fifth month.

Textbox 1. Standard of care for diabetes at the study site.

- Quarterly follow-up visits during which patients receive ongoing, comprehensive assessment and treatment. When patients with diabetes whose HbA_{1c} is 8.0 or above exceed a 4-month period without a visit, they are contacted to schedule a follow-up appointment.
- Pharmacologic treatment of diabetes and comorbidities
- Behavioral management—diabetes self-management education and support (DSMES), that covers lifestyle modification counseling (nutrition and physical activity), medication-taking behaviors, foot care, how to monitor blood glucose (especially for those on insulin), and how to administer insulin if on insulin. This ongoing DSMES is provided through different means as follows:
  - Directly by primary care providers
  - Via health education handouts in the form of printed materials and via an electronic patient portal
  - By referral to a registered dietitian located at the clinic
- Referral to an ophthalmology clinic for annual eye check-up
- Psychological management—as part of a newly developed quality improvement project, and in line with the 2018 American Diabetes Association's Standards of Medical Care in Diabetes [10], the clinic has implemented psychological screening (depression and diabetes distress) for patients not meeting their glycemic targets (defined as HbA_{1c} ≥8.0). The plan of action is as follows:
  - Patients who screen positive for depression (using the Patient Health Questionnaire) [17] will be referred to colocated mental health providers.
  - A diabetes distress (DD)-specific education program has been developed for patients with DD and is being piloted through this study (Multimedia Appendix 1). This education program is oriented around the 4 domains of DD—regimen distress, emotional burden, interpersonal distress, and physician distress. Patients are provided feedback on DD screening results and are advised on ways to deal with the areas of greatest distress. Screening for DD is done using the 17-item DD scale (DDS17) [18].

Description of the Coaching Intervention for Patients With Diabetes Distress

Coaching Approach

Even as HC is becoming more common in primary care, there is a wide and varied understanding of what constitutes HC [12]. For the purposes of this study, the authors use the term HC to refer to an intervention with a goal of facilitating health behavior change, conducted by a health care professional (eg, registered nurse, registered dietitian, medical assistant, clinical psychologist) who has additional training and certification as a health coach. Thus, interventions carried out by peers or lay people will not meet this standard. The authors align with the conceptualization of HC as articulated in the reviews by Olsen [12] and Wolever et al [13] and reflected in the following definition:

> *A patient-centered approach wherein patients at least partially determine their goals, use self-discovery or active learning processes together with content education to work toward their goals, and self-monitor behaviors to increase accountability, all within the context of an interpersonal relationship with a coach. The coach is a healthcare professional trained in behavior change theory, motivational strategies, and communication techniques, which are used to assist patients to develop intrinsic motivation and obtain skills to create sustainable change for improved health and well-being.* [12]

Interventions for alleviating DD need to address 2 issues: the first is helping the patient express his or her feelings about diabetes, and the second is to work with the patient to figure out what can be done to meet the patient's needs [19]. Coaching techniques suitable for achieving the first objective include building a growth-promoting relationship with the client, establishing trust and rapport through the application of 3 core coaching skills, namely mindful listening, open-ended inquiry, and perceptive reflections [20], and helping clients handle negative emotions through an empathy protocol such as nonviolent communication [21]. To address the second objective of meeting the patient's needs, the coach will help participants elicit self-motivation, build self-efficacy, and journey through a process of change to reach their desired goals, relying on techniques such as exploring and amplifying the best in the client through appreciative inquiry [22] and building self-efficacy through motivational interviewing [23].

The abovementioned techniques for addressing the 2 issues in DD provide the overall framework that the coach will work with to help participants address DD and overcome the underlying challenges contributing to their distress. Among these techniques, motivational interviewing is probably the best described and standardized, and it has been demonstrated to be effective in many settings [24-28].

A true HC approach recognizes that each patient is unique, focuses on meeting the needs of the patient, and emphasizes relationship development between the coach and client [12,13]. As each participant's needs and values will be unique, the coach will tailor the intervention to the needs of each participant while staying within the overall coaching framework described above. This approach of not restricting the intervention to a rigid protocol is in keeping with the understanding that flexibility within the overall coaching paradigm is key to successful coach-client collaboration [12,13].

All coaching sessions will be delivered over the phone (ie, telecoaching) to minimize inconvenience, transportation time, and cost demands to participants. Telecoaching has been previously shown to be highly acceptable, low-cost, and

effective in increasing autonomy and self-efficacy among adult patients with diabetes [29].

Participant Assessment

Before the first coaching session, the participant will fill out the diabetes distress scale (DDS) [18] and a subset of the Summary of Diabetes Self-Care Activities questionnaire [30] focused on medication-taking, dietary, and physical activity behaviors. Only patients with significant DD (DDS score ≥2.0) will be included in this study. The health coach will review the DDS report to obtain information on the specific type of distress (eg, regimen distress) and the primary sources of distress, that is, the specific things about diabetes management that are upsetting to that particular person (eg, not feeling motivated to keep up with diabetes self-management; see Table 1).

First Coaching Session

At the first coaching session, building on the findings from the participant assessment, the coach will probe further to identify possible targets for the coaching intervention (Table 1). The targets define the specific goals related to DD or the underlying stressors that the participant would like to resolve or achieve at the end of the intervention. As necessary, the coach might also explore participant's priorities, confidence, and readiness to change concerning different aspects of diabetes self-management. The coach then explores the participant's willingness to embark on the coaching journey, discusses the findings from the assessment, and works with the participant to identify possible coaching targets (Table 1). The participant prioritizes the coaching targets and creates goals that he or she will like to achieve and a 3-month action plan.

Subsequent Coaching Sessions

Participants' progress will be reviewed at subsequent coaching sessions. Most coaching sessions focus on a specific topic, helping clients navigate and overcome emerging challenges on their change journey [9]. As necessary, the coach will tap into her or his coaching toolbox to help elevate the participant's energy, brainstorm strategies for problem solving, develop solutions, meet challenges, and set and agree on subsequent goals [9].

For purposes of quality control, the health coach will take notes on client interactions and coaching techniques used for review with the investigators. This allows ongoing feedback to ensure appropriateness of the intervention.

Training of Intervention Staff

HC will be provided by a registered dietitian trained and certified as a Health and Wellness Coach by one of the "Transition Programs" approved by the International Consortium for Health and Wellness Coaching [31]. The International Consortium for Health and Wellness Coaching is an organization working to standardize HC practice in the United States and across the world. DD-specific education (Multimedia Appendix 1) for participants in both arms of the study will be provided by designated medical assistants in the clinic who were trained to provide this education in a consistent manner (Textbox 1).

Study Population, Inclusion, and Exclusion Criteria

The target population is adult patients with diabetes and DD at the study clinic. Textbox 2 summarizes the inclusion and exclusion criteria.

Table 1. Identifying the focus of the coaching intervention from the type and sources of diabetes distress using the diabetes distress scale.

DDS[a] subscale	Questions (from DDS)	Possible coaching targets
Regimen distress	Not feeling confident in my day-to-day ability to manage diabetes; Feeling that I am not testing my blood sugars frequently enough; Feeling that I am often failing with my diabetes routine; Feeling that I am not sticking closely enough to a good meal plan; Not feeling motivated to keep up my diabetes self-management	Perception of low self-efficacy for diabetes self-care; Perception of low motivation for diabetes self-care; Perception of lack of success in following diabetes self-care plan
Emotional burden	Feeling that diabetes is taking up too much of my mental and physical energy every day; Feeling angry, scared, depressed, or a mixture of these feelings when I think about living with diabetes; Feeling that I will end up with serious long-term complications, no matter what I do; Feeling that diabetes controls my life; Feeling overwhelmed by the demands of living with diabetes	Low level of perceived ability to influence outcomes; Low level of perceived ability to manage emotions
Interpersonal distress	Feeling that friends or family are not supportive enough of self-care efforts; Feeling that friends or family do not appreciate how difficult living with diabetes can be; Feeling that friends or family do not give me the emotional support that I would like	Perception of low levels of social support for dealing with diabetes
Physician-related distress	Feeling that my doctor does not know enough about diabetes and diabetes care; Feeling that my doctor does not give me clear enough directions on how to manage my diabetes; Feeling that my doctor does not take my concerns seriously enough; Feeling that I do not have a doctor who I can see regularly enough about my diabetes	Perception of dissatisfaction with the quality of patient-provider communication; Perception of the need to seek a better or regular provider

[a]DDS: diabetes distress scale.

Textbox 2. Inclusion and exclusion criteria for the Coaching and Education for Diabetes Distress trial.

Inclusion criteria

- Has had a diagnosis of type 2 diabetes for at least 6 months
- Aged 18 to 75 years
- Most recent hemoglobin A_{1c} taken within 30 days was 8.0 or above
- At least a moderate diabetes distress, operationalized as a mean score of 2.0 or more on the 17-item diabetes distress scale [32]

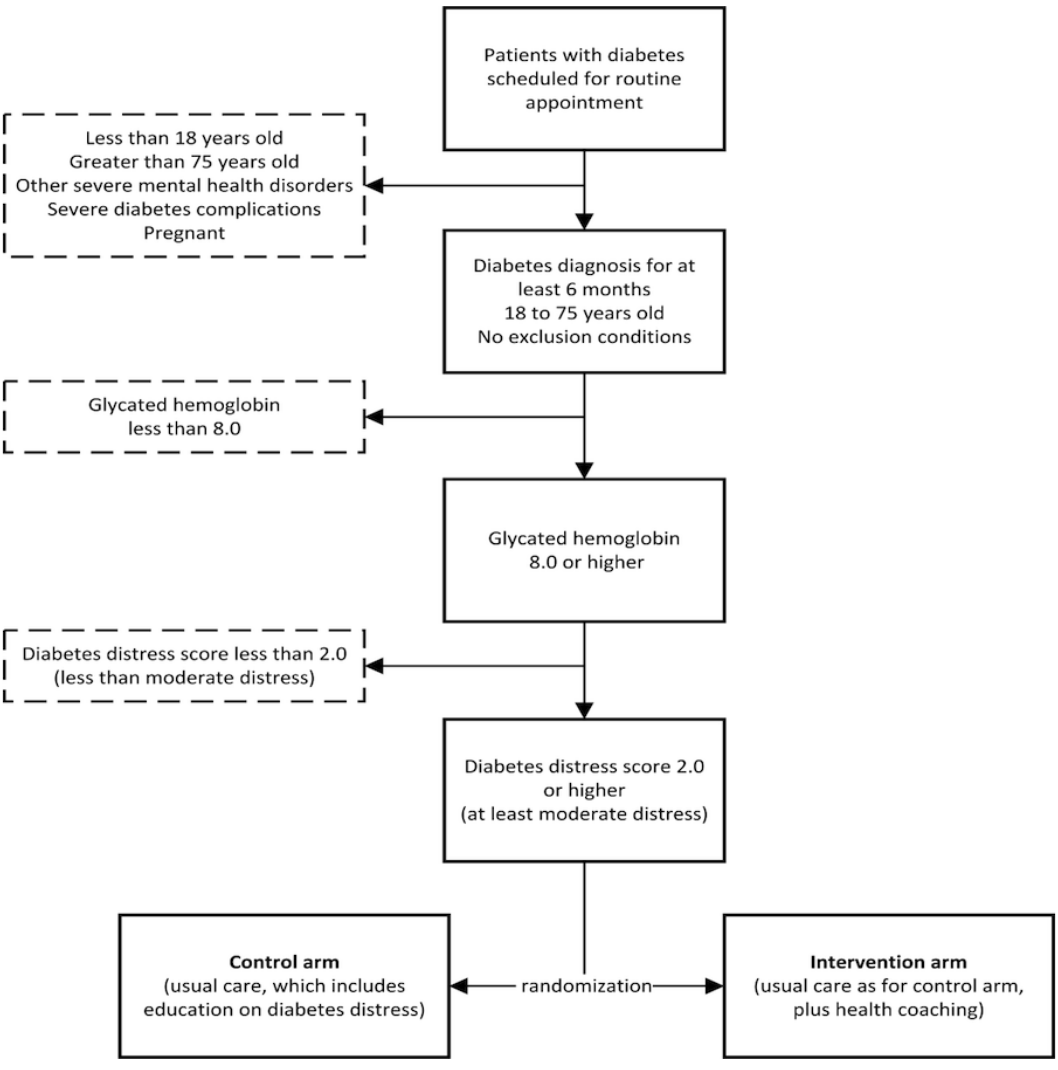
Exclusion criteria

- Moderately-severe to severe depression: Patient health questionnaire-9 score 15 or above [17]
- Other severe mental health disorder (eg, Alzheimer's or schizophrenia)
- Current pregnancy
- Severe diabetes complications or functional deficits (eg, kidney failure requiring dialysis, amputation, or blindness)

Study Arm Assignment

Figure 1 outlines the screening, recruitment, and randomization process for the study. A random sorting randomization algorithm will be implemented using PASS software version 15.0.3 (NCSS LLC, Kaysville, UT) to generate a randomization list that will dictate assignment of patients into either the intervention or control (usual care) arm. To ensure the algorithm results in the desired group sample sizes, the program search is conducted by creating a randomization list using the user-specified randomization algorithm and then looking at the final sample sizes. If the sample sizes do not match the target sample sizes for all groups, then the list is discarded and the algorithm is restarted. This process continues until a list with the exact sample sizes is found.

Figure 1. Screening, recruitment, and randomization process for Coaching and Education for Diabetes Distress trial.



Sample Size Determination

The study requires a total sample of 156 participants, 39 in the intervention arm and 117 in the control arm. Calculations were based on the following assumptions: a power of 80%, alpha (type I error rate) of 5%, an effect size (difference in mean change in DD between the 2 groups) of 0.5, which is considered both clinically significant and at least of moderate magnitude [7], a DD SD of 0.89 and 0.81, respectively, at baseline and at follow-up [15], a correlation (ρ) of 0.5 between a pair of observations made longitudinally on the same subject, and accounting for a possible attrition rate of 20%. It has been shown that when research costs vary among treatments, it is economically efficient to randomize more participants to the cheaper arm without compromising validity [33]. Therefore, to achieve adequate statistical power within fiscal constraints, more participants will be recruited in the control arm than in the intervention arm (at a ratio of 3:1). On the basis of these assumptions and the stated sample size, this study achieves 80% statistical power to detect differences in the mean change in DD of 0.5 between the 2 groups, but it has more than 90% power to detect differences in mean changes in DD of 0.6 or higher (Figure 2).

Measures and Data Collection

The variables that will be measured and the timeframe for data collection are summarized in Table 2. The primary outcome measure will be short-term (6 months) changes in DD score. Secondary outcome measures of interest are willingness-to-pay (WTP) for and satisfaction with HC, as well as changes in HbA_{1c} and diabetes self-care practices, specifically dietary intake, physical activity, and medication-taking behaviors.

DD, self-care behaviors, and HbA_{1c} will be assessed at 3 measurement periods, at baseline (randomization), and at the third and sixth month postrandomization. DD will be assessed using the previously validated 17-item DDS [18]. HbA_{1c} will be tested at every 3-month follow-up visit as part of usual care for patients not meeting glucose targets. Self-care practices (diet, physical activity, and medication-taking behaviors) will be assessed with the respective subscales of the Summary of Diabetes Self-Care Activities questionnaire [30]. Satisfaction with HC will be assessed for the intervention arm at the end of the study (sixth month) through self-administered surveys, including Likert scale-type questions and open-ended questions. WTP for HC will be assessed through an indirect survey approach, which has been shown to be preferable because of higher internal and external validity compared with other methods [34]. In such indirect approaches, participants are confronted with different attribute combinations of various products or services (eg, HC vs alternative interventions) with assigned prices, and they choose the most preferred scenarios. Specifically, we will conduct a discrete choice experiment to assess WTP.

Figure 2. Statistical power of Coaching and Education for Diabetes Distress trial to detect effect sizes from 0.4 to 1.0.

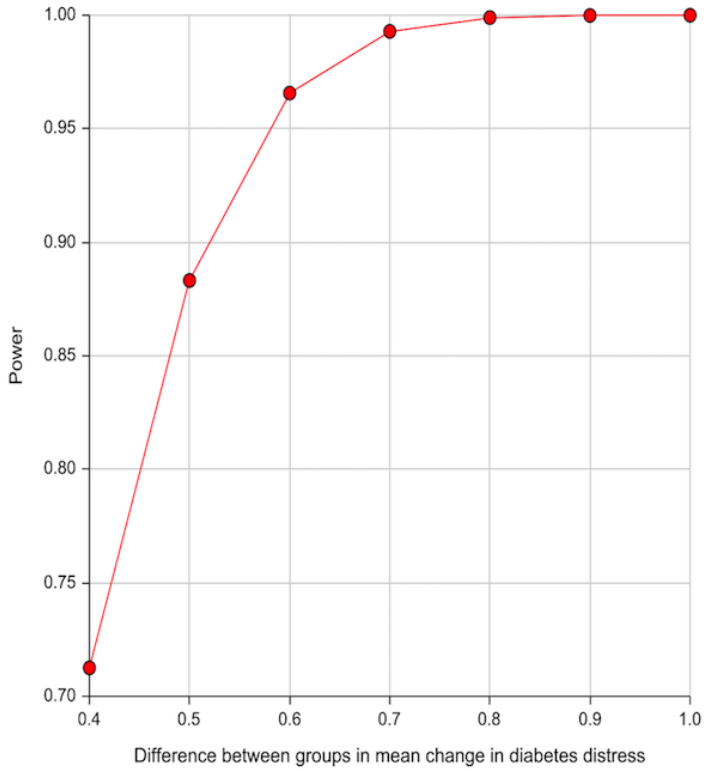


Table 2. Measures and time frame for the Coaching and Education for Diabetes Distress trial.

Measure	Baseline	3 months from baseline	6 months from baseline
Primary outcome measure			
Diabetes distress score [18]	X	X	X
Secondary outcome measures			
Hemoglobin A_{1c}	X	X	X
Self-care behaviors (Medication-taking, dietary, and physical activity behaviors) using the Summary of Diabetes Self-Care Activities questionnaire [30]	X	X	X
Willingness to pay for health coaching	X	—[a]	X
Satisfaction with health coaching (intervention arm only)	—	—	X

[a]Not applicable.

Data Analysis

The primary analysis will use repeated measures analysis of variance to compare mean change in DD, HbA_{1c}, and self-care scores between baseline and months 3 and 6 for the 2 study arms. Satisfaction with HC will be reported as the proportion of respondents agreeing with different grades of a Likert scale. The open-ended questions on the HC satisfaction questionnaire will be analyzed qualitatively using thematic analysis. On the basis of the choices that the participants make in the discrete choice experiment, WTP for HC will be estimated by logistic regression models.

Ethical Clearance

Patients eligible for the study will be offered the opportunity to enroll; however, the decision to enroll will be completely up to the patient. Patients who decline to enroll will continue to receive the usual standard of care; therefore, they will be informed that their decision to opt out will not affect their care in any way. An informed consent will be obtained from all patients who decide to participate. Ethical approval for the study has been obtained from the Institutional Review Board of the Baylor College of Medicine, Houston, Texas.

Results

As of March 2019, screening and recruitment for the Coaching and Education for Diabetes Distress (CEDD) trial are ongoing and will continue through December 2019. The results will be expected by July 2020.

Discussion

Over 30 million Americans (9.4% of the US population) were living with diabetes mellitus in 2015 [35]. With an estimated expenditure of US $101.4 billion in 2013, the United States spent more on managing diabetes than any other condition [36]. Furthermore, diabetes is the seventh leading cause of death [35] and the leading cause of adult-onset blindness, kidney failure, and nontraumatic limb amputations in adults [37]. Therefore, interventions that demonstrate real-world effectiveness in improving diabetes management have the potential to improve quality of life, reduce mortality, and decrease costs to patients, their families, and society at large.

The need to address psychological and behavioral factors as essential components of comprehensive diabetes care is increasingly being recognized. However, an effective and easily scalable intervention for DD, the most common psychological barrier to diabetes management, is not yet known. Whittemore et al [15] found that HC resulted in better self-care and reduced DD, but it had no significant effect on HbA_{1c}; however, their study was limited to a small sample of women who previously voluntarily participated in diabetes education at an outpatient diabetes education center. Such women might have more intrinsic motivation than a general population of primary care patients, and they certainly might have different results from a population which includes men; therefore, the findings may not be generalizable to a general population of primary care patients. This paper reports on the design of an ongoing RCT of HC and education for DD (CEDD trial) that overcomes the methodological limitations of previous studies of coaching-related interventions for DD. The findings of this study will provide targeted evidence as to whether HC has significant value in addressing important unmet psychological and behavioral needs of patients with diabetes.

As coaching services are typically not covered by medical insurance plans at the point of care, cost has been a barrier to greater integration of HC in chronic illness care [16]. Therefore, assuming that this study finds that HC is superior to distress-specific education in addressing DD, issues of payment might constitute a barrier to scalability. By also assessing the degree to which patients with diabetes would be willing to pay for HC out of pocket, this study could pave the way for mainstreaming of HC in diabetes care. These findings would have far-reaching implications for diabetes management in routine primary care settings.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Diabetes Distress Education Script.

[PDF File (Adobe PDF File), 90KB - resprot_v8i4e12166_app1.pdf]

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Abbreviations

ADA: American Diabetes Association
CEDD: Coaching and Education for Diabetes Distress
DD: diabetes distress
DDS: diabetes distress scale
HbA_{1c}: hemoglobin A_{1c} (glycated hemoglobin)
HC: health coaching
MDD: major depressive disorder
RCT: randomized controlled trial
WTP: willingness to pay

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Protocol

Promotion of Family Routines and Positive Parent-Child Interactions for Obesity Prevention: Protocol for the 3 Pillars Study Randomized Controlled Trial

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Abstract

Background: Childhood obesity is a challenging public health issue, with 30% of children aged 2 to 4 years classified as being overweight or obese in New Zealand. This is concerning, given that up to 90% of obese 3-year-old children are overweight or obese by the time they reach adolescence. Interventions that target this age range often fail to demonstrate long-term effectiveness and primarily focus on traditional weight-related behaviors, including diet and physical activity. However, research suggests that targeting nontraditional weight-related behaviors, such as sleep, screen time, and family meals, may be a more effective approach in this age group, given the immense challenges in changing traditional weight-related behaviors in the long term.

Objective: The aim of the proposed study was to develop and pilot the 3 Pillars Study (3PS), a 6-week program for parents of New Zealand toddlers and preschoolers aged 2 to 4 years to promote positive parent-child interactions during 3 family routines, specifically adequate sleep, regular family meals, and restricted screen time.

Methods: Screen time at the end of the 6-week program is the primary endpoint. The effects of the program on screen time, frequency of family meals, parent feeding practices, diet quality, and sleep duration will be piloted using a randomized controlled trial, with outcomes compared between the active intervention group and a wait-list control group at 6 weeks (at the end of the program) and 12 weeks (at final follow-up). We aim to recruit 50 participants (25 per arm). Eligibility criteria include parents of children aged 2 to 4 years who are currently exceeding screen use recommendations (ie, greater than 1 hour of screen time per day). The 3PS program involves a half-day workshop, run by a community worker trained to deliver the program content, and 6-week access to a study website that contains in-depth information about the program. All participants will also receive a study pack, which includes resources to encourage engagement in the 3 family routines promoted by the program. Study data will be collected in REDCap. All statistical analyses will be performed using SAS version 9.4 and have been specified a priori in a statistical analysis plan prepared by the study statistician.

Results: Trial recruitment opened in July 2018. Final follow-up was completed in December 2018, with trial findings expected to be available in early 2019.

Conclusions: Findings from this pilot study will provide relevant data to inform the design of a larger effectiveness study of the 3PS program.

Trial Registration: Australian New Zealand Clinical Trials Register ACTRN12618000823279; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=375004 (Archived by WebCite at http://www.webcitation.org/773CALeTK)

International Registered Report Identifier (IRRID): DERR1-10.2196/12792

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KEYWORDS

screen time; family routines; parent-child relations; child, preschool; randomized controlled trial; health behavior; pediatric obesity; sleep; parenting; New Zealand

Introduction

Background

Childhood obesity remains one of the most pervasive and challenging public health issues, with 30% of children aged 2 to 4 years classified as being overweight or obese in New Zealand [1]. Once a child has developed obesity, it is difficult to reverse, with weight status in the first years of life a strong predictor for adult obesity [2]. In particular, the interval between 2 and 6 years has been identified as the earliest and most critical period of growth with respect to the future risk of obesity in adolescence [3] or adulthood [4]. Of concern is recent evidence suggesting that almost 90% of children who are obese at the age of 3 years are classified as overweight or obese as an adolescent [3]. Given the intractable nature of obesity, there has been a shift in recent years toward focusing on early prevention of obesity [5].

Although a number of interventions targeting obesity prevention in toddlers and preschoolers have been undertaken, results have been mixed [6,7], with a 2011 systematic review finding no evidence for effectiveness with respect to body weight outcomes [8]. Most studies have focused on traditional weight-related behaviors, including diet, physical activity, and sedentary behaviors. However, recent research has suggested the need to consider other nontraditional weight-related behaviors [9], which seems appropriate given the immense challenges in changing these behaviors in the long term [10,11].

For example, the Prevention of Overweight in Infancy study found that children randomized to receive additional support for more traditional weight-related behaviors, including breastfeeding, healthy eating, and physical activity during the first 2 years of life, had significantly higher body mass index (BMI) z scores compared with controls at age 5 years (adjusted difference: 0.25; 95% CI 0.04 to 0.47) [12]. Perhaps even more interesting was the observation that those randomized to receive education and support for sleep, either alone or in combination with support for the traditional weight-related behaviors, had significantly lower BMI z scores at both age 3.5 years (−0.24; 95% CI −0.38 to −0.10) and 5 years (−0.23; 95% CI −0.38 to −0.07), compared with children who did not receive the sleep intervention [12].

There are now a growing number of experts calling for a shift to identify and focus on these nontraditional weight-related behaviors, including adequate night-time sleep, regular participation in family meals, and limiting screen time [5,12-20], which are frequently referred to as family routines. In fact, these family routines are showing promise with respect to obesity prevention in young children. In the United States, preschool children from households that regularly engaged in these 3 family routines had approximately 40% lower prevalence of obesity compared with those exposed to none of the routines [13]. Similar findings have been reported in New Zealand, where 3 primary distinctions between low socioeconomic status (SES) Pacific families with healthy-weight children and low SES Pacific families with overweight children were identified: engagement in regular family meals, presence of food-related rules at home, and limitations on screen time [20]. Furthermore, promoting family routines in an intervention has been shown to increase engagement in healthy body weight–related behaviors and reduce BMI, in low-income minority families with young children [15].

It is likely that family routines actually represent the broader constructs of family functioning and family organization [21,22]. With respect to family functioning, ongoing participation in a routine may be an indication that family members experience the routine to be a positive and rewarding activity. In this case, other members of the family, rather than just an individual parent, may work to ensure regular engagement in the routine. Alternatively, if individual members of the family find a routine to be stressful, for example, if sitting down to eat dinner together often results in parent-child conflict, then it is less likely that they will actively try to overcome barriers to making the routine work on a regular basis.

Second, it makes sense pragmatically that organized families will simply be better placed to arrange their time and resources in such a way that it facilitates both structuring of routines in the first instance and then ongoing participation in them. For example, children from disorganized families are significantly more likely to demonstrate sleep problems, and it is proposed that the disorganization these families experience interferes with their ability to engage in a regular bedtime routine, which is known to support healthy sleep in children [23].

The approach of targeting family routines, such as sleep and family meals, rather than traditional weight-management behaviors, such as diet and physical activity, may have a number of benefits. First, parents do not need to perceive their child to be at risk of being overweight or feel criticized for their parenting behaviors [13]. This may be particularly important for New Zealand families, where negative cultural discourses around *skinny* children exist [24] and where findings from a longitudinal study recently found that 73% of mothers with an overweight or obese child reported their child to be normal weight [25]. Second, family routines appear to offer nonweight-related benefits, including improved resiliency,

cognitive skills, self-regulation, school readiness, behavior, and psychosocial well-being [26-29].

Third, although family routines are directly modifiable by parents, more traditional weight-management behaviors, such as what and how much a child eats, are also affected by a child's individual characteristics, such as temperament [30] and self-regulation [31]. As a result, although these traditional behaviors may be more difficult for the parent to modify directly, changing family routines around meals, bedtime, and screen use may represent a pathway to influencing these behaviors indirectly. Finally, lack of family routines, as represented by family disorganization, appears to be overrepresented in socioeconomically disadvantaged families [32], with children from these families appearing to also be more susceptible to the adverse effects of disorganization [33]. Indeed, research suggests that family disorganization may play a mediating role in the relationship between SES and child outcomes [33-35]. Although we currently do not know if household chaos can readily be reduced in disadvantaged families, although preliminary evidence suggests it can [15], it may represent a more actionable and immediate target for improving child outcomes, particularly with respect to childhood obesity.

It may also be valuable to consider the importance of promoting positive parent-child interactions during family routines associated with obesity prevention. It is possible that families eating together at mealtimes may only protect against childhood obesity because of positive parent-child interactions [36,37]. Focusing primarily on the association between family meal frequency and body weight, with no consideration for parent-child interactions at family meals, may fail to capture the complexity of the family meal experience. Negative family meal experiences and food-related parenting practices such as coercive feeding may actually increase the risk for unhealthy dietary choices in children and result in an increased risk for obesity [36-38]. Similarly, for sleep, the quality of parent-child interactions appears to be positively associated with night-time sleep in preschool-aged children [39], and positive, connecting routines before bedtime not only have been shown to reduce the number of bedtime tantrums in toddlers and preschoolers but also significantly improved marital satisfaction [40].

The parent-child relationship appears important with respect to obesity prevention, with poorer quality of interactions during playtime interactions, lower maternal sensitivity, and insecure attachment, all associated with obesity risk [41-44]. Researchers, therefore, propose that obesity interventions should include a component that promotes positive parent-child interactions [43,45,46]. Specifically, a 2011 systematic review that investigated the role of parent-child interactions and obesity prevention identified the importance of extending the current model of parent-child interactions [46]. Current models typically focus on unidirectional aspects of parenting, such as parenting practices and parenting styles; however, moving to a bidirectional model would help underscore the importance of dyadic mutuality, defined as the existence of warm, *mutually* responsive, and synchronized interactions between the parent and child [47-49]. This approach acknowledges that the development and maintenance of health-related behaviors is a bidirectional process between the parent and child, whereby exchanges during health-promoting routines, such as family meals and bedtime, need to be mutually rewarding and positive to encourage ongoing engagement in them [46,50].

Objectives

The aim of the proposed study was to develop and pilot the 3 Pillars Study (3PS), a 6-week program for parents of New Zealand toddlers and preschoolers aged 2 to 4 years to promote positive bidirectional interactions between the parent and child during 3 family routines shown to protect against childhood obesity. Specifically, the program targets adequate night-time sleep, engaging in regular family meals, and restricting screen time. These 3 routines represent the *3 Pillars*. The effects of the program on screen time, frequency of family meals, parent feeding practices, diet quality, and sleep duration will be assessed using a randomized controlled trial (RCT), with outcomes compared between the active intervention group and a wait-list control group at 6 weeks (at the end of the program) and 12 weeks (at final follow-up).

Methods

Study Design

A 2-arm, 6-week pilot RCT, with final follow-up at 12 weeks (ie, 6 weeks after the end of the 6-week program), will be conducted to assess 3PS. Intervention participants will attend 1 half-day workshop and have access to a study website with supplementary information for a period of 6 weeks. Both the intervention group and wait-list control group will undergo study measures at baseline, 6 weeks, and 12 weeks. After the final data collection at 12 weeks, the control group will be offered the intervention. The study has been approved by the University Auckland Human Participants Ethics Committee (UAHPEC; reference 021311) and is registered with the Australian New Zealand Clinical Trial Registry (ACTRN12618000823279).

Participants

A total of 50 participants, 25 in the intervention group and 25 in the wait-list control group, will be recruited to the free 3PS program through social media (ie, targeted Facebook advertising), playgroups, and word of mouth. Participants will be eligible for inclusion if they are the parent or primary caregiver of a child aged 2 to 4 years, if they are aged at least 18 years, and if their child exceeds recommendations for screen use, that is >1 hour per day for this age group, as reported by the parent. Participants will be required to live in Auckland, have internet access, be available to attend 1 half-day workshop, and be able to provide electronic informed consent and speak and read English. Due to the exploratory nature of the intervention, parents of children with serious physical or mental illness or known developmental problems will not be eligible to participate.

Setting

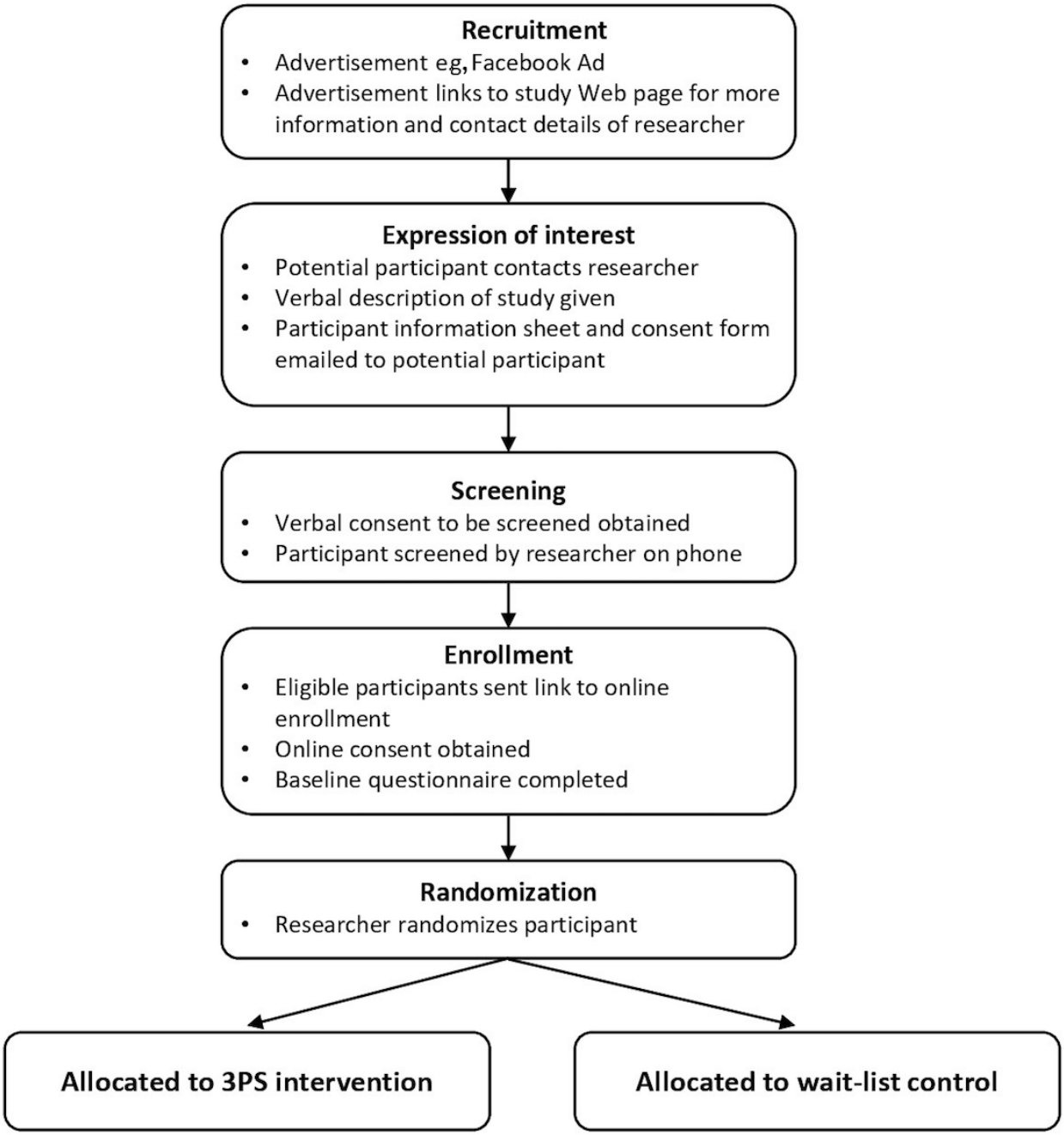
This study will be conducted in Auckland, New Zealand. The 3PS workshop will take place at the University of Auckland,

and participants will be able to access the study website wherever they have access to the internet.

Recruitment

Figure 1 illustrates the recruitment process. A Facebook advertisement will be used for recruitment purposes, with the advertisement offering help to parents having trouble with their child's screen time, meals, or sleep. This method has been used successfully in the past by the research team for recruiting parents of young children. The advertisement will link to the University of Auckland Faculty of Medical and Health Sciences research study recruitment page, where participants will be given more information about the study and provided with the contact details for the research assistant involved in the study. When potential participants contact the research assistant, an explanation of the study will be given verbally, and they will be sent the Participant Information Sheet and Consent Form via email. If the potential participant expresses their interest in participating, then the research assistant will ask for verbal consent to screen them. Upon agreement, they will be screened by the research assistant over the phone and, if eligible, sent a link to the Web-based baseline questionnaire. Before completing the baseline questionnaire, they will be asked to provide electronic consent to participate in the study. Once they agree to participate, they will be able to complete the baseline questionnaire.

Figure 1. Flowchart illustrating the enrollment and randomization process. 3PS: 3 Pillars Study.



After the baseline questionnaire is complete, the research assistant will randomize the participant to either the intervention group or the wait-list control and inform them of their randomization group. Completion of the baseline questionnaire and randomization will take place during the 2 weeks before the first workshop.

Randomization

The research assistant will use sequentially numbered, opaque, sealed envelopes to randomize participants. Participants will be allocated to 1 of the 2 groups in a 1:1 ratio using block randomization with varying block sizes of 2 and 4. The randomization sequence will be generated by the study statistician, who will also prepare and seal the envelopes.

Intervention Development

The 3PS program is designed to promote mutually responsive, positive parent-child interactions and help primary caregivers, herein referred to as parents, of children aged 2 to 4 years to engage in 3 family routines shown to be protective against childhood obesity: adequate night-time sleep, restricted screen time, and regular participation in family meals. The content development process took place over an 18-month period and involved 2 sets of community focus groups, face-to-face parent interviews, and a series of end-user panels with parents. Recruitment criteria used for the formative work was the same as that described above for the pilot study.

Community focus groups (5 focus groups; n=26) and one-on-one interviews (n=8) with parents of 2- to 4-year olds were conducted to establish perceived barriers to engaging in healthy weight-related behavior recommendations in the context of a young family, in addition to establishing the preferred delivery method for a parent intervention. Feedback from the focus groups revealed that one of the biggest barriers to engaging in health-promoting activities was being too busy, either due to family commitments; rushing between activities and chores; or having 2 parents who worked outside the home. In particular, parents said they wanted help with managing the *busyness* of daily life and support for dealing with their children's challenging behaviors around bedtimes and mealtimes. Furthermore, they indicated that any intervention should be framed in such a way as to avoid feelings of guilt.

When asked how they deal with busyness, parents frequently reported using screens to distract their children while they got things done; yet, at the same time described harboring feelings of guilt about the amount of time their child spent on screens. These conflicting feelings around child screen use were further highlighted when parents conveyed negative responses to messages promoting the importance of reducing screen time. As a result of these discussions, the decision was made to reframe the family routine of *restricting screen time* as *promoting free play*, with screen time messages then embedded into the free play component, and also threaded throughout the intervention content.

Responses from the focus groups regarding the delivery format of the program were mixed, with some parents preferring the potential for more tailored information during face-to-face workshops and others preferring the convenience and lower level of commitment required of a Web-based resource. Furthermore, focus group participants revealed that parents would like the workshop delivered by members of the community who were parents themselves and who could report back on their personal experience using the program content. On the basis of this feedback, the decision was made to deliver the program via a workshop and a study website, with the workshop facilitated by a member of the community, rather than a researcher or health professional. Furthermore, given that parents frequently cited lack of time as a barrier to attending workshops, the decision was made to deliver the workshop as an intensive half-day course, rather than requiring parents to commit to several sessions over a number of weeks.

Findings from the initial set of focus groups and parent interviews were then integrated with scientific literature focusing on family routines and rituals [51-55], household chaos [23,56-61], mutually responsive orientation and positive parent-child interactions [47,49,62-64], and developmental science and attachment theory [65-69], and more specifically, how each of these may relate to childhood obesity and weight-related behaviors [23,45,46,58,70-74]. An initial model of the 3PS was then created, which incorporated practical advice for reducing household chaos [75] and promoting positive bidirectional parent-child interactions between young children and their parents [68,76,77]. The 3PS model program was then refined further using an iterative feedback process from 2 end-user panels and 5 focus groups (n=32) with parents. During this process, preferences with respect to the look and feel of the website and study materials, feedback on the program messages and framing, and suggestions for improving the program were explored. In particular, parents reported their partiality for focusing on parent-child relationships as part of the program, which they described as being a neglected aspect of parenting programs to date. The 3PS content to be piloted was then finalized, and the community facilitator who was to deliver the content was trained over 4 days spread over a 4-week period.

Trainings took place at the University and were divided into 4 units. The first unit focused on general skills facilitating groups. During the second unit, the intent, philosophy, and theory behind the 3PS program were delivered. Unit 3 focused primarily on how to deliver the content of the workshop, and unit 4 involved practicing delivery of the content in front of an audience and dealing with any questions or concerns that might arise. The facilitator was also provided with a detailed training manual and access to readings to provide further knowledge and understanding of the program content.

Intervention

Participants randomized to the intervention group will participate in a half-day, face-to-face workshop and have access to the study website for a period of 6 weeks. The first part of the workshop is theory based and provides parents with insight into their children's behavior and development [68,76]. It then introduces the Connecting Activities, Routines, and Environments (CARE) framework, which provides a blueprint for introducing routines, while ensuring consideration is given to developing positive bidirectional parent-child interactions and a supportive home environment. The framework is explored

in detail, with a particular focus on the importance of family routines [51,53]; positive parent-child interactions [41,43,45,78,79]; and reducing household chaos [56,57,80-82] for supporting child well-being, health, and development. Practical ideas for promoting the parent-child relationship are given [68,76]. These are referred to as *connecting activities*.

A 5-step process for implementing the CARE framework is then introduced to guide parents in finding practical solutions within their own family around getting adequate night-time sleep, participating in family meals, and reducing screen time and promoting free play. In brief, parents identify things they do that might interfere with positive parent-child interactions (step 1). For example, at family meals, a parent using their mobile phone at the dinner table may interfere with positive parent-child interactions. These things are referred to as *disconnecting* activities, and parents are encouraged to identify disconnecting activities that might be modifiable within their own family. Parents then design a simple routine around the activity (step 2) and actively incorporate connecting activities, that is, positive parent-child interactions, into the routine (step 3). An example of bedtime might be a parent tying an imaginary ribbon between the child's bed and their own bed to *stay connected* through the night. Parents then consider how aspects of the home environment, such as chaos and background distractions, may interfere with the child's ability to participate fully in the routine (step 4), and then, they are asked to create 1 small, detailed change that they can implement immediately in their home (step 5).

The second part of the workshop is more practical and divided into 3 sections that correspond with the 3 study pillars—supporting sleep, screen-free play, and family meals. Each of the pillars is introduced using a similar format; there is a background reading, which provides a brief overview as to why the activity is important to health and child development, and then the workshop facilitator walks the parents through the 5-step process outlined above as it relates to each specific pillar. For each of the 3 pillars, a number of group activities are used to encourage parent engagement and highlight the study messages and learnings. At the end of the workshop, parents will be given a study pack [15], which includes a meal planner and candle, to promote creating a routine around family meals (eg, lighting a candle at the start of each meal); a child's book, to encourage reading during the bedtime routine; and a sketch pad and crayons, to encourage free play.

Due to the intensive nature of the workshop, parents will also be given access to a study website. This website will allow parents to return to the material covered during the 3PS workshop and review it at their own pace. In addition to providing all the content delivered during the workshop, the website will also include links to related readings, selected references (as a number of parents said they wanted to know the *science* behind the approach), and extra tips around common feeding and sleep issues in preschoolers. Parents will be sent a link to the study website after the workshop.

Participants log-in to the 3PS website on the study landing page and then are taken to a homepage, which has links to 4 additional pages: (1) the CARE Framework page, which discusses the framework used in detail; (2) the 3 Pillars page, which links to 3 subpages that reflect each of the pillars; (3) an Info page, which provides study-related information; and (4) a Contact Us page, which provides the contact information for the study team. For each of the 3 Pillars subpages, background is provided about how the specific pillar is related to child health and well-being, and a step-by-step approach to using the CARE Framework to address the pillar. For example, with respect to sleep, there is information about what children find disconnecting at bedtime, what a simple bedtime routine might look like, a list of ideas for how parents might be able to infuse connection into the bedtime routine, and then ideas for reducing household chaos to create a peaceful sleep environment. Their access to the study website will be active for a period of 6 weeks.

Participants will be given the choice of attending 1 of the 3 half-day workshops. The day before the workshop, participants will be contacted via email with a reminder of the workshop and also detailed instructions of where to find the room and parking. If a participant does not turn up to the workshop, they will be contacted via phone or email to reschedule the workshop they attend, in an attempt to improve study adherence. The workshop will be catered and dietary requirements provided for.

Control

Parents allocated to the wait-list control group will not receive the intervention until final follow-up is complete, that is, at the end of the 12-week study period. At this stage, participants will be offered the 3PS program, including the opportunity to participate in the workshop and access to the study website.

Outcomes

Participants in the intervention group will be asked to complete their 6- and 12-week questionnaires 6 and 12 weeks after the date of the workshop they attend, respectively. Furthermore, 3 workshop dates will be offered on 3 consecutive Saturdays. Participants in the wait-list control group will complete their 6- and 12-week questionnaires 6 and 12 weeks from the date of the first workshop, respectively.

Table 1 illustrates the schedule of outcome assessments for both study groups. All measures will be taken at baseline, 6 weeks, and 12 weeks in both the intervention and control groups, unless stated otherwise. The baseline will contain sociodemographic questions focused on the child, including age, sex, and ethnicity, in addition to questions focused on the caregiver, including age, gender, ethnicity, marital status, employment status, household income, relationship with child, household size, and family structure.

Table 1. Schedule of assessments.

Outcomes	Baseline	6 weeks	12 weeks
Screen use (primary)			
Total screen time[a] (minutes)	x[b]	x	x
Percentage of children meeting screen recommendations[c]	x	x	x
Sleep			
Brief Screening Questionnaire for Infant Sleep Problems-Extended [83]	x	x	x
Family meals and nutrition			
Frequency of family meals [84]	x	x	x
Fruit servings per day[a]	x	x	x
Vegetables servings per day[a]	x	x	x
Frequency of sugar-sweetened beverages in the previous week[a]	x	x	x
Frequency of fast foods in the previous week[a]	x	x	x
Feeding Practices and Structure Questionnaire [85]	x	x	x
Daily routines and household			
Child Routine Inventory[d] [86]	x	x	x
Chaos, Hubbub, and Order Scale [87]	x	x	x
Program feedback[e]			
Exit questionnaire	—[f]	—	x
Exit interview	—	—	x

[a]New Zealand Health Survey Questions.

[b]x: measure taken.

[c]Less than 1 hour per day.

[d]Daily Living Routines subscale only.

[e]Intervention group only.

[f]Not applicable.

Primary Outcomes

The primary outcome is screen time at 6 weeks, which is one of the program's targeted routines and the primary endpoint used in a previous study [15]. Furthermore, although increasing screen-free play and, in turn, reducing screen use is one of the targeted routines of the 3PS program, reducing screen use is also promoted as a way to increase connection during family meals and bedtime. For example, parents are advised to turn off screens during family meals and to avoid screen use during the bedtime routine. Given that screen use is either targeted directly or indirectly in each of the 3 routines included in the 3PS program, the decision was made to include it as the primary endpoint for the study.

Screen time will be assessed using 4 questions from the New Zealand Health Survey [88], which were developed by the New Zealand Ministry of Health to measure the amount of time New Zealand children aged 2 to 14 years spend using screens recreationally. Parents report the time (in hours) that their child spends watching television or using *other* screen devices, including mobile phone, tablets, video game consoles, and computers, during weekdays and on weekends. Screen time will be measured as both a continuous variable, that is a decrease from baseline in average screen time, and a binary variable, that is the proportion of children meeting the screen time recommendations of less than 1 hour per day.

Secondary Outcomes

Family meals, diet, and parent feeding practices: A single item investigating the frequency of family meals, taken from the validated Family Routines Inventory questionnaire [84] and used in the 45-month *Growing Up in New Zealand* data collection wave, will assess participation in family meals. Moreover, 4 questions from the New Zealand Health Survey will investigate the number of fruit and vegetable servings, fizzy drink consumption, and fast-food consumption. A modified version of the Feeding Practices and Structure Questionnaire [85], which includes 17 questions investigating 4 domains of parental feeding behaviors, will also be administered: (1) reward for behavior, (2) reward for eating, (3) persuasive feeding, and (4) structured meal setting.

Sleep: Sleep will be assessed using the Brief Screening Questionnaire for Infant Sleep Problems-Extended [83] -Adapted. The questionnaire asks parents to report outcomes

investigating their child's nocturnal sleep duration, night waking, method of falling asleep, sleeping arrangements, bedtime rituals, and parental interventions. The Web-based version of the questionnaire has been validated for toddler sleep in a New Zealand and Australian sample [89].

Routines and Home Environment: The *Daily Living Routines* subscale of the Child Routine Inventory [86] will investigate engagement in standard routines of daily life. The subscale involves 11 parent-reported questions. Scores will be summed with higher scores indicating greater frequency of routines. The 15-item Chaos, Hubbub, and Order Scale [87] investigates the level of chaos in the home. A total score will be derived by obtaining a sum of responses for the 15 items, where higher scores represent a more chaotic, disorganized, and hurried home environment.

Exit Questionnaire: The exit questionnaire, completed at 6 weeks by intervention participants only, will assess acceptability and feedback of the 3PS program using 5 open-ended questions about what the participants liked and disliked about the program and what they would keep the same or change.

Exit Interviews: A subgroup of 6 to 10 intervention participants will take part in an exit interview at the 6-week follow-up. The exit interview will be conducted by a trained research assistant on the telephone or face-to-face at a community venue and will take approximately 20 min. Participants will be asked to provide informed consent before participating in the interview. Participants will be prompted to explore in more depth their responses to the exit questionnaire, in particular, whether they used the study website and if they found it helpful. Furthermore, given that the formative work revealed that many parents had concerns about parenting interventions making them feel guilty and judged, we will explore their perceptions of the language and tone used in the program and explore ways in which we could avoid any negative experiences in the future.

Sample Size

We will aim to recruit 50 people (25 in each group). As this is a pilot trial, it is not powered to detect significant differences between the 2 groups but will provide sufficient data to ascertain recruitment and the direction and likely effect size for the screen-time outcomes.

Reporting of Results

Statistical Analysis

Study data will be collected in REDCap. All statistical analyses will be performed using SAS version 9.4 and will be specified a priori in a statistical analysis plan prepared by the study statistician. All baseline variables will be summarized by group and descriptive summary statistics provided. Analyses will be carried out on an intention-to-treat basis. Chi-square tests, incidence rates, relative risks, and 95% CI will be calculated for all binary variables followed by multiple logistic regression analysis adjusting for other variables if needed. Continuous data will be analyzed using multiple linear regression modeling or nonparametric analysis. Sensitivity analyses will be undertaken to determine the impact of missing data. Repeated measures models will be used to analyze data collected repeatedly over time. A trained research assistant will conduct interviews. Interviews will be recorded (with permission) and transcribed verbatim. A general inductive thematic approach will be followed that allows research findings to emerge from multiple readings of the raw data. NVivo9 software will be used to manage the transcripts and facilitate the analysis process and to identify themes and categories.

Results

Trial recruitment started in July 2018. Final follow-up was completed in December 2018, with trial findings expected to be available in early 2019.

Discussion

Overview

This paper presents the design of an RCT to pilot the effectiveness of the 3PS program. Findings from the pilot study will be used to inform the design of a larger effectiveness study of the 3PS program. Family meals, restricting screen time, and adequate night-time sleep have been shown to promote obesity resilience in young children [13], with evidence that interventions promoting these routines have potential in reducing BMI [15]. At the same time, parents play a central role in instigating and facilitating participation in these daily activities, and as such, promoting positive parent-child interactions and mutually responsive orientation may further foster the development of healthy behaviors with respect to these routines [43,45]. To our knowledge, this is the first reported intervention of a parent-based program that aims to prevent obesity in young children by focusing on positive bidirectional parent-child interactions [47] during the 3 family routines shown to prevent obesity.

Limitations

This pilot study intervention with short-term follow-up is not able to assess the effect of the 3PS program on child body size. Although the ultimate goal of this approach is to prevent obesity, the decision not to measure children's body weight was pragmatic, due to limited resources and the short duration of the study. Indeed, although promoting family routines, creating a supportive home environment, and facilitating positive parent-child interactions have the potential to prevent overweight and obesity in later childhood and adulthood, we would not expect to see changes in body weight during the 12-week study period. Finally, although preventing obesity is the long-term aim of this approach, the short-term aims are to improve engagement in the 3 routines shown to protect against obesity, increase engagement in positive parental feeding practices at mealtimes, and reduce household chaos. As such, the study measures have been chosen to reflect these aims.

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Authors' Contributions

SM primary investigator, conceptualization, funding acquisition, investigation, methodology, project administration, content development, and writing; SG content development (family meals), review and editing; RT methodology, intervention content development (sleep), review and editing; BG methodology, intervention content development (sleep), review and editing; VP formal analysis and methodology; RM conceptualization, funding acquisition, methodology, review and editing.

Conflicts of Interest

None declared.

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Abbreviations

3PS: 3 Pillars Study
BMI: body mass index

CARE: Connecting Activities, Routines, and Environments
RCT: randomized controlled trial
SES: socioeconomic status

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Protocol

Double-Blind, Single-Center, Randomized Three-Way Crossover Trial of Fitted, Thin, and Standard Condoms for Vaginal and Anal Sex: C-PLEASURE Study Protocol and Baseline Data

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Abstract

Background: Male condoms are underused despite their ability to prevent transmission of HIV and other sexually transmitted infections. The perception of decreased sexual pleasure and poor condom fit are major contributors to condom nonuse.

Objective: The purpose of this study was to compare event-level performance and pleasure using fitted, thin, and standard condoms among men who have sex with men (MSM) and men who have sex with women (MSW). We also sought to assess condom type preference. We present the study design and enrollment data from the trial.

Methods: This study recruited sexually active men aged 18 to 54 years in Atlanta, Georgia, United States. We enrolled 252 MSM and 252 MSW in a double-blind, 3-way randomized crossover trial with conditions of fitted, thin, and standard condoms. A permuted block randomization scheme was used to assign each participant to the sequence in which they received each type of study condom. After a baseline screening and enrollment visit, randomized participants were followed for at least 6 and up to 12 weeks depending on their use of study condoms in each 2-week period between scheduled, in-person study visits. Participants were instructed to complete mobile-optimized coital logs as soon as possible after using condoms for anal or vaginal sex acts. The logs collected event-level pleasure and performance measures for the study condoms as well as other relevant data. A questionnaire was administered at the final study visit to assess overall study condom preference.

Results: The study enrolled 252 MSM and 252 MSW, a total of 504 participants. MSM and MSW study arms were similar for a number of key traits including race and ethnicity, marital status, self-rated condom experience, and recent experience of condom failure. Men in the MSM arm were older, however, and fewer MSM were students. The majority of participants in both arms rated themselves as very experienced with using condoms, and the majority had used condoms recently. Over one-third of participants in each arm reported experiencing condom failure in the last 6 months.

Conclusions: This is the first condom trial to compare the performance of standard, thin, and fitted condoms and to use pleasure and preference as primary outcomes. Given the disparate impact of HIV on MSM, equal enrollment of MSM and MSW was a key feature of this study. Trial results may inform an FDA label indication for anal sex and provide new information regarding the relative performance of different types of condoms.

Trial Registration: ClinicalTrials.gov NCT02753842; https://clinicaltrials.gov/ct2/show/NCT02753842 (Archived by WebCite at http://www.webcitation.org/76RLTFyf0)

International Registered Report Identifier (IRRID): DERR1-10.2196/12205

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KEYWORDS

condoms; HIV prevention; sexual health; clinical trial

Introduction

Male condoms effectively prevent HIV and sexually transmitted disease (STD) transmission but are underused in large part due to perceived reductions in the experience of pleasure. In the United States, diagnosis of chlamydia, gonorrhea, and syphilis has increased in each of the last 4 years, with approximately 2.3 million diagnoses in 2017 [1]. HIV incidence remains high, with an estimated 38,500 incident infections in 2015 [2]. Condoms have high efficacy in preventing HIV transmission [3], and the highest priority for any condom promotion effort is to change factors that lead to condom nonuse [4].

A broad array of factors influence condom use spanning policy, cultural, interpersonal, and individual levels. Condom accessibility through public supply chains, which are largely determined by purchase and distribution policies, has been demonstrated to impact condom uptake [5,6]. Cultural norms may also influence condom use, both when values are held that discourage condom use [7] and when values are held that make condom use normative [8]. Relationship-level variables may be important, including marital status and trust in a particular relationship [9,10]. Individual-level skills also matter, in particular condom use self-efficacy and the ability to negotiate condom use in a relationship [11], which in turn may be inextricably linked to cultural roles and norms [12,13]. Even if nearly ideal conditions were reached (eg, readily available condoms for users with self-efficacy amid supportive community norms) condoms might remain underused due to the widely held belief and perception that condoms decrease sexual pleasure [14-17].

Across several studies, between one-third and one-half of condom users report poor condom fit [14,18-20]. Men who have sex with men (MSM) who either perceive condoms as too tight [21] or report larger than average penis size [18] were more likely to report unprotected sex. One reason for this is that men who perceive poor condom fit have been found to be more likely to report reduced pleasure due to condom use [14,20].

The premise of fitted condoms is that better fitting condoms may enhance perceptions of pleasure or influence overall preference for men considering condom use. There are two biologically plausible hypotheses for this premise. First, men reporting larger penile size are more likely to describe standard condoms as feeling tight [19,21], and this tightness could lead to decreased perceptions of pleasure. Second, men who report smaller penis size are more likely to describe condoms as feeling loose [19], and this additional slack (circumference) or rolled (length) latex could lead to decreased perceptions of pleasure.

MSM are a group meriting particular consideration because they are disproportionately impacted by HIV, accounting for 2 out of every 3 new HIV diagnoses in the United States, with anal sex being the predominant mode of transmission for this group [22]. Previous estimates of clinical condom failure (slippage or breakage) during anal sex often have not measured failure at the event level or used prospective designs. The two studies that assessed clinical condom failure prospectively at the event level reported failure in 6.3% [23] and 6.9% [24] of anal sex acts.

The purpose of this research was to better understand whether different types of condoms lead to different experiences of pleasure and clinical failure. This trial compared the performance of fitted, thin, and standard condoms.

Methods

Study Design and Aims

This study was a double-blinded, randomized crossover trial of 252 MSM and 252 men who have sex with women (MSW). Participants were enrolled from May 2016 to May 2017. Over a series of in-person study visits, participants received in randomized order a set of 5 fitted condoms, a set of 5 thin condoms, and a set of 5 standard condoms. Participants were followed for 6 to 12 weeks, depending on their use of study condoms in each 2-week period between study visits (Figure 1). Event-level data based on a home coital log were collected regarding pleasure and total clinical failure, and data regarding overall condom preference were collected at the final study visit.

As specified at trial registration [25], we conducted this trial with the objectives of establishing label indications for pleasure and patient preference for fitted condoms (aims 1 and 2), establishing a label indication for anal sex for fitted, thin, and standard condoms (aim 3), and establishing a label indication for decreased clinical failure of fitted condoms for anal sex (aim 4). This will be accomplished by comparing fitted condoms with standard condoms regarding levels of reported pleasure as determined by rating per condom use event (aim 1), comparing fitted condoms with standard condoms regarding preference as determined by ranking of the two conditions at the study conclusion (aim 2), assessing the total clinical failure rate of each type of condom (fitted, thin, standard) for anal sex among MSM relative to a cut-point to be determined by the US Food and Drug Administration (FDA) (aim 3), and comparing fitted condoms with standard condoms regarding total clinical failure for anal sex among MSM (aim 4). Detail around the hypotheses and rationale for each primary aim as well as secondary aims

of the study and other areas of interest are provided in Multimedia Appendix 1.

Ethics

The study was conducted in accordance with Title 21 US Code of Federal Regulations (CFR) Part 11 and Good Clinical Practice guidelines. The researchers obtained Emory University institutional review board (IRB) approval for the protocol and informed consent forms prior to initiating the study. All participants signed consent forms. All changes to the protocol were submitted to the Emory University IRB for review and approval as appropriate. The principal investigator followed the requirements of the Emory University IRB on periodic reporting of the progress of the study, reporting of serious or unexpected adverse events, and safety monitoring reports. Participants were informed that collected data were intended for publication and that individual details would be de-identified and stored in a secure, password-protected location available only to members of the research team. Additional ethical details can be found in Multimedia Appendix 2.

Study Population and Recruitment

Primary recruitment for both MSM and MSW was face-to-face venue-based recruitment that took place in a variety of public and private venues in Atlanta where men congregate. Study staff also used secondary recruitment methods that included flyers, paid online advertisements, and recruitment from previous studies. Study sites were the Rollins School of Public Health at Emory University and the Emory Programs, Research, and Innovation in Sexual Minority Health research site. Eligible participants were HIV-negative at their baseline test, aged 18 to 54 years, lived in the Atlanta metro area, and were currently sexually active. We enrolled 252 HIV-negative MSM and 252 HIV-negative MSW. For purposes of study assignment, men were eligible for the MSM arm if they intended to only have sex with other men in the next 12 weeks, and men were eligible for the MSW arm if they intended to only have sex with women in the next 12 weeks. Per FDA guidance [26], only individuals who were willing to be the insertive partner for use of study condoms and therefore best able to ascertain study outcomes were eligible. Further details around participant inclusion criteria as well as recruitment procedures are provided in Multimedia Appendix 1.

Eligibility was assessed in three stages: (1) recruitment screening of less sensitive criteria such as age, (2) phone screening of more sensitive criteria such as genital piercing, and (3) in-person (baseline) screening for reassessment of all eligibility criteria in addition to a negative point-of-care HIV test. Prior to the baseline visit, participants determined their fitted condom size after being mailed instructions and a fitting tool consisting of a paper template graduated with nonsequential numbering and lettering. Multimedia Appendix 1 details participant retention procedures.

Figure 1. Study visit flowchart.

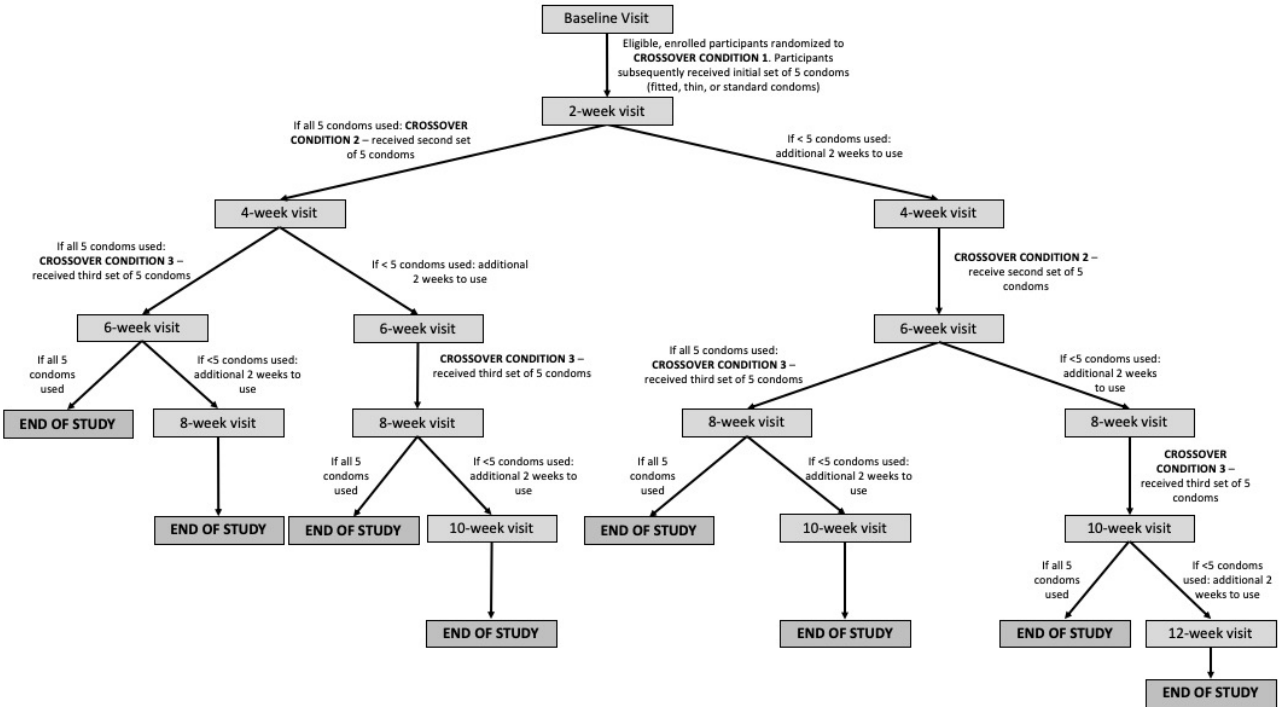
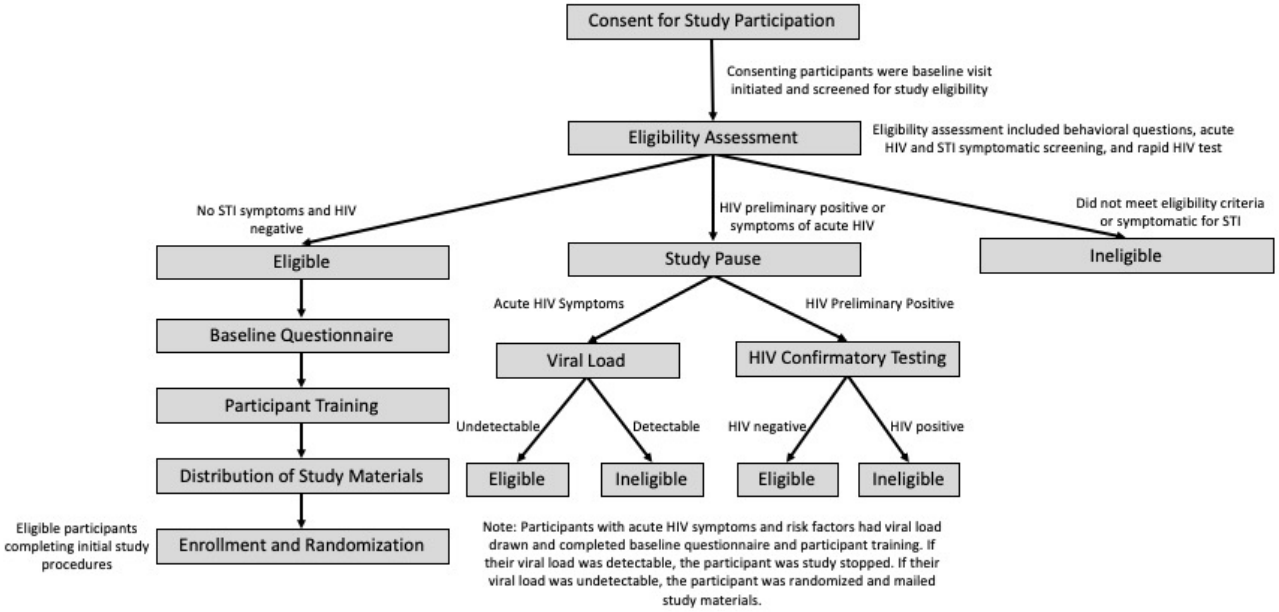


Figure 2. Baseline visit structure.



Study Product

For purposes of this study, a standard condom is defined by dimensions commonly sourced by the United Nations Population Fund: 185 mm (±10 mm) in length, 53 mm (±2 mm) in width, and 70 microns (±10 microns) in thickness (Lai Peng Lim, BS, email communication, June 23, 2015). Thin condoms for this study were of identical width and length to standard but 50 microns (±5 microns) thick. Fitted condoms with a thickness of 70 microns (±10 microns) were produced in a range of sizes. Participants were given two 10-mL packets per condom of commercially available, condom-compatible water-based lubricants in plain foil packets. All condoms and lubricant used in the study were manufactured for the study by Karex Berhad. See Multimedia Appendix 1 for more information regarding study product.

Randomization, Crossover, and Blinding Procedures

Within each study arm (MSM or MSW), the crossover condition order (the order in which condoms were provided) was determined by permuted block randomization as indicated by the clinical data management system (CDMS). Eligible study participants were randomized to 1 of 6 orders, with the 6 orders balancing the allocation of conditions (Multimedia Appendix 2). Each participant was given 5 of each study condom set and had up to 4 weeks to use all 5 condoms. If all 5 condoms in a set were used by the end of the 2-week follow-up period, participants were crossed over to the next condition. If not, participants were given an additional 2-week period to use condoms in that condition. The purpose of this structure was to maintain realistic use periods for study condoms; national survey data indicate that many men in the age range included in this study report sex at a rate that equates to between 1 and 2 sex acts per week [27,28].

In this closed label trial, study condoms were manufactured in plain foil packaging with identifying 2-digit random codes printed on each foil. Blinding of study staff was role-based; the study statistician and the principal investigator, who are responsible for analyses and reporting results to the FDA, will be blinded until after the initial analysis of study results has been conducted. To allow for blinded participants to identify preferred condoms (aim 2), we provided condom sets in color-coded bags. We selected colors that could accommodate common forms of color vision deficiency. Further information on study blinding is available in Multimedia Appendix 1.

Study Visit Procedures

Enrollment/Baseline Visit

A visual depiction of the baseline visit structure is provided in Figure 2. Upon arrival at the visit, all participants completed informed consent and eligibility assessment. Participants received HIV counseling, rapid testing, and test results per US Centers for Disease Control and Prevention guidelines [29]. Participants with confirmed HIV infection, detectable viral loads, or with self-reported STD or symptoms for STD were ineligible to continue the study. We referred these participants to appropriate care (Multimedia Appendix 2). If the participant self-reported symptoms of acute HIV infection and an exposure risk in the past 30 days, blood was drawn for HIV viral load testing with results usually returned within two days. Those with detectable viral loads were study stopped and referred to care, with test results shared with providers upon participant consent; those with undetectable viral loads continued in the study.

Eligible participants completed a self-administered electronic survey and were trained on using the home coital log and correct use of condoms (Multimedia Appendix 2). Participants were instructed to only use study lubricant when using condoms. Guidance from the World Health Organization found substantial evidence that use of additional water-based lubricant decreases anal sex failure and that lubricant use is normative among many MSM [30]. Therefore, MSM were instructed to use study lubricant for all anal sex acts. The same guidance found equivocal evidence for MSW, with some studies showing a small benefit of additional lubricant and a similar number

showing no benefit. Given limited evidence of benefit, and MSW not normatively using lubricant during condom-protected sex [31], we instructed MSW to use lubricant as needed or desired. Participants were scheduled for follow-up visits and provided study lubricant, printed study materials, and a biohazard bag to return any broken condoms.

Follow-Up Visits

A visual depiction of follow-up visit events is provided in Multimedia Appendix 3. At each follow-up visit, study staff performed a manual count of returned condoms. Staff compared the number of returned unused or broken condoms to the number of condom uses and breakages reported in home coital logs during the study period. If there were discrepancies, study staff worked with the participant to resolve them. If participants reported losing condoms at interim study visits, we replaced their lost stock. We conducted adverse event screening for potential partner pregnancy, self-reported acute HIV symptoms, self-reported STD or symptoms for STD, instances of condom failure, and side effects from condom or lubricant use (based on determination by the independent study clinician). Study participants screening positive for these events were referred to care (Multimedia Appendix 2). All assessments at follow-up visits were recorded on electronic case report forms (eCRFs). Study staff instructed participants to throw away any unused study condoms from the previous study period.

Coital Log Description

For event-level measurement, we used a mobile-optimized, Web-based home daily coital log that was 21 CFR Part 11–compliant. We anticipated that use of this system would minimize recall bias due to shorter time period for recall [32]; moreover, previous sexual health research has found that Web diaries produce improved data relative to other methods with longer recall periods [33]. Electronic diaries have an additional benefit over paper-based recall systems in the form of time stamping to accurately determine the time of form completion, and they allow for question piping/logic that converts otherwise complex paper forms into a sequence of brief, easily intelligible questions. Participants were instructed to complete coital logs as soon as possible following any vaginal or anal sex acts. Further, participants received an autogenerated coital log reminder either via text or email every 24 hours to check-in and catch any unreported sex events. The first coital log question determined whether a participant had sex since their last coital log entry. If no was selected, the coital log entry was complete. If yes, the coital log proceeded to query the sexual event. Participants not completing the coital log regularly were contacted by study staff to encourage more consistent completion. To further incentivize regular use of the coital log and therefore minimize recall bias, participants who completed at least 10 coital logs during each 2-week study period were compensated an extra $15 at their next study follow-up visit. Participants were informed that incentives were provided to encourage daily interaction with the system; equal compensation was provided for completions that reported sex and completions that reported no sex. For participants without access to Web browsers, we provided mobile phones.

Measures

Electronic Case Report Forms

Study staff collected key data using eCRFs. For the baseline visit, information collected included eligibility criteria, basic demographic information, and acute HIV and STD symptoms. For follow-up visits, eCRFs included information regarding documentation of condition crossover, number of condoms distributed and returned, adverse events, and study stops.

Baseline Survey

The baseline survey included questions in the domains of (1) sexual history, (2) condom history, (3) sexual dysfunction, (4) condom slippage and breakage, (5) lubricant use, (6) therapeutic methods, (7) condom fit and feel, (8) condom perceptions, (9) self-efficacy around condom use, (10) HIV and STD history, (11) partner history, and (12) pleasure at last sex. The baseline questionnaire, which annotates the question source for each area of assessment, has been provided in Multimedia Appendix 4. Average completion time was 30 to 45 minutes.

Coital Log Measures

The coital log assessed the outcome of pleasure (aim 1) and the outcomes of clinical failure (aims 3 and 4). Based on a literature search and consultation with experts, we identified no extant event-level scale to assess aim 1. Therefore, we developed and validated the Event-level Male Sexual Pleasure Scale (EMSexPleasure), described elsewhere [34]. International Organization for Standardization (ISO) guidance defines clinical failure as combined clinical breakage and slippage [35], and we will follow ISO guidance reporting clinical failure for aims 3 and 4. For instance, any condom failure in which breakage and slippage occur for the same condom will be counted as a single failure for calculation of total clinical failure. The coital log also measured event-level domains regarding the nature and context of condom use: (1) date and time of report (source: ISO); (2) whether a study condom, other condom, or no condom was used (ISO); (3) partner name (cohort study of MSM [36]); (4) lubricant use (ISO); (5) type of sex act (ISO); and (6) drug or alcohol use by participant (cohort study of MSM).

We developed a procedure in the coital log to minimize error in self-report of clinical failure events. After initial completion of questions, the system autogenerated a message that provided a summary of participant's self-report data, with an option to confirm it or to correct it. This message was provided for all reports, whether clinical failure was reported or not reported. For example, for a participant reporting that a condom broke but did not slip, the participant was asked, "You told us that this condom broke but did not slip. Is this correct?" Response options were yes, which led to continuation of the coital log, and no, which led to reinitiation of questions regarding condom failure.

To prevent recall bias from unduly influencing data, we established a set of rules regarding coital log completion at study events. At a study event, if a participant reported using study condoms but had not completed coital logs for them, we allowed a maximum of the past two condom uses to be reported. In these reports, participants entered data regarding clinical

failure outcomes (aims 3 and 4) but not regarding event-level pleasure (aim 1) due to the higher potential recall bias for pleasure, which was considered an ephemeral phenomenon.

Follow-Up Visit Measures

At crossover visits, participants completed a self-administered behavioral survey in the domains of (1) perceived condom fit of the last study condom used, (2) perceived crossover condition, (3) new sexual partners, and (4) condom preference (at applicable visits). If participants reported any condom use that had not been previously recorded with coital logs, they were allowed to enter coital log data for up to their two most recent condom uses.

End Line Measures

Preference, the outcome measure for aim 2, was measured at the final study visit. For each of 3 possible combinations of 2 crossover conditions (standard/thin, thin/fitted, standard/fitted), there was a paired comparison asking participants to select their preferred condom between the 2 relevant study conditions. To maintain blinding, preference question response options were the color assigned to each condom type.

Statistical Considerations

Statistical Power and Sample Size

For aim 2 at 80% and 90% power, assuming 80% retention, the minimum underlying values of fitted-condom preference $\hat{\pi}_{2,1}$ that would be detectable as significantly higher than 0.5 ranged from 0.56 to 0.57. Given these calculations, we sought to have at least 404 participants complete the trial. Based on our previous studies in Atlanta, we anticipated 20% loss to follow-up from the 504 enrolled participants. This sample size provides an estimated >99% power to detect a statistically significant contrast for aim 1 across a wide range of possible event-level pleasure scores.

Data Analysis

The planned primary analysis of aims is described in Table 1. Aim 1 involves the pair-wise comparison of pleasure scores between fitted and standard condoms. A linear mixed effects model with random effects for person and including arm, condom type, crossover period, and an arm*condom type interaction term will be conducted to account for repeated measures within participants (ie, the crossover design) and for repeated measures on coital acts within each of the 3 conditions. Model-based estimates and confidence intervals of the difference in pleasure score will be used to compare fitted and standard condoms. Additional control for participant-, partner-, and event-level correlates of pleasure in the above model will be considered in secondary analyses.

The primary analysis of aim 2 will be conducted at the participant-level using binary preference responses for comparison of fitted and standard condoms, collected at the final study visit (Table 1). For aim 2, we will assess whether a majority of participants preferred fitted over standard condoms using a logistic regression model with preference as the outcome and arm and crossover period as covariates. A confidence interval around the estimated probability of fitted condom preference will be computed.

A descriptive assessment for aim 3 will consist of calculating the per–anal sex act clinical failure proportion for the 3 condom conditions by dividing the number of total clinical failures by the total number of acts contributed for each condom type by participants in the MSM arm of the study. We will assess whether the proportion of failure for each condom type is below the threshold value that is to be determined by FDA. In order to adjust for study design, failure will also be assessed with a logistic mixed effects model with random effects for person with arm, condom type, crossover period, and an arm*condom type interaction term. For aim 4, we will use the logistic mixed model described in aim 3 to assess the odds of failure for fitted versus standard condoms within the MSM arm. Instances of anal sex among MSW will not be included in primary analyses because anal sex events occur frequently at the lifetime level for MSW but infrequently at monthly and even yearly levels [37]. This indicates lower levels of experience with this type of sex for many MSW, an issue that could introduce bias into study outcome assessment.

Table 1. Outcome measures used to assess each study aim.

Aim number and description		Outcome measure
1	To compare fitted condoms with standard condoms regarding levels of reported pleasure as determined by rating per condom use event	Pleasure-scale score (response item mean) for fitted condoms and standard condoms following each coital event
2	To compare fitted condoms with standard condoms regarding preference as determined by dichotomous preference among the 2 conditions at the study conclusion	Binary preference of fitted versus standard condoms at final study visit
3	To assess for fitted, thin, and standard condoms the total clinical failure rate of each type of condom for anal sex among MSM[a] relative to a cut-point to be determined by the FDA[b]	Binary occurrence of clinical failure for each type of condom at each coital event
4	To compare fitted condoms with standard condoms regarding total clinical failure for anal sex	Binary occurrence of clinical failure for fitted and standard condoms at each coital event

[a]MSM: men who have sex with men.

[b]FDA: US Food and Drug Administration.

Data Procedures

Study data collection was predominantly electronic and conducted through the study CDMS. The study used the Dacima Clinical Suite CDMS platform (Dacima Software Inc) compliant with all relevant FDA standards. For all office visits, eCRFs and the coital log were conducted on the CDMS. The study CDMS was a Web-based application, allowing participants to complete electronic coital logs at home with any device with an up-to-date Web browser. Information collected during recruitment and phone screenings was not collected using the CDMS but instead was collected through an electronic survey system, SurveyGizmo (covered by a Health Insurance Portability and Accountability Act business associate agreement) and transferred to a secure Emory database that allowed for potential participants to be contacted regarding the study. None of the data collected during recruitment and phone screenings was used as part of the study dataset. For coital log entries, participants used a secure link to access study forms that required a log-in with username and password protection. Details on methods for data quality assurance and laboratory procedures are in Multimedia Appendix 2.

Results

The study assessed a total of 13,524 individuals for phase 1 eligibility through field-based screening. Of the 2819 initially eligible individuals, 1037 (36.8%) completed phase 2 eligibility assessment by phone; 681 were eligible and 542 attended a baseline visit. Of the 542 who attended the baseline visit, 504 were enrolled in the trial (93%). Baseline demographic and behavioral characteristics of study participants, by study arm and study condom type, are described in Table 2. MSM and MSW were similar across many traits such as race and ethnicity, marital status, portion circumcised, self-rated condom experience, erectile function, and condom failure in the last 6 months. Men in the MSM arm were older, with 47% (119/252) over the age of 30 years compared to 19% (48/252) of MSW being over 30 years. Fewer MSM were students than MSW (11% [28/252] and 53% [133/252], respectively), likely an artifact of recruitment. Nearly three-quarters of participants in both arms rated themselves as very experienced with using condoms (186/252 MSM and 187/252 MSW), the majority had used condoms in the past 30 days, and just over one-third in each arm reported condom failure in the last 6 months (81/252 MSM and 86/252 MSW).

Table 2. Baseline demographic and behavioral characteristics of study participants.

Characteristics	Participant strata		Condom type used		
	MSM[a] (n=252), n (%)	MSW[b] (n=252), n (%)	Blue (n=464), n (%)	Black (n=468), n (%)	Yellow (n=469), n (%)
Demographics					
Age at baseline in years					
< 20	10 (4)	46 (18)	53 (11)	50 (11)	50 (11)
20-24	54 (21)	104 (41)	146 (31)	149 (32)	151 (32)
25-29	69 (27)	54 (21)	110 (24)	113 (24)	111 (24)
30-39	71 (28)	37 (15)	98 (21)	100 (21)	100 (21)
40-54	48 (19)	11 (4)	57 (12)	56 (12)	57 (12)
Race and ethnicity					
Hispanic	31 (12)	31 (12)	56 (12)	57 (12)	57 (12)
White non-Hispanic	122 (48)	119 (47)	217 (47)	219 (47)	220 (47)
African-American non-Hispanic	79 (31)	52 (21)	125 (27)	124 (27)	126 (27)
Other non-Hispanic	20 (8)	49 (20)	65 (14)	67 (14)	65 (14)
Prefer not to answer, non-Hispanic	0 (0)	1 (0)	1 (0)	1 (0)	1 (0)
Sexual identity					
Homosexual/gay	228 (90)	0 (0)	204 (44)	210 (45)	205 (44)
Bisexual	21 (8)	5 (2)	24 (5)	25 (5)	24 (5)
Heterosexual/straight	1 (0)	245 (97)	234 (50)	231 (49)	236 (50)
Other	2 (1)	2 (1)	2 (0)	2 (0)	4 (1)
Education					
College, postgraduate, or professional school	160 (63)	116 (46)	253 (55)	254 (54)	256 (55)
Some college, associate's degree, or technical school	71 (28)	80 (32)	138 (30)	141 (30)	142 (30)
High school, GED[c], or less	21 (8)	56 (22)	73 (16)	73 (16)	71 (15)
Income					
<$20,000	62 (25)	85 (34)	136 (29)	136 (29)	138 (29)
$20,000-$29,999	35 (14)	24 (10)	54 (12)	55 (12)	56 (12)
$30,000-$39,999	27 (11)	17 (7)	42 (9)	43 (9)	40 (9)
$40,000-$49,999	28 (11)	18 (7)	42 (9)	42 (9)	44 (9)
≥50,000	90 (36)	85 (34)	159 (34)	160 (34)	160 (34)
Don't know	10 (4)	23 (9)	31 (7)	32 (7)	31 (7)
Marital status, current					
Legally married/registered domestic partnership/civil union	19 (8)	26 (10)	41 (9)	42 (9)	43 (9)
Divorced/separated	11 (4)	8 (3)	18 (4)	17 (4)	18 (4)
Never married	222 (88)	218 (87)	405 (87)	409 (87)	408 (87)
Employment					
Employed	203 (81)	111 (44)	284 (61)	291 (62)	285 (61)
Student	28 (11)	133 (53)	152 (33)	150 (32)	155 (33)
Unemployed/retired/other	21 (8)	8 (3)	28 (6)	27 (6)	29 (6)
Homeless, last 6 months					
Yes	8 (3)	7 (3)	13 (3)	12 (3)	12 (3)

Characteristics	Participant strata		Condom type used		
	MSM[a] (n=252), n (%)	MSW[b] (n=252), n (%)	Blue (n=464), n (%)	Black (n=468), n (%)	Yellow (n=469), n (%)
No	244 (97)	245 (97)	451 (97)	456 (97)	457 (97)
Sex history					
Circumcised					
Circumcised (cut)	207 (82)	211 (84)	385 (83)	385 (82)	387 (83)
Uncircumcised (uncut)	45 (18)	41 (16)	79 (17)	83 (18)	82 (17)
Number of insertive anal sex partners (MSM) or vaginal sex partners (MSW), past 30 days					
1	129 (51)	206 (82)	307 (66)	311 (66)	314 (67)
2	56 (22)	35 (14)	85 (18)	87 (19)	86 (18)
3	40 (16)	9 (4)	45 (10)	46 (10)	45 (10)
≥4	27 (11)	2 (1)	27 (6)	24 (5)	24 (5)
Erectile function scale, with condom, past 6 months[d]					
No erectile dysfunction	157 (62)	186 (74)	323 (70)	317 (68)	323 (69)
Mild erectile dysfunction	57 (23)	39 (15)	84 (18)	90 (19)	90 (19)
Moderate to severe erectile dysfunction	9 (4)	1 (0)	8 (2)	10 (2)	8 (2)
Missing	29 (12)	26 (10)	49 (11)	51 (11)	48 (10)
Used the following (choose all that apply)					
Pill such as Viagra, Cialis, or Levitra	28 (11)	2 (1)	29 (6)	28 (6)	29 (6)
Testosterone	5 (2)	1 (0)	6 (1)	6 (1)	6 (1)
Injection into your penis to get an erection	1 (0)	0 (0)	1 (0)	1 (0)	1 (0)
Vacuum or penis pump to get an erection	3 (1)	0 (0)	3 (1)	2 (0)	3 (1)
Penile implant	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
None of the above	219 (87)	245 (99)	426 (93)	431 (93)	431 (93)
Missing	1 (0)	4 (2)	4 (1)	4 (1)	4 (1)
Condom use and failure, at baseline					
Used a condom for insertive anal sex (MSM) or vaginal sex (MSW), past 30 days					
Yes	181 (72)	201 (80)	358 (77)	353 (75)	358 (76)
No	56 (22)	40 (16)	84 (18)	92 (20)	90 (19)
Missing	15 (6)	11 (4)	22 (5)	23 (5)	21 (4)
Self-rated condom experience					
Not very experienced	11 (4)	6 (2)	17 (4)	17 (4)	17 (4)
Somewhat experienced	55 (22)	59 (23)	105 (23)	108 (23)	105 (22)
Very experienced	186 (74)	187 (74)	342 (74)	343 (73)	347 (74)
Rating of length of last condom used, measured at baseline					
Very good	36 (14)	53 (21)	82 (18)	83 (18)	82 (17)
Good	85 (34)	105 (42)	179 (39)	175 (37)	179 (38)
Moderate	47 (19)	34 (13)	77 (17)	75 (16)	77 (16)
Poor	12 (5)	9 (4)	19 (4)	19 (4)	19 (4)
Very poor	1 (0)	0 (0)	1 (0)	1 (0)	1 (0)
Missing	71 (28)	51 (20)	106 (23)	115 (25)	111 (24)
Rating of width of last condom used, measured at baseline					
Very good	28 (11)	44 (17)	66 (14)	67 (14)	67 (14)

Characteristics	Participant strata		Condom type used		
	MSM[a] (n=252), n (%)	MSW[b] (n=252), n (%)	Blue (n=464), n (%)	Black (n=468), n (%)	Yellow (n=469), n (%)
Good	73 (29)	99 (39)	166 (36)	165 (35)	166 (35)
Moderate	49 (19)	44 (17)	86 (19)	81 (17)	85 (18)
Poor	29 (12)	14 (6)	38 (8)	38 (8)	38 (8)
Very poor	2 (1)	0 (0)	2 (0)	2 (0)	2 (0)
Missing	71 (28)	51 (20)	106 (23)	115 (25)	111 (24)
Condom self-efficacy score[e]					
Scored below 16	116 (46)	130 (52)	226 (49)	229 (49)	227 (48)
Scored 16	136 (54)	122 (48)	238 (51)	239 (51)	242 (52)
Started having sex without condom, then pulled out and put one on					
Yes	59 (23)	94 (37)	140 (30)	142 (30)	140 (30)
No	164 (65)	132 (52)	275 (59)	275 (59)	281 (60)
Missing	29 (12)	26 (10)	49 (11)	51 (11)	48 (10)
Started having sex with condom, then pulled out and took it off before sex was over					
Yes	77 (31)	72 (29)	138 (30)	141 (30)	138 (29)
No	146 (58)	154 (61)	277 (60)	276 (59)	283 (60)
Missing	29 (12)	26 (10)	49 (11)	51 (11)	48 (10)
Condom broke, slipped, or both during sex, past 6 months					
Yes	81 (32)	86 (34)	158 (34)	154 (33)	152 (32)
No	142 (56)	140 (56)	257 (55)	263 (56)	269 (57)
Missing	29 (12)	26 (10)	49 (11)	51 (11)	48 (10)

[a]MSM: men who have sex with men.

[b]MSW: men who have sex with women.

[c]GED: general education development.

[d]Erectile function scaled using the 5-item International Index of Erectile Function questionnaire [38].

[e]Condom self-efficacy scored using a 7-item scale adapted from previous work and with demonstrated evidence of internal reliability [39,40].

Discussion

This protocol describes a blinded, crossover randomized clinical trial designed to compare the performance of standard, thin, and fitted condoms. To our knowledge, this is the first clinical trial of condoms to include preference or pleasure as primary outcomes. Pleasure is an inherently ephemeral experience, and yet is essential to the sexual experience. Qualitative literature is rife with critiques of how condoms are perceived to limit pleasure. For instance, condom use has been described as similar to "eating candy with the wrapper on" in settings as diverse as Brazil [41], Tanzania [7], and the Philippines [42]. There is growing consensus that issues regarding pleasure and condoms merit consideration, exemplified by a Bill and Melinda Gates Foundation grant call directly addressing this issue by instigating funding to develop new condom innovations [43]. The call noted the many health benefits of condoms and that "the primary drawback...is that condoms decrease pleasure as compared to no condom, creating a trade-off that many men find unacceptable." Explicitly incorporating pleasure into the primary aims and hypotheses of future clinical trials could, in many instances, be accomplished without substantial additional effort.

A key feature of the study design is recruitment of equal numbers of MSM and MSW. Studies assessing condom performance among MSM are merited due to disparate impact of HIV, with over 2 out of every 3 new HIV diagnoses in the United States in 2015 occurring among MSM [44]. Equal enrollment of MSM and MSW will allow for assessment of whether study condoms of all types have sufficiently low failure rates as to merit an FDA label indication for anal sex.

This study incorporated a number of practices to minimize potential bias of primary outcomes. To minimize recall bias, participants were provided with the electronic coital log to complete following sex acts. Automated daily electronic reminders encouraged participants to complete a coital log entry for any sex acts not previously reported. Another advantage of electronic data collection is that it allowed for show/hide and piping features that turned what would have been a confusing paper report form into a short series of simple, answerable questions. Survey logic enabled by electronic data collection also allowed for us to incorporate a methodological innovation

to decrease misreporting of condom failure; the survey system autogenerated a message that provided a summary of participant's self-report data, with an option to confirm it or to correct it. Given that a small proportion of incorrectly reported data (eg, 3%) could substantially influence the likely rare study outcome of condom failure, we view this data validation step as holding substantial potential value.

To minimize response and recall bias, financial incentives were provided for regular participant use of the coital log; the same incentive amount was provided for coital log reports of no sex as for coital log reports of using study condoms. In contrast, some past studies required participants to use all of a set of study condoms prior to receiving incentives at their next study visit [45,46], or participants were given additional incentives for reporting on each additional condom use [45]. Such incentives could lead to participant overreporting use of study product to enhance their ability to receive further incentives.

This study is subject to a number of limitations. There is no gold standard laboratory measurement of clinical condom failure, condom preference, or pleasure. Instead, study outcomes rely on self-report, which multiple reviews have identified as problematic for reporting of outcomes relating to sex [47,48]. We sought to mitigate potential areas of bias along lines suggested by these reviews, such as shorter periods of recall and measurement specific to a sexual act and partner. For measurement bias regarding pleasure and preference, such as these constructs being potentially subjective and challenging to quantify, we expect bias would be random given that the study is blinded and thus would bias toward the null hypothesis.

In conclusion, this study protocol describes a clinical trial of condoms that incorporates novel outcomes of pleasure and preference into the primary aims and uses a number of methods to minimize potential sources of bias. The trial includes outcomes for both MSM and MSW, allowing for enhanced understanding of condom performance among a key population. Trial results may inform FDA label indication for anal sex and provide new information regarding the relative performance of different types of condoms.

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Authors' Contributions

AJS, PSS, MPC, and EMR were the lead investigators and were responsible for study conception and design. ESR was the coordinating researcher and was responsible for overseeing recruitment and data collection. CFK was the study physician. CCM and RHM contributed to the data cleaning and analysis. AJS, EMR, and LA drafted the manuscript. All authors read, edited, and approved the final manuscript.

Conflicts of Interest

AJS, EMR, PSS, LA, CFK, CCM, RHM, and ESR have no conflicts of interest to declare. MPC is the owner of TheyFit LLC. On January 26, 2016, TheyFit LLC sold all assets pertaining to the study aims including trademarks, intellectual property, inventory, website, and regulatory approvals to Karex Berhad. MPC has no financial interest in Karex Berhad.

Multimedia Appendix 1

World Health Organization registration and extended information.

[DOCX File, 35KB - resprot_v8i4e12205_app1.docx]

Multimedia Appendix 2

Text appendices.

[DOCX File, 17KB - resprot_v8i4e12205_app2.docx]

Multimedia Appendix 3

Follow-up visit structure.

[PNG File, 120KB - resprot_v8i4e12205_app3.png]

Multimedia Appendix 4

Baseline visit questionnaire.

[DOCX File, 230KB - resprot_v8i4e12205_app4.docx]

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Abbreviations

CDMS: clinical data management system
CFR: US Code of Federal Regulations
eCRF: electronic case report form
FDA: US Food and Drug Administration
IRB: institutional review board
ISO: International Organization for Standardization
MSM: men who have sex with men
MSW: men who have sex with women
STD: sexually transmitted disease

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Protocol

Evaluating the Noninferiority of a New Photodynamic Therapy (Flexitheralight) Compared With Conventional Treatment for Actinic Keratosis: Protocol for a Phase 2 Study

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Abstract

Background: Actinic keratosis (AK) is characterized by preinvasive, cancerous lesions on sun-exposed skin that negatively affect patient quality of life and may progress to invasive squamous cell carcinoma (SCC). If untreated, AK may either regress or progress to SCC, with significant morbidity and possible lethal outcomes. The most commonly used treatments for AK are cryotherapy, topical chemotherapy and, more recently, photodynamic therapy (PDT). This clinical study is part of a project that aims to create specific light-emitting fabrics (LEFs) that strongly improve the efficiency and reliability of PDT as a treatment for AK.

Objective: This study aims to compare the efficacy and tolerability of a new PDT protocol involving the Flexitheralight device (N-PDT) with the classical protocol involving the Aktilite CL 128 device (C-PDT; Galderma Laboratories) for the treatment of AK. All participants receive both protocols. The primary objective of this study is to compare the lesion response rate after 3 months of N-PDT with C-PDT. Secondary objectives are evaluations of pain and local tolerance during treatment, clinical evolution of the subject's skin, and evaluations of patient quality of life and satisfaction.

Methods: The study is a split-face, intraindividual comparison of two PDT protocols. The total number of patients recruited was 42. Patients were exposed to a continuous red light with the Aktilite CL 128 device on one side of the face and to fractionated red illumination with the new device, Flexitheralight, on the other side of the face. Males or females over the age of 18 years with a clinical diagnosis of at least 10 previously untreated, nonpigmented, nonhyperkeratotic grade I and II AK lesions of the forehead and/or scalp were included and were recruited from the Department of Dermatology of the Centre Hospitalier Universitaire de Lille. The patients came to the investigational center for one treatment session (day 1), and they were followed up after 7 days, 3 months and 6 months. A second treatment session was performed on day 111 in cases in which an incomplete response was observed at the 3-month follow-up. Data will be analyzed using SAS software version 9.4 (SAS Institute Inc). Continuous variables will be reported as means and standard deviations, and categorical variables will be reported as frequencies and percentages. The Shapiro-Wilk test will be used to assess the normality of the distribution.

Results: The clinical investigation was performed by July 2018. Data analysis was performed at the end of 2018, and results are expected to be published in early 2019.

Conclusions: This phase II clinical trial aims to evaluate the noninferior efficacy and superior tolerability of N-PDT compared to that of C-PDT. If N-PDT is both efficacious and tolerable, N-PDT could become the treatment of choice for AK due to its ease of implementation in hospitals.

Trial Registration: ClinicalTrials.gov NCT03076918; https://clinicaltrials.gov/ct2/show/NCT03076918 (archived by WebCite at http://www.webcitation.org/771KA0SSK)

International Registered Report Identifier (IRRID): DERR1-10.2196/11530

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KEYWORDS

photodynamic therapy; actinic keratosis; light-emitting fabrics; Aktilite CL 128 (Galderma Laboratories)

Introduction

Actinic keratosis (AK) is characterized by common, preinvasive, cancerous lesions in sun-exposed skin [1-4] that negatively affect the quality of life in patients and may progress to invasive squamous cell carcinoma (SCC) [5]. AK usually develops on areas that are frequently exposed to the sun (eg, face, ears, scalp, neck, forearms, backs of hands). Patients with AK often express embarrassment, worry, and irritation related to the change in appearance of their skin and the unsightly nature of the lesions [6]. In addition causing emotional strain, AK lesions can be painful and easily traumatized, causing bleeding [5,7-9]. If untreated, AK may either regress or progress to SCC, with significant morbidity and possible lethal outcomes [10]. The malignant potential and impossibility of predicting which AK lesions will evolve into SCC have led to the common consensus that AK lesions must be treated [11]. The most commonly used treatments for AK are cryotherapy, topical chemotherapy, and, more recently, photodynamic therapy (PDT) [2,12-16].

PDT is based on the activation of light-sensitive molecules (photosensitizers) that are preferentially localized in the diseased tissues, resulting in the formation of reactive oxygen species and subsequently tissue injury and cell death; 5-aminolevulinic (ALA) and its ester, methyl aminolevulinate (MAL), are both photosensitizer precursors that are most often used for topical PDT. After being topically applied to the skin, these photosensitizer precursors are endogenously converted by the heme biosynthetic pathway into the photosensitizer protoporphyrin IX (PpIX) and other intermediate photosensitizing porphyrins [17]. As abnormal cells accumulate substantially higher levels of PpIX than normal cells [18], the subsequent illumination leads to their selective destruction. PDT with MAL has been shown to be an attractive treatment modality for AK because it enables the treatment of large areas with a high response rate and an excellent cosmetic outcome [19-22].

Classical PDT (C-PDT) is already used, but it involves rigid, planar light source devices (like Aktilite C128, Galderma Laboratories) that do not allow the homogeneous illumination of convex surfaces such as the scalp. Therefore, the dermatologist does not know the actual light dose that is delivered during C-PDT, and some lesions may be undertreated. This limitation could explain some treatment failures [23]. Moreover, C-PDT is only available in specialized environments (hospitals and clinics) and has not been sufficiently developed and widely used.

This clinical study is part of a project that aims to create specific light-emitting fabrics (LEFs) that improve the efficiency and reliability of PDT [24] as a treatment for AK. Flexitheralight is a new device for PDT treatment (N-PDT; U1189, Inserm) that appears to be perfectly adapted for treating skin zones because of its homogeneity, low weight, flexibility, optimal conformability, and low cost. Moreover, the Flexitheralight device can be used at home, following the diagnosis and treatment definition by specialists.

Methods

Trial Design

The trial was a proof-of-concept study and was a comparative (split-face and intraindividual comparison), randomized, open-label, single-center evaluation of the noninferiority of N-PDT compared with C-PDT.

Setting

The study was conducted at the Lille University Hospital in the Department of Dermatology over a period of 24 months until the end of 2017. Forty-two patients were included and were followed for 6 months.

Device

Flexitheralight is a new illumination device consisting of LEFs connected to a laser source (Figure 1). For fractionated illumination, 3 juxtaposed LEFs, each 20 cm x 5 cm, are positioned on the patient's head.

Each LEF is connected to a 635 nm laser source, which is tuned to deliver an irradiance of 12.3 mW/cm^2. This irradiance is controlled by a PD300 photodiode sensor connected to a StarBright laser power meter (both Ophir Optronics Solutions Ltd).

The 3 LEFs are activated sequentially as follows (Figure 2): on for 60 seconds and off for 120 seconds, with the sequence being repeated 50 times. When using these parameters, the total fluence is 37 J/cm^2 for an illumination time of 2 hours and 30 minutes.

Figure 1. Flexitheralight device.

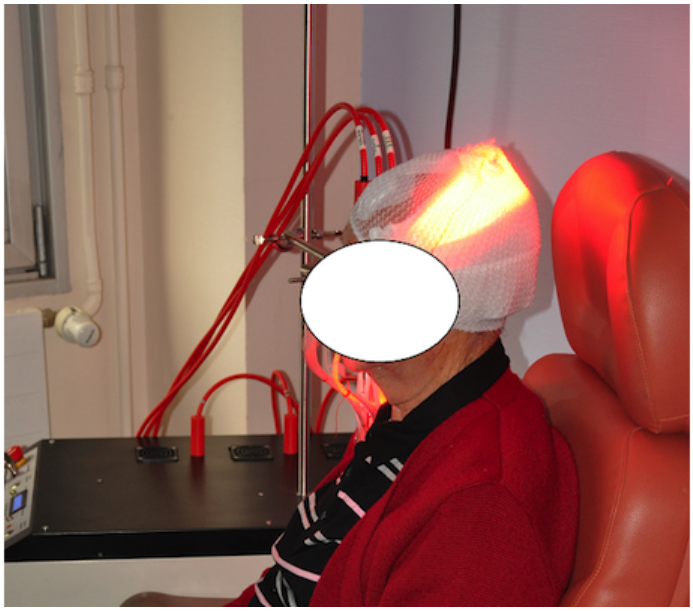
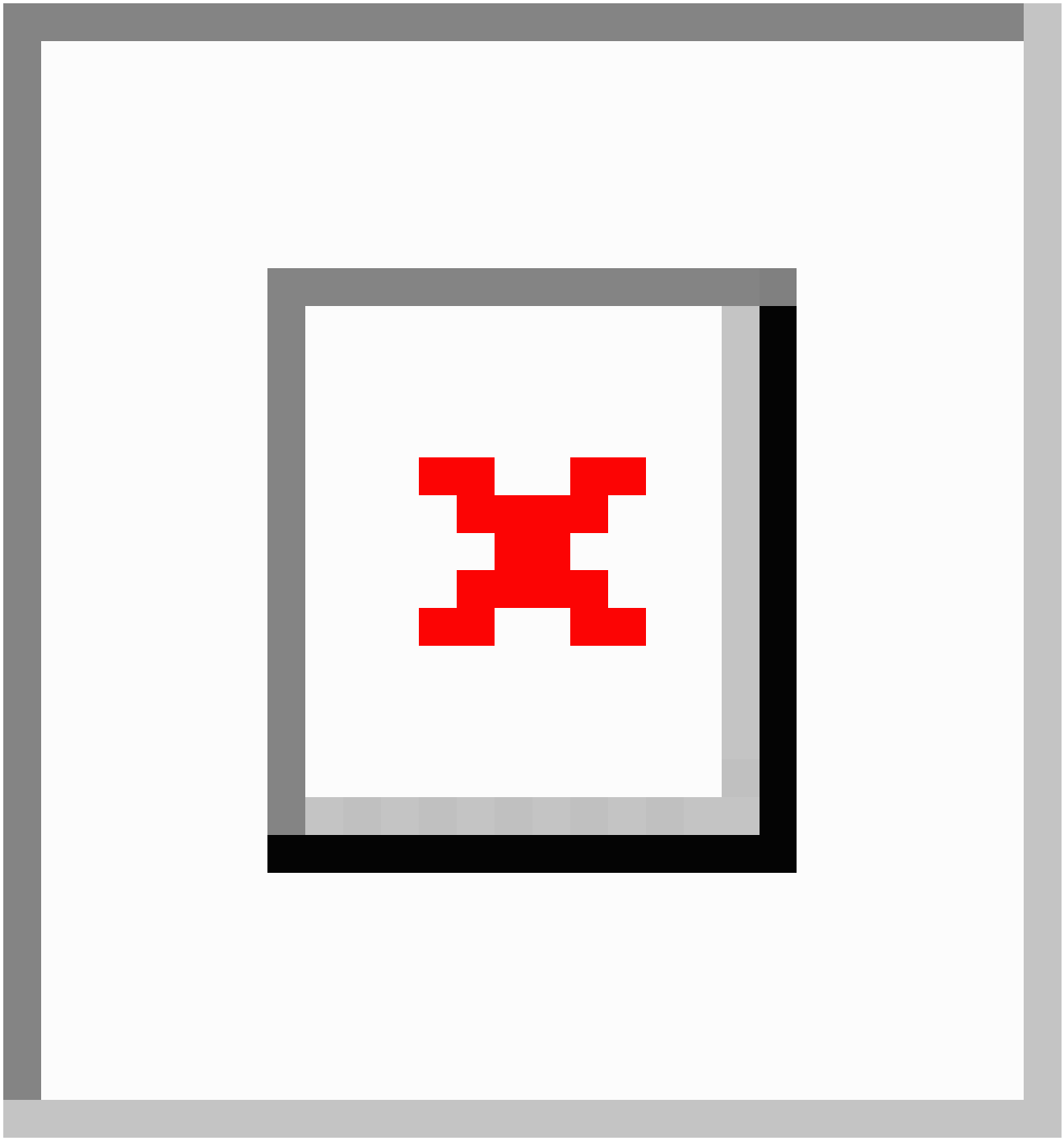


Figure 2. Fractionated illumination with LEF.



Participants

To be eligible for the study, patients had to fulfill all the inclusion criteria described in Textbox 1 below. If they had only one of the noninclusion criteria, they were excluded from the study.

Information about the trial was provided to the patients, both orally and in a written format. Written informed consent was obtained from patients at the screening visit before entering the study.

The tolerability of the device was assessed on the first five patients. The study would have been completely interrupted if at least one patient had pain rated at 5 or higher out of 10 in the N-PDT area as measured by the pain assessment scale or at least one serious adverse event related to N-PDT occurred.

Textbox 1. Selection criteria.

Inclusion criteria:

- Males or females over the age of 18 years
- Clinical diagnosis of at least 10 previously untreated, nonpigmented, nonhyperkeratotic, grade I and II actinic keratosis (AK) lesions of the forehead and/or scalp (according to Olsen et al [25])
- Other therapies are not unacceptable or considered medically less appropriate
- Symmetrical repartition of AK in terms of number and severity of lesions on both areas of the forehead and/or scalp. The axis of symmetry between the two areas is defined by the investigator according to the distribution of lesions
- AK is diagnosed upon a clinical evaluation (ie, visual inspection and palpation) performed by the investigator
- No treatment of AK received in the previous 30 days
- The two areas to be treated should not be coalescing. A minimum distance of 10 mm between the lesions located on the 2 symmetrical areas is required. A minimum distance of 2 mm between the lesions on the same area is required
- A minimum of 5 lesions and a maximum of 7 lesions with similar dimensions at both symmetrical areas are included. If the number of lesions is more than 7, only 7 lesions in each area are considered

Noninclusion criteria:

- Patients with porphyria
- Patients who are immunosuppressed for idiopathic, disease-specific, or therapeutic reasons
- Use of topical corticosteroids on the lesioned areas within 2 weeks before photodynamic therapy (PDT)
- Patients receiving local treatment (including cryotherapy, curettage-electrocoagulation, or any PDT treatment) of the face/scalp area within the last 30 days
- Patients receiving topical treatment (including imiquimod, fluorouracil, diclofenac, or ingenol mebutate) of the face/scalp area within the last 3 months
- Use of topical retinoids, alpha hydroxy acids, urea, or systemic retinoids or chemotherapy or immunotherapy within the 4 last weeks
- Pigmented AK lesions
- Known allergy to ester methyl aminolevulinate or similar PDT compound or excipients of the cream including arachis, peanut, or soya oil
- Participation in other clinical studies either currently or within the last 30 days
- Female subjects must meet one of the following criteria:
  - Nonchildbearing potential: postmenopausal or have a confirmed clinical history of sterility (eg, the subject does not have an uterus)
  - Childbearing potential: confirmed negative urine pregnancy test or blood analysis prior to study treatment to exclude pregnancy
- Any condition that may be associated with a risk of poor protocol compliance
- Patients currently receiving regular ultraviolet radiation therapy

Study Objectives and Outcomes

The primary objective is the comparison of the lesion response rate 3 months after either N-PDT or C-PDT. Key secondary objectives are treatment tolerability, complete response rate after 6 months, cosmetic results, patient quality of life, and satisfaction (Table 1).

Sample Size

The study is designed to have a statistical power of 80% with a one-sided alpha level of .025 to determine noninferiority in terms of a complete lesion response rate 3 months after N-PDT compared with C-PDT. Assuming a complete lesion response rate of 75% in both areas, an intrapatient correlation in both lesions and areas, and a noninferiority margin of 10%, the number of required lesions per area is 245. This value corresponds to 42 patients, assuming 12 lesions per patient (6 lesions per patient per area).

Allocation and Randomization

Patients who met all of the eligibility criteria were included in the study by central randomization. The randomization schedule was generated by a statistician using the PROC PLAN procedure in SAS statistical software (SAS Institute Inc) with a 1:1 allocation ratio and a block size of 6. The allocation was concealed using sequentially numbered, opaque, sealed envelopes that were opened sequentially by the investigator at the beginning of the treatment.

Implementation and Blinding

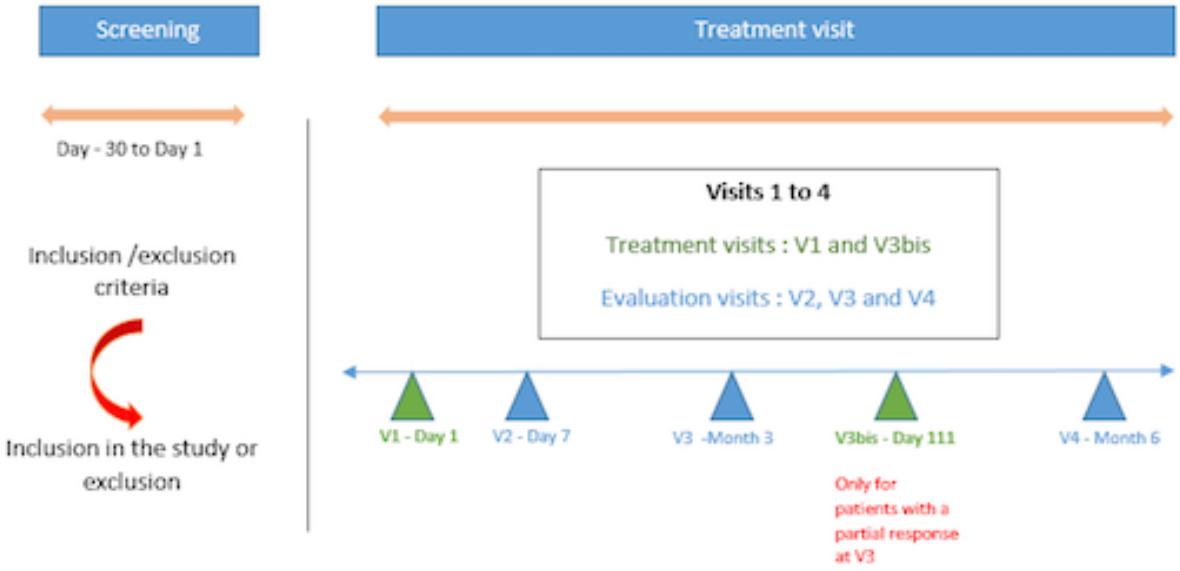
The study was not blinded, and patients and investigators knew the procedure allocation. Efficacy and tolerability were evaluated by investigators who knew the type of treatment assigned to each area. Data will also be analyzed without blinding.

Table 1. Criteria for objectives evaluation.

Outcome and description	Visit				
	1[a]	2[b]	3[c]	3bis[d]	4[e]
Complete response rate					
Total disappearance of each lesion			x		x
Number of patients presenting a 75% lesion reduction rate			x		x
Tolerability					
Evaluation of pain (visual analogic scale)	x			x	
Local tolerance (adverse event, serious adverse event, concomitant treatments)	x	x		x	
Cosmetic results					
Clinical assessment of the subject's skin aspect (excellent, good, fair, or poor)	x		x		x
Quality of life and satisfaction					
DLQI[f] and satisfaction questionnaire	x	x	x	x	x

[a]Visit 1: day 1.
[b]Visit 2: day 7.
[c]Visit 3: at 3 months.
[d]Visit 3bis: day 111.
[e]Visit 4: at 6 months.
[f]DLQI: Dermatology Life Quality Index.

Figure 3. Schematic of the study procedure. V: visit.



Interventions

As shown in Figure 3, after screening, patients who met all the inclusion criteria and none of the exclusion criteria were randomized and invited to come to the investigation site for 4 visits: day 1, day 7, month 3, and month 6. If an incomplete clinical response was observed at month 3, patients were retreated with PDT during visit 3bis on day 111.

Initial Visit: Preparation and Treatment of Lesions

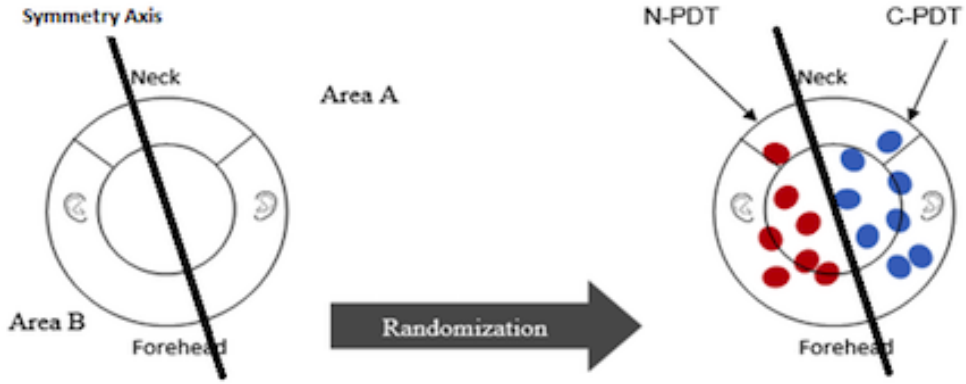
Selection of Treatment Areas

Each subject's skin aspect was evaluated, and the two areas were treated according to the study protocol and randomization design. Randomization was performed after the definition of the axis of symmetry to avoid selection errors (Figure 4).

The global area of the scalp and front of the face was divided into two symmetrical areas (area A and area B) containing the same number and same grades of AK lesions. The areas to be treated were localized between the eyebrows and the neck. Included AK lesions were located, counted, graded, and photographed.

For each patient, *n* lesions in area A were treated with one technique (N-PDT or C-PDT) and *n* lesions in area B were treated with the other technique (C-PDT or N-PDT) ($5 \leq n \leq 7$).

Figure 4. Schematic of the randomization process for area A and area B. C-PDT: Aktilite CL 128 device; N-PDT: Flexitheralight device.



Before applying MAL, the areas were prepared by removing the crusts with a small curette and gently scraping the surface of the lesions to roughen the surface.

Pain in the two treated areas was scored by the patient after treatment: first for the N-PDT area and then for the C-PDT area.

Patients complete a quality of life questionnaire (Dermatology Life Quality Index [DLQI]) and a satisfaction questionnaire at the end of the procedure.

The total duration of the treatment procedure (treatment of areas A and B) was approximately 3 hours and 20 minutes.

Area A: Classical Photodynamic Therapy

MAL was applied (approximately 1 mm thick) with a spatula on the selected lesions and over an area of 5 to 10 mm of normal skin surrounding the lesions. The treated area was covered with an occlusive (Tegaderm, 3M) and light-proof (aluminium foil) dressing for 3 hours. Afterward, the dressing was removed, the area was cleaned with a saline solution, and the skin was then immediately exposed to a continuous red light spectrum delivered by an Aktilite CL 128 device (Galderma Laboratories) (570 to 670 nm) for 10 minutes for a total light dose of 37 J/cm^2 (Figure 5).

Area B: New Photodynamic Therapy

MAL was applied as described for the area A treatment, and the area was covered with an occlusive and transparent dressing (Tegaderm, 3M) for 30 minutes whereas both a transparent occlusive dressing and a light-proof dressing (aluminium foil) was applied over the area randomized to receive C-PDT. Afterward, the dressing was retained, and irradiation was applied with the Flexitheralight device (635 nm) for 2 hours and 30 minutes. A total light dose of 37 J/cm^2 was administered (Figure 6). After the end of the illumination, area B was protected with aluminium foil.

Follow-Up and Retreatment Visits

Visit 2 occurred 7 days after treatment to evaluate the tolerability and adverse effects of the treatments. Patients completed the DLQI and satisfaction questionnaires. Photographs of the treated areas were captured under standardized conditions.

Visit 3 occurred 3 months after treatment. The investigator evaluated the response to treatment by comparing the lesions between the current visit and the first visit (by referring to paper tracings and photographs taken during the first visit). If some of the treated AK lesions remained, a new visit was scheduled within 3 weeks to treat the remaining lesions. The remaining lesions in each area were located, counted, and graded. Only the presence of lesions was considered and not any changes in their sizes. If a new lesion appeared, it was treated (by the same procedure), but it was not considered for the comparison of lesions between months 3 and 6. Photographs of the two treated areas were taken. Patients completed the DLQI and the satisfaction questionnaires, and all adverse events and concomitant medications were recorded. Patients for whom the AK lesions had completely disappeared were invited to participate in an assessment visit at month 6.

Visit 3bis was optional and scheduled only in cases where at least one AK lesion remained after the first treatment session and only if the investigator considered it necessary for the subject to be treated again with PDT. The same treatment was applied as in visit 1.

Visit 4 occurred 6 months after the initial treatment. The investigator evaluated the treatment response by comparing the lesions between the current visit and the first visit. Photographs of the two treated areas were taken. Patients completed the DLQI and the satisfaction questionnaires, and all adverse events and concomitant medications were recorded.

Variables and Data Collection

Collected data consisted of demographic data, medical history reviews, previous radiotherapy histories, history of surgery and treatment for AK, definition of AK lesions (localization, number, grade, and photographs), and assessments of the subjects' skin aspects.

For women of childbearing age, a urine pregnancy test was performed at screening or before the beginning of the treatment.

Several scales (pain, aesthetic aspect, and treatment tolerance) and questionnaires (DLQI and satisfaction) were used.

Figure 5. Illustration of the classical photodynamic therapy treatment procedure.

Figure 6. Illustration of the new photodynamic therapy treatment procedure.

Data Management

All medical observations were maintained in the patient's file; the data to be analyzed in the study were reported on an electronic case report form according to Good Clinical Practices and the sponsor's standard operating procedures. The data collection procedure was exhaustive and verified regularly by a clinical research associate according to the protocol. Any deviation from the protocol was noted, and the reason for the deviation was documented. Discrepancies in the data were brought to the attention of the clinical team and investigational site personnel in the form of a query. Resolutions to these issues are reflected in the database.

Statistical Methods

Continuous variables will be reported as means and standard deviations, and categorical variables will be reported as frequencies and percentages. The Shapiro-Wilk test will be used to assess the normality of the distribution. This normality will also be evaluated graphically.

Analysis of Primary Objective

In this study, each patient could have several lesions. We considered the "patient" effect. Indeed, a correlation could exist between the outcome measures in a single patient (cluster effect). The complete response rate of lesions will be analyzed according to the treatment groups (N-PDT or C-PDT) using the generalized linear mixed model to consider the cluster effect with an adjustment for the period (by the area). The 95% confidence interval of the absolute difference in response rates between the two groups will be calculated (D=N-PDT – C-PDT). We will conclude noninferiority if the lower limit of this 95% confidence interval is greater than 10%. If noninferiority is confirmed, a superiority test will be performed.

Analysis of Secondary Objectives

The percentage of patients in each group with a reduction in the lesion number greater than 75% will be calculated and compared using a generalized linear mixed model. The aforementioned method will be used for comparisons of the other qualitative variables between the two groups (N-PDT or C-PDT). For continuous variables, we will use the linear mixed model. The pain levels reported at the end of each treatment will be compared using a linear mixed model, with patients as the random effects (the significance level will be set to .05). All statistical analyses will be performed using SAS software version 9.4 (SAS Institute Inc).

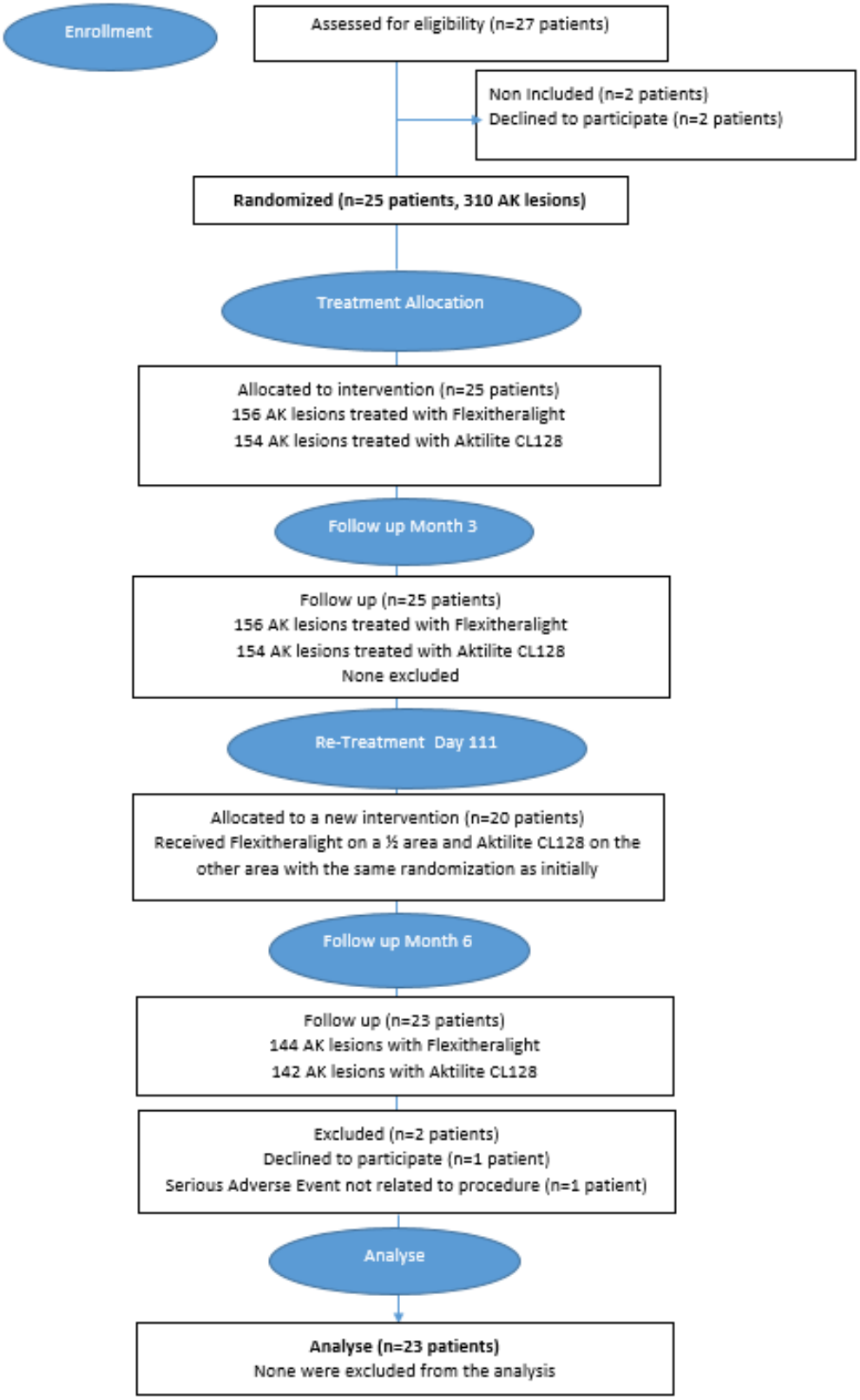
Ethical Approval

This study was performed in accordance with the ethical principles of the Declaration of Helsinki (2008) and the International Conference on Harmonisation–Good Clinical Practices and in compliance with Article L. 1121-4 of the French Public Health Code. The study design was reviewed and approved by the French National Agency for the Safety of Medicines and Health Products (authorization number 2013-A01096-39) and the French Ethics Committee (authorization number CPP-03/051/2013).

Results

Figure 7 shows the evolution of the number of subjects included, followed, and considered in the statistical analysis. Enrollment is closed. A total of 27 patients were recruited and followed instead of the planned 42 subjects due to the early termination of the Flexitheralight study, resulting from the launch of the competing Phos-Istos European study. Of the 27 patients, 23 completed all visits of the study.

Figure 7. Study flowchart. AK: actinic keratosis.



The clinical investigation was performed by July 2018. Data analysis was performed at the end of 2018, and results are expected to be published in early 2019.

Discussion

As part of the primary objective, we hope to demonstrate that N-PDT is not inferior to C-PDT in terms of the lesion response rate at month 3. As part of the secondary objectives, we seek to demonstrate that N-PDT is less painful and better tolerated than C-PDT as a treatment for AK.

The adverse effects associated with C-PDT are usually a local reaction at the treatment site that is attributable to the toxic effects of PDT (phototoxicity) or to the preparation of the lesion. The most common symptoms are pain and discomfort, which are described as burning and stinging sensations, erythema, and encrusting sensations of skin pain. Usually, the symptoms begin with or immediately after illumination, last for a few hours, and disappear on the day of treatment.

The possible risks related to N-PDT have been analyzed. Based on the results from this analysis, the Flexitheralight device has been classified as an exempt risk group, according to International Electrotechnical Commission 60601-2-57/2012.

Regarding the irradiance, the objective was to deliver 12.3 mW/cm^2, lower than the 75 mW/cm^2 irradiance delivered by the Aktilite CL 128 device or the 22 mW/cm^2 delivered by sunlight at midday in the summer in Munich. The expected benefit for patients included in the study is a reduction of pain experienced during treatment, increasing comfort. Indeed, illumination during C-PDT is intensively administered for a short period of time, which is known to increase pain [26].

In addition to the impact on pain, the flexibility of the Flexitheralight device enables a homogeneous illumination, which should yield better efficiency. Moreover, N-PDT could be performed in all weather conditions, in any geographic location, year round, and could therefore become the treatment of choice for AK.

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Authors' Contributions

LM, the principal investigator, designed the study and critically reviewed and approved the protocol. CV drafted the manuscript and selected and followed patients. ASV-D, ET, and PD helped by revising the protocol, participating in the conception of the study, and performing technical maintenance of the device. SM critically reviewed and approved the final manuscript for publication. AD wrote the statistical analysis plan, and his unit will analyze the results of the study.

Conflicts of Interest

CV received travel grants and accommodation expenses from Galderma International to attend the 16th Annual Congress of the European Society for Photodynamic Therapy in Munich, Germany, February 10-11, 2017. All other authors have no conflicts of interest to declare.

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Abbreviations

AK: actinic keratosis
ALA: aminolevulinic acid
C-PDT: classical photodynamic therapy
DLQI: Dermatology Life Quality Index

LEF: light-emitting fabric
MAL: ester methyl aminolevulinate
N-PDT: new photodynamic therapy
PDT: photodynamic therapy
PpIX: protoporphyrin IX
SCC: squamous cell carcinoma

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Protocol

A New Light-Emitting, Fabric-Based Device for Photodynamic Therapy of Actinic Keratosis: Protocol for a Randomized, Controlled, Multicenter, Intra-Individual, Phase II Noninferiority Study (the Phosistos Study)

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Abstract

Background: Actinic keratosis (AK) is a common early in situ skin carcinoma caused by long-term sun exposure and usually develops on sun-exposed skin areas. Left untreated, AK may progress to squamous cell carcinoma. To prevent such risk, most clinicians routinely treat AK. Therapy options for AK include cryotherapy, topical treatments, curettage, excision surgery, and photodynamic therapy (PDT).

Objective: The aim of this study is to assess the noninferiority, in terms of efficacy at 3 months, of a PDT protocol involving a new light-emitting device (PDT using the Phosistos protocol [P-PDT]) compared with the conventional protocol (PDT using the conventional protocol [C-PDT]) in the treatment of AK.

Methods: In this randomized, controlled, multicenter, intra-individual, phase II noninferiority clinical study, subjects with AK of the forehead and scalp are treated with P-PDT on one area and with C-PDT on the contralateral area. In both areas, lesions are prepared and methyl aminolevulinate (MAL) is applied. Thirty minutes after MAL application, the P-PDT area is exposed to red light at low irradiance (1.3 mW/cm^2) for 2.5 hours so that a light dose of 12 J/cm^2 is achieved. In the control area (C-PDT area), a 37 J/cm^2 red light irradiation is performed 3 hours after MAL application. Recurrent AK at 3 months is retreated. The primary end point is the lesion complete response rate at 3 months. Secondary end points include pain scores at 1 day, local tolerance at 7 days, lesion complete response rate at 6 months, cosmetic outcome at 3 and 6 months, and patient-reported quality of life and satisfaction throughout the study. A total of 45 patients needs to be recruited.

Results: Clinical investigations are complete: 46 patients were treated with P-PDT on one area (n=285 AK) and with C-PDT on the contralateral area (n=285 AK). Data analysis is ongoing, and statistical results will be available in the first half of 2019.

Conclusions: In case of noninferiority in efficacy and superiority in tolerability of P-PDT compared with C-PDT, P-PDT could become the treatment of choice for AK.

Trial Registration: ClinicalTrials.gov NCT03076892; https://clinicaltrials.gov/ct2/show/NCT03076892 (Archived by WebCite at http://www.webcitation.org/779qqVKek)

International Registered Report Identifier (IRRID): DERR1-10.2196/12990

(JMIR Res Protoc 2019;8(4):e12990) doi:10.2196/12990

KEYWORDS

photodynamic therapy; actinic keratosis; Aktilite CL 128 lamp; light-emitting fabric

Introduction

Background

Actinic keratosis (AK) is a common early in situ skin carcinoma caused by long-term sun exposure and usually develops on sun-exposed skin areas such as the face, ears, scalp, neck, forearms, and back of the hands. Left untreated, AK will progress to invasive squamous cell carcinoma (SCC) in approximately 10% of patients [1]. To reduce the risk of developing SCC, consensus guidelines recommend that clinicians routinely treat AK [2]. Treatment options include cryotherapy, topical treatments, curettage, surgical excision, and photodynamic therapy (PDT).

PDT is a cancer treatment modality combining light of appropriate wavelengths, a nontoxic photosensitizer, and sufficient molecular oxygen to generate reactive oxygen species and destroy target cells [3]. Over the last 15 years, PDT using 5-aminolevulinic acid (ALA) and PDT using methyl aminolevulinate (MAL) have been extensively investigated for the treatment of AK [4-8]. Topical application and incubation of ALA or MAL lead to selective accumulation of the endogenous photosensitizer protoporphyrin IX (PpIX) in the AK cells, and subsequent activation of PpIX by light of appropriate wavelengths induces, in the presence of oxygen, photochemical reactions leading to cell death [3].

Activation by red light using a total light dose of 37 J/cm^2 after 3 hours of incubation with MAL is a conventional protocol, usually referred to as PDT using the conventional protocol (C-PDT), that is approved and likely the most widely used in Europe for PDT of AK [9-11]. This protocol has been reported to be an effective PDT treatment option for AK and to result in similar response rates and improved cosmetic outcomes compared with standard therapies [9]. However, high pain scores have been demonstrated with this protocol, and concurrent use of cold air analgesia may be required to prevent discomfort [12,13].

Objectives

Recently, several protocols involving an incubation with MAL for a maximum of 30 min followed by an activation by daylight for between 1 hour 30 min and 2 hours 30 min have been investigated [14-17]. From a European consensus [18], using a 2-hour daylight activation within 30 min after MAL application leads to a protocol (photodynamic therapy using the daylight European consensus protocol [D-PDT]) as effective as and better tolerated by patients than C-PDT. This better tolerability results from the maximum of 30 min for MAL incubation and the subsequent continuous activation of small amounts of PpIX. Nonetheless, using daylight as the irradiation source is not realistic for all weather conditions [19].

New protocols designed to be as effective as C-PDT, as nearly painless as D-PDT, and usable all year round are therefore emerging. Among these alternative protocols are the Flexitheralight protocol that we have recently published [20,21] and the Phosistos protocol (PDT using the Phosistos protocol [P-PDT]) that is discussed in this study. Developed within the Phosistos project supported by the European Commission under the Competitiveness and Innovation Framework Programme (Project identifier: CIP-ICT-PSP-2013-7-621103), P-PDT uses a 30-min MAL incubation followed by 2 hours and 30 min of irradiation with a light-emitting, fabric-based device. Due to the short incubation time, P-PDT should be as nearly painless as D-PDT. Furthermore, from a recent study that discusses potential PDT overtreatment when using some protocols including C-PDT [22], P-PDT with a total light dose almost 3 times lower than that of C-PDT could prove noninferior in efficacy. Moreover, the high flexibility of the light-emitting, fabric-based device ensures an optimal irradiation of the treatment area, which is not the case with the rigid flat light sources used in C-PDT.

The aim of this randomized, controlled, multicenter, intra-individual, noninferiority study is to assess the efficacy and tolerability of P-PDT compared with those of C-PDT in treating patients with AK of the forehead and scalp.

Methods

Study Design

This study is a randomized, controlled, multicenter, intra-individual, noninferiority study comparing P-PDT versus C-PDT in the treatment of AK of the forehead and scalp. The study was conducted at 2 investigational sites: the department of dermatology at the Lille University Hospital in France and the Klinikum Vest in Germany.

Study Status

Recruitment is closed and data collection is completed. Data analysis is ongoing and is expected to be completed in the first half of 2019.

Ethical Approval

This study was performed in accordance with the ethical principles of the Declaration of Helsinki (2008) and the International Conference on Harmonization Good Clinical Practice guidelines. The study design was reviewed and approved by the French National Agency for the Safety of Medicines and Health Products (Agence Nationale de Sécurité

du Médicament et des Produits de Santé; authorization number: 2016-A00010-51), the French Ethics Committee (Comités de Protection des Personnes, CPP; authorization number: CPP 03/008/2016), the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte; authorization number: 2015_79 1.1), and the ethics committee of the University of Münster (Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität; approval number: 2016-513-f-M).

Study Population

Patients were recruited from the patient population of the investigational sites.

The inclusion and exclusion criteria for patients to be included and excluded in the study are provided in Textboxes 1 and 2, respectively.

Textbox 1. Inclusion criteria for patients.

Patients were eligible to be included in the study if they met all of the following criteria:

- They had a clinical diagnosis through visual inspection and palpation of 10 to 14 previously untreated, nonpigmented, nonhyperkeratotic, grade I or II (according to the classification of Olsen et al [23]) actinic keratosis (AK) on the forehead and scalp (in case of more than 14 AK, only 14 AK were considered).
- These AK had to be distributed in 2 noncoalescing areas with a similar number and grade of AK according to the following conditions:
  - a minimum distance of 2 mm between 2 AK in the same area
  - a minimum distance of 10 mm between 2 AK, each in a different area
- Other AK treatment options were considered as unacceptable or medically less appropriate
- They did not have any AK treatment in the previous 30 days
- They are older than 18 years and affiliated to a social security system

Textbox 2. Exclusion criteria for patients.

Patients were not eligible for inclusion in the study if they fulfilled 1 or more of the following criteria:

- They had a clinical diagnosis of porphyria
- They were immunosuppressed
- They used topical corticosteroids on the forehead or scalp in the previous 2 weeks
- They received local treatment (including cryotherapy; curettage and electrocoagulation; topical treatments with imiquimod, 5-fluorouracil, diclofenac, or ingenol mebutate; or photodynamic therapy) on the face or scalp in the previous 30 days
- They used topical retinoids, alpha-hydroxy acids, systemic retinoids, chemotherapy, or immunotherapy in the previous 30 days
- They had pigmented actinic keratosis
- They had known allergy to methyl aminolevulinate (MAL) or to any other ingredient of the MAL cream, peanut, or soya
- They participated within the last 30 days in other clinical studies
- They were pregnant
- They had any condition with a risk of poor protocol compliance
- They currently received regular ultraviolet radiation therapy
- They were protected by a legal regime, in emergency situations, or kept in detention

Figure 1. The light-emitting, fabric-based device involved in photodynamic therapy using the phosistos protocol: 635-nm red light is emitted at 1.3 mW/cm^2 by a fiber optic–based fabric that lines the inside of a cap.

All patients received oral and written information before signing informed consent forms and subsequently entering the study.

The Phosistos Protocol (Photodynamic Therapy Using the Phosistos Protocol [P-PDT])

P-PDT includes application of MAL cream under transparent occlusive dressing immediately followed by the installation on the patient's head and turn-on of a light-emitting, fabric-based device for 3 hours. This device consists of a power control unit delivering 635-nm red light to a fiber optic–based fabric lining the inside of a cap (Texinov, Saint-Didier-de-la-Tour, France; Figure 1). The device, classified as exempt risk group according to IEC (International Electrotechnical Commission) 60601-2-57/2012, is configured to automatically start a 1.3mW/cm^2 irradiation 30 min after it is turned on (resulting in an incubation time of 30 min) and to stop 2 hours and 30 min later (resulting in a light dose of 12 J/cm^2).

Study Objectives/Outcomes

The primary objective of the study is to assess the noninferiority, in terms of efficacy at 3 months, of P-PDT compared with C-PDT. Outcome for the primary objective is the lesion complete response rate at 3 months.

The secondary objectives are as follows:

- To evaluate the treatment tolerance including pain at the end of treatment and adverse effects at 7 days
- To evaluate the complete response rate at 6 months
- To evaluate the cosmetic results at 3 and 6 months
- To estimate the number of patients with AK reduction higher than 75% at 3 and 6 months
- To evaluate the patient's quality of life and satisfaction throughout the study.

The corresponding outcomes are as follows:

- The pain score reported by the patient using a visual analog scale ranging from 0 (no pain) to 10 (worst pain) at the end of treatment
- The adverse effects/reactions including erythema, skin exfoliation, skin burning sensation, and skin edema reported by the patient at 7 days
- The complete response rate at 6 months
- The skin appearance (3 stands for excellent, 2 for good, 1 for fair, and 0 for poor) at 1 day, 3 months, and 6 months: the cosmetic outcome at 3 months (at 6 months) is defined as the change in skin appearance between 1 day and 3 months (6 months) and has the following possible values: –3, –2, –1, 0, 1, 2, 3
- The Dermatology Life Quality Index (DLQI) and the standard satisfaction questionnaire both completed by the patient throughout the study.

The lesion complete response ("complete response" and "incomplete response") and the skin appearance were clinically assessed by the investigators.

Study Schema

The study flowchart is shown in Table 1. After screening, patients entering the study had to come to the investigational site for 1 treatment visit (V1) and 3 evaluation visits (V2, V3, and V4). In case of recurrent AK at the 3-month evaluation visit (V3), patients had a second treatment visit within the 3 following weeks (V3bis).

Table 1. Study flowchart.

Time point	From day 30 to day 1	Day 1	Day 7±1 day	Months 3±7 days	Day 111±7 days	Months 6±7 days
Visit denomination	Screening	V1	V2	V3	V3bis in case of recurrent AK[a]	V4
Visit type	Screening	Treatment	Evaluation	Evaluation	Treatment	Evaluation
Informed consent	✓[b]	__[c]	—	—	—	—
Medical history	✓	—	—	—	—	—
Check of inclusion and exclusion criteria	✓	—	—	—	—	—
Documentation of AK including location, number, and grade	—	✓	—	✓	✓	✓
Photo-documentation of AK	—	✓	✓	✓	✓	✓
Separation of AK in 2 areas	—	✓	—	—	—	—
Randomization	—	✓	—	—	—	—
Pain score during treatment	—	✓	—	—	✓	—
Adverse effects/reactions	—	—	✓	—	—	—
Skin appearance/cosmetic outcome	—	—	—	✓	—	✓
Completion of the Dermatology Life Quality Index	—	✓	✓	✓	✓	✓
Completion of the satisfaction questionnaire	—	✓	✓	✓	✓	✓
Documentation of adverse events and serious adverse events	—	✓	—	✓	✓	✓
Pregnancy test	✓	✓	✓	✓	✓	✓

[a]AK: actinic keratosis.

[b]Indicates during which visits the actions reported in the first column were performed.

[c]Indicates that the corresponding action was not performed at the considered visit.

On the day of treatment (V1), 10 to 14 AK were located, graded, photographed, and divided into 2 areas (area A and area B) similar to each other in terms of number and grade of AK. The location of each AK was marked on plastic sheets. Randomization was then performed by opening the next envelope in sequence. This envelope specified the protocol that each area had to receive: either P-PDT for area A and C-PDT for area B or C-PDT for area A and P-PDT for area B. In both cases, P-PDT (30-min MAL incubation followed by 2.5 hours of irradiation) was performed first, so that the 3-hour MAL incubation required for C-PDT was achieved after P-PDT was completed.

Both the areas were prepared by removing crusts, gently scraping the lesion surface, and applying MAL cream (Metvixia, Galderma, France) under a transparent occlusive dressing (Tegaderm, 3M, London Ontario, Canada) to the AK and surrounding normal skin (5-10 mm margin). An aluminum foil was placed over the transparent occlusive dressing, which covered the area randomized to receive C-PDT. The device involved in P-PDT was immediately set up and turned on. After 3 hours, P-PDT was completed as described in the Phosistos Protocol section. The device involved in P-PDT was removed, and the MAL cream was washed off with saline solution. The patient rated his pain on a pain scale. The area that just received P-PDT was then protected with aluminum foil, whereas an Aktilite CL128 lamp (Galderma SA, Lausanne, Switzerland) was placed 5 to 8 cm away from the other area and programmed to deliver 37 J/cm^2 in 7 to 10 min. At the end of C-PDT, the corresponding pain level was rated by the patient, who also completed the DLQI and the satisfaction questionnaire.

A total of 7 days after the treatment day (V2), patients were invited to report adverse effects/reactions and to complete the DLQI and the satisfaction questionnaire.

The treatment response was assessed 3 months after the treatment (V3) by the investigators by comparison with the

photographs at the treatment day (V1). An investigator's assessment of the skin appearance followed by the determination of the resulting cosmetic outcome was also performed. The DLQI and the satisfaction questionnaire were completed by patients. In case of recurrent AK, these latter were counted, graded, and photographed, and a second treatment visit, identical to the above-described first treatment (V1), was scheduled within 3 weeks after V3 (V3bis).

The last follow-up visit (V4) was performed 6 months after V1. During this visit, the treatment response and the cosmetic outcome were investigator-assessed by comparison with the photographs and the skin appearance at V1, respectively. The patients were asked to complete the DLQI and the satisfaction questionnaire.

Note that any AK appearing between V1 and V4 was not included in the assessment of the study outcomes.

Randomization

Patients were randomly allocated to 1 of the 2 treatment options (either P-PDT for area A and C-PDT for area B or C-PDT for area A and P-PDT for area B) in a 1:1 ratio. The randomization sequence with stratification by treatment center in blocks of 4 was generated by an independent statistician using the PROC PLAN procedure of SAS (SAS Institute Inc, Cary, North Carolina, USA) and transferred to a sequence of sealed, opaque, and consecutively numbered envelopes. When a patient entered the study, randomization was performed by opening the next envelope in sequence.

The study is unblinded; both investigators and patients are aware of the treatment allocation.

Statistical Methodology

Study Hypothesis

The study primary hypothesis is the noninferiority of P-PDT compared with C-PDT in terms of the lesion complete response rate at 3 months.

Sample Size Determination

The study was designed to have a statistical power of 80% with a 1-sided alpha level of .05 to demonstrate noninferiority in terms of lesion complete response rate at 3 months of P-PDT compared with C-PDT. Assuming a lesion complete response rate at 3 months of 75% in both areas, a correlation between lesions within the same patient, a correlation between lesions within the same area, an absolute noninferiority margin of –10%, a mean lesion number per patient per area of 6, and a possible sample loss of 10%, 270 lesions per area (ie, 45 patients) are required.

Statistical Analysis of the Primary Outcome

Continuous variables will be expressed as mean and SD, and categorical variables will be expressed as frequency and percentage. The normality of distribution will be assessed graphically and using the Shapiro-Wilk test.

The lesion complete response rate at 3 months will be analyzed according to the protocol using the generalized linear mixed model to take into account the patient cluster effect (a correlation between the complete responses of lesions within a same patient may exist), with adjustment on the area period (all lesions within a same area will receive the same protocol). The 1-sided 95% CI of the absolute difference in lesion complete response rate at 3 months between the 2 protocols will be calculated (D=P-PDT−C-PDT). In case of a lower limit of the 1-sided 95% CI higher than –10%, P-PDT will be declared noninferior to C-PDT and a 2-sided superiority test will be performed at an alpha level of 5%.

All statistical analyses will be performed using SAS software version 9.4 (SAS Institute Inc, Cary, North Carolina, USA).

Statistical Analysis of the Secondary Outcomes

The lesion complete response rate at 6 months will be processed using the same statistical analysis as the lesion complete response rate at 3 months (previous paragraph). The differences in pain scores at the end of treatment between P-PDT and C-PDT will be assessed using a linear mixed model, with patients as random effects (the significance level will be set at a 2-sided alpha level of 5%). The cosmetic outcomes at 3 and 6 months and the DLQI scores throughout the study will be compared between C-PDT and P-PDT using the Wilcoxon signed-rank test.

Data Management

All patient data were collected using an electronic case report form according to Good Clinical Practice and Standard Operating Procedures. Data collection was regularly monitored by a clinical research associate. Any deviation from the protocol was noted and the reason for the deviation documented. Any data inconsistency was brought to the attention of the clinical team and investigational site personnel (if required, data queries were sent). Resolutions to these data inconsistencies were reflected in the database.

Results

Population Study

The recruitment is closed and the clinical investigations are complete (Figure 2). Of the 47 recruited patients, 1 withdrew consent and did not receive any treatment protocol. A total of 46 patients were, therefore, treated with P-PDT on 1 area (for a total of 285 AK) and with C-PDT on the contralateral area (for a total of 285 AK). All these patients were evaluated at 3 months. Due to recurrent AK, 19 patients were required to undergo a second treatment visit. One of these patients dropped out because of fear of pain as intense as that experienced with C-PDT during the first treatment visit. As a result, 18 patients were retreated and 45 patients completed the study at 6 months.

All treated patients were men, and their mean age was 72.2 years. A total of 63% (29/46) of these patients had a Fitzpatrick skin type of II (Table 2). Whatever the protocol, approximately 45% of the AK were grade I and 55% were grade II (Table 3).

Figure 2. Study flow diagram. V1: first treatment visit; V2: first evaluation visit; V3: second treatment visit; V3bis in case of recurrent actinic keratosis: second treatment visit; V4: third treatment visit.

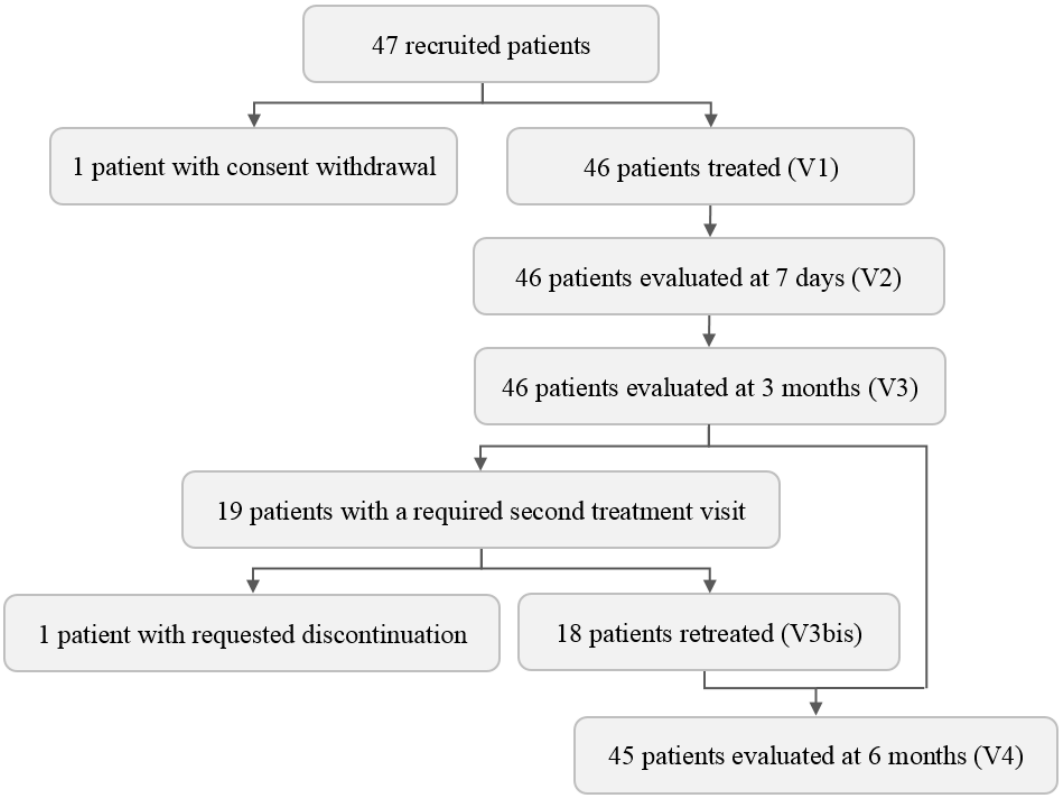

Table 2. Demographics and clinical characteristics of the 46 treated patients.

Patients characteristics	Values
Age (years), mean (SD)	72.2 (9.1)
Sex, n (%)	
Male	46 (100)
Female	0 (0)
Fitzpatrick skin phototype, n (%)	
I	8 (17)
II	29 (63)
III	8 (17)
IV	1 (2)

Table 3. Lesions characteristics according to the protocol applied.

Lesions characteristics	Photodynamic therapy using the conventional protocol (N=285 AK[a]), n (%)	Photodynamic therapy using the Phosistos protocol (N=285 AK), n (%)
Grade of lesions		
Grade I	130 (45.6)	128 (44.9)
Grade II	155 (54.4)	157 (55.1)

[a]AK: actinic keratosis.

Data Analysis

Data analysis is ongoing, and statistical results are expected to be available in the first half of 2019.

Discussion

C-PDT that has been proven to be effective in many studies [9-11] is likely the most widely used approved protocol in Europe for PDT of AK. The major adverse effect of C-PDT is

pain during treatment, which has been described as a burning and stinging sensation localized to the treatment area [24-26].

Several studies have recently shown that the Europe-approved D-PDT is as effective as C-PDT but better tolerated and nearly painless [18,27]. This painless characteristic comes from the short MAL incubation, which results in a continuous activation of small amounts of PpIX. Unfortunately, PDT using daylight activation depends on weather conditions [19] and cannot be performed in rainy, windy, or cold conditions unless a greenhouse is used [28]. Moreover, because of the varying intensity of daylight depending on the weather conditions and the locations, it is impossible to control the light dose.

New PDT protocols including the Flexitheralight protocol [20,21] have been designed to be as effective as C-PDT, as nearly painless as D-PDT, usable all year round, and associated with a known light dose. Consisting of a 30-min incubation with MAL followed by 2.5 hours of activation with a quite cumbersome, light-emitting, fabric-based device, which delivers 37 J/cm^2 at an irradiance of 12.3 mW/cm^2, the Flexitheralight protocol has been shown to be noninferior to C-PDT while being nearly pain-free [21]. We have revised downward the irradiation parameters of the Flexitheralight protocol: the new version of the Flexitheralight protocol, referred to as P-PDT, involves an irradiance of 1.3 mW/cm^2 and a light dose of 12 J/cm^2. The choice of such a light dose was based on a study that demonstrated the ability of 2 light sources with light doses lower than 15 J/cm^2 to completely photobleach PpIX [28]. Regarding the irradiance, the value of 1.3 mW/cm^2 was selected based on the study by Ibbotson and Ferguson, which reported effective PDT treatment when using a 7 mW/cm^2 red light source [29]. These choices are in line with studies reporting similar efficacy for different irradiances [30] and light doses [22]. With these new irradiation parameters, the light-emitting, fabric-based device has been significantly modified to be more user friendly in terms of dimensions and ergonomics.

This study aims to assess the noninferiority in efficacy at 3 months (primary objective) and superiority in tolerability (secondary objective) of P-PDT compared with C-PDT in the treatment of AK of the forehead and scalp.

Data collection is completed, and data analysis is ongoing. The results are expected in the first half of 2019. In case of a positive assessment, P-PDT could be preferred to the conventionally used C-PDT. Moreover, as P-PDT can be performed in all weather conditions, in any geographic location, and year-round, it could also be preferred to D-PDT. Hence, P-PDT could become the treatment of choice for AK. Furthermore, an ambulatory version of P-PDT could be further investigated.

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Authors' Contributions

The manuscript was written by ASVD. The study protocol was created by SM. SM, ET, FL, ASVD, and PD contributed to the design of the study and to the development of the device. HB and AD were responsible for statistical advice and planning. HAR, TH, RMS, and LM contributed to the clinical aspects of the study. SM, ET, and FL critically reviewed the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

SM, ASVD, HAR, ET, FL, CV, PD, HB, DK, TH, and AD declare that they have no competing interest. RMS is the vice president of EURO-PDT. He has been a member of advisory boards for Almirall, Biofrontera, Galderma, ISDIN, LEO Pharma, photonamic, and Pierre-Fabre and has received speakers' honoraria from the aforementioned companies. LM has been a member of advisory boards for BMS, Roche, GSK, Novartis, LEO Pharma, and MSD. He has received travel grants for attending congresses from BMS, Roche, GSK, Novartis, and LEO Pharma. He has been the principal investigator of clinical trials performed for BMS, Roche, GSK, Novartis, LEO Pharma, and MSD.

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Abbreviations

AK: actinic keratosis
ALA: 5-aminolevulinic acid
C-PDT: photodynamic therapy using the conventional protocol
CPP: Comités de Protection des Personnes (the French Ethics Committee)
D-PDT: photodynamic therapy using the daylight European consensus protocol
MAL: methyl aminolevulinate
PDT: photodynamic therapy
P-PDT: photodynamic therapy using the Phosistos protocol
PpIX: protoporphyrin IX
SCC: squamous cell carcinoma

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Protocol

Process Evaluation of a Medical Student–Delivered Smoking Prevention Program for Secondary Schools: Protocol for the Education Against Tobacco Cluster Randomized Trial

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Abstract

Background: Most smokers start smoking during their early adolescence under the impression that smoking entails positive attributes. Given the addictive nature of cigarettes, however, many of them might end up as long-term smokers and suffering from tobacco-related diseases. To prevent tobacco use among adolescents, the large international medical students' network Education Against Tobacco (EAT) educates more than 40,000 secondary school students per year in the classroom setting, using evidence-based self-developed apps and strategies.

Objective: This study aimed to evaluate the long-term effectiveness of the school-based EAT intervention in reducing smoking prevalence among seventh-grade students in Germany. Additionally, we aimed to improve the intervention by drawing conclusions from our process evaluation.

Methods: We conduct a cluster-randomized controlled trial with measurements at baseline and 9, 16, and 24 months postintervention via paper-and-pencil questionnaires administered by teachers. The study groups consist of randomized schools receiving the 2016 EAT curriculum and control schools with comparable baseline data (no intervention). The primary outcome is the difference of change in smoking prevalence between the intervention and control groups at the 24-month follow-up. Secondary outcomes are between-group differences of changes in smoking-related attitudes and the number of new smokers, quitters, and never-smokers.

Results: A total of 11,268 students of both sexes, with an average age of 12.32 years, in seventh grade of 144 secondary schools in Germany were included at baseline. The prevalence of cigarette smoking in our sample was 2.6%. The process evaluation surveys were filled out by 324 medical student volunteers, 63 medical student supervisors, 4896 students, and 141 teachers.

Conclusions: The EAT cluster randomized trial is the largest school-based tobacco-prevention study in Germany conducted to date. Its results will provide important insights with regards to the effectiveness of medical student–delivered smoking prevention programs at school.

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KEYWORDS

schools; tobacco prevention; smoking prevention; medical students; medical school

Introduction

Background

Most smokers start smoking during their early adolescence with the idea that smoking entails positive attributes; at this age, the health risks of smoking such as those related to vascular disease, lung cancer, and chronic pulmonary disease are too far in the future for them to fathom. Given the addictive nature of cigarettes, however, many smokers might end up as long-term smokers and suffering from severe and potentially deadly tobacco-related diseases [1].

Despite the fact that effectiveness of inpatient smoking cessation was demonstrated in major trials [2] and that these measures were implemented in the guidelines of almost all medical specialties [3], research has shown that physicians in Germany lack both motivation (eg, role incongruence as a major barrier [4,5]) and education to deliver such measures [4-7], especially before the onset of chronic disease [5]. The issue of undertreatment of tobacco use by physicians is known on a global scale [8,9]. It is estimated that global tobacco-attributable mortality will double from 5 million (2010) to 10 million per year in a few decades [1].

Education Against Tobacco (EAT) is a multinational network of medical students that aims to provide science-based tobacco prevention to a large number of adolescents and to thereby sensitize prospective physicians toward the importance of inpatient smoking cessation [10-12]. The network currently involves about 80 medical schools in 12 countries, with 3500 medical students educating more than 40,000 secondary school students in the classroom setting per year using and optimizing self-developed apps and strategies (Multimedia Appendix 1) [13-15]. The two free science-based quit apps of EAT ("Smokerface" and "Smokerstop") were downloaded more than 400,000 times and translated in the most spoken languages worldwide (Multimedia Appendix 1) [14,15].

The 2018 KiGGS report by the German Robert Koch Institute revealed that 9.3% of German boys and 8.9% of German girls aged 14-17 years smoke cigarettes at least once a week [16]. In spite of the decline in adolescent smoking over the last two decades, prevalence in Germany is among the highest in Europe, and strong socioeconomic differences in smoking habits exist [17-19].

Current Knowledge on School-Based Tobacco Prevention

Most school-based smoking prevention–related curricula are ineffective, and the evaluation of new curricula is warranted [20]. A recently published evaluation of a short student and student-parent smoking prevention program in Germany did not show significant effectiveness among seventh-grade students (7.6% and 7% prevalence in intervention groups, respectively, vs 10.1% in the control group) at the 24-month follow-up. However, this might have been due to a very low sample size: Only 47 schools were randomized because of an underestimated intracluster correlation coefficient [21,22]. The largest

tobacco-prevention program for secondary schools in Germany—the smoke-free class competition—has demonstrated limited effectiveness in making students quit and increasing knowledge among students and was not able to prevent smoking onset [23-25].

Physician-based programs relying on fear-inducing statements show no overall long-term effectiveness in reducing the prevalence of smoking [26-29]. Limited new evidence suggest that asking questions about health consequences rather than making statements might be more effective to at least motivate current smokers to quit [30].

A physician-based multimodal program in Berlin, where students attended a 2-h interactive presentation of smoking-related health consequences, evaluated in a quasi-experimental study suggested significant short-term effects of preventing smoking onset, which might be a promising alternative to the traditional fear approaches of physician-based programs [31]. Outside of schools, a systematic review on inpatient physician-based smoking prevention and cessation for adolescents revealed that behavioral interventions show overall effectiveness in primary care [32].

Previous Research on Education Against Tobacco

The effectiveness of an earlier version of the EAT curriculum on reducing smoking prevalence among adolescents has only been investigated with a quasi-experimental design (n=1474) with potential sources of bias [10,11]. However, the study showed a significant association of the intervention with lower smoking prevalence among secondary school students in Germany at 6 months of follow-up by motivating them to quit. After this first evaluation, the curriculum was optimized for students with a lower educational level by using cognitive interviewing, as the intervention was found to be less effective in this subgroup. The curriculum received more age-appropriate content, was optimized to be more interactive and gain framed [33], and was equipped with app-based strategies [10,14].

Education Against Tobacco Apps: “Smokerstop” and “Smokerface”

Photoaging desktop programs in which an image is altered to predict future appearance were effective in motivating girls aged 14-18 years to quit smoking and increased the quit rate in young adults aged 18-30 years of both genders by 21% [34,35]. We took advantage of the broad availability of smartphones and adolescents' interest in appearance to create a free 3D-photoaging smartphone app “Smokerface” [15], which animates the users’ selfies and reacts to touch (Multimedia Appendix 2). It is downloaded 200 times per day, and the current version of the app has a rating of 4.2/5 in the Google Play Store (Google LLC, Mountain View, CA) and 4.5/5 in the Apple AppStore (Apple Inc, Cupertino, CA).

Our second free quit app is called “Smokerstop” and was developed based on theory [36] and evidence [37] from conventional smoking-cessation programs. The underlying concept is the PRIME Theory, which has been described in great detail elsewhere [38,39]. Our app takes into account recent research on adequate coping strategies for craving [40,41]. About 1000 smokers per day use this app to support their quit attempt, and it has an average rating of 4.5/5 in the AppStore and Play Store. Smokerface motivates people to remain smoke free or to make a quit attempt and is likely to help with continuous abstinence [14]; in contrast, Smokerstop supports quitters who are already prepared to set a quit date. Both apps are a part of our school-based intervention.

We designed this randomized trial to answer the following questions:

- Does medical student–delivered prevention by EAT show effectiveness in reducing smoking prevalence in secondary schools?
- Which subgroups (ie, gender, education level, and cultural background) benefit most from this intervention?
- Is this low-cost campaign effective in convincing students to use the apps?
- Which students are more likely to use an app revealing the photoaging effects of smoking?

Methods

Ethics Approval

The study protocol was approved by the ethics committee of the University of Giessen and the ministries of cultural affairs of the five participating federal states. Written informed consent was obtained by the responsible teachers from both the participants themselves and their parents. All participant information will be stored in locked file cabinets in areas with limited access. Participants’ personal information will not be released outside of the study without written permission of the participants. Study results will be disseminated at national and international conferences, in peer-reviewed journals, on our websites, and throughout the multinational EAT network.

Trial Design

A randomized controlled multicentered trial with two parallel groups is underway (ClinicalTrials.gov: NCT02697409). A total of 13 German EAT groups are participating, each functioning as a study center. The primary outcome is the between-group difference in smoking prevalence from baseline to follow-up. Randomization was externally and centrally performed via a computer on a school level with a 1:1 allocation.

A total of 144 secondary schools in five federal states of Germany participated in the baseline survey in the first half of the school year (September 2016 to April 2017, depending on the federal state) prior to randomization. The randomization of schools based on the baseline data was performed from November 2016 through May 2017 by the Coordination Center for Clinical Studies Marburg (KKS Marburg) as a blocked randomization combined with stratified randomization by study center and smoking prevalence, in order to ensure a balance of participant characteristics in each group. Immediately after randomization, schools were informed of their group allocation (intervention or control) and appointments were made for the implementation of the EAT curriculum in the intervention group. To assess the quality of the intervention, we implemented a process evaluation including four points of view: medical student volunteers and training supervisors after training via the EAT curriculum as well as teachers and students within 24

hours postintervention. The first follow-up survey was conducted 9 months after the intervention. The second follow-up was conducted at 16 months (April 2018 to February 2019), and the third follow-up will be conducted at 2 years (December 2018 to October 2019). In order to assure comparability between the two groups, we calculated the average number of days between randomization and intervention in each study center for the intervention group and added these numbers to the randomization date of the schools in the control group when assessing the dates for the follow-up surveys.

Intervention

Before the Visit

We sent letters to teachers to prepare them for our visit. Parents received letters to motivate them to quit smoking via the Smokerface App and to attempt to quit with the Smokerstop App [42] in case they are smokers themselves while informing them on how to best ensure that their children do not take up the behavior, summing up recent pertinent scientific publications in layman's terms [43-46]. The students were advised to prepare for our intervention by downloading the Smokerface App on their smartphone [14]. The medical student volunteers were trained in the 2016 EAT curriculum by experienced supervisors in all cases and by long-term group leaders of the EAT network of medical students, via a standardized preparation curriculum.

In Schools

In the first part of the intervention, lasting for about 45 minutes, all participating classes of Grade 7 will gather in a large room under the supervision of at least two medical students. For the first 30 minutes, students will be interactively involved in a PowerPoint (Microsoft Corp, Redmond, WA) presentation that discusses how smoking affects the performance of German soccer players, addiction, costs, relaxation/happiness, and strategies of the tobacco industry and are interviewed about how they would advertise cigarettes to the rest of their grade. In the last 15 minutes, our photoaging app is implemented into the school setting via a self-developed strategy called "mirroring": The students' altered 3D self-portraits on mobile phones or tablets are "mirrored" via a projector in front of their whole grade [14]. In a recently published pilot study, we were able to demonstrate that this type of implementation influences multiple predictors of smoking in accordance with the theory of planned behavior [14,47].

The second part of the intervention, lasting about 90 minutes, is designed to be as interactive as possible: The students are sent to their classrooms where they are split into three groups with three medical students per room. There, they rotate to four different stations in the classroom, which discuss age-appropriate information, ask about their own experiences, and have them conduct their own experiments.

Different Tobacco Products and Extraction of Substances of Tobacco Smoke

In the first part, different products (including electronic cigarettes [e-cigarettes], waterpipe, and cigarettes) are displayed and explained, and their harmfulness is discussed in a gain-framed manner.

In the second part, the students will observe an experiment using a napkin, a prepared plastic bottle filled with water, and a cigarette. The cigarette is fixated at the bottleneck via a rubber plug and burned, while the water is drained through a hole in the bottom of the bottle to create a vacuum. After the vacuum makes the smoke flow into the bottle, the cigarette is removed, and the napkin is put around the bottleneck. The smoke then gets blown out of the bottle through the napkin, which demonstrates the tar in the smoke by the discoloration of the napkin. When proper ventilation is not ensured, the medical students and school students will conduct the experiment outside to avoid unnecessary exposure to second-hand smoke.

Attractiveness and Mechanisms Related to the Face

In the first part, pictures of monozygotic smoking/nonsmoking twins are displayed, which are extracted from the publication of Okada et al [48]. The students are asked which twin is the smoker and what differences they note between the twins.

In the second part, Galaxy Tab A tablets (Samsung Electronics Inc, Seoul, Korea) are used to show each student the effects of smoking/nonsmoking on their own faces by the help of the photoaging app Smokerface that we described and piloted in great detail elsewhere [14,15]. As such, the students' faces are captured via a selfie and photoaged into a 1- to 15-year older version of themselves (normal aging vs normal aging + smoking) with animated touch effects (Figures 1-4,Multimedia Appendix 1). This intervention has been shown to influence numerous predictors of smoking in students of this age group in accordance with the theory of planned behavior and as demonstrated in our recent paper [14].

Figure 1. Female poster at baseline.

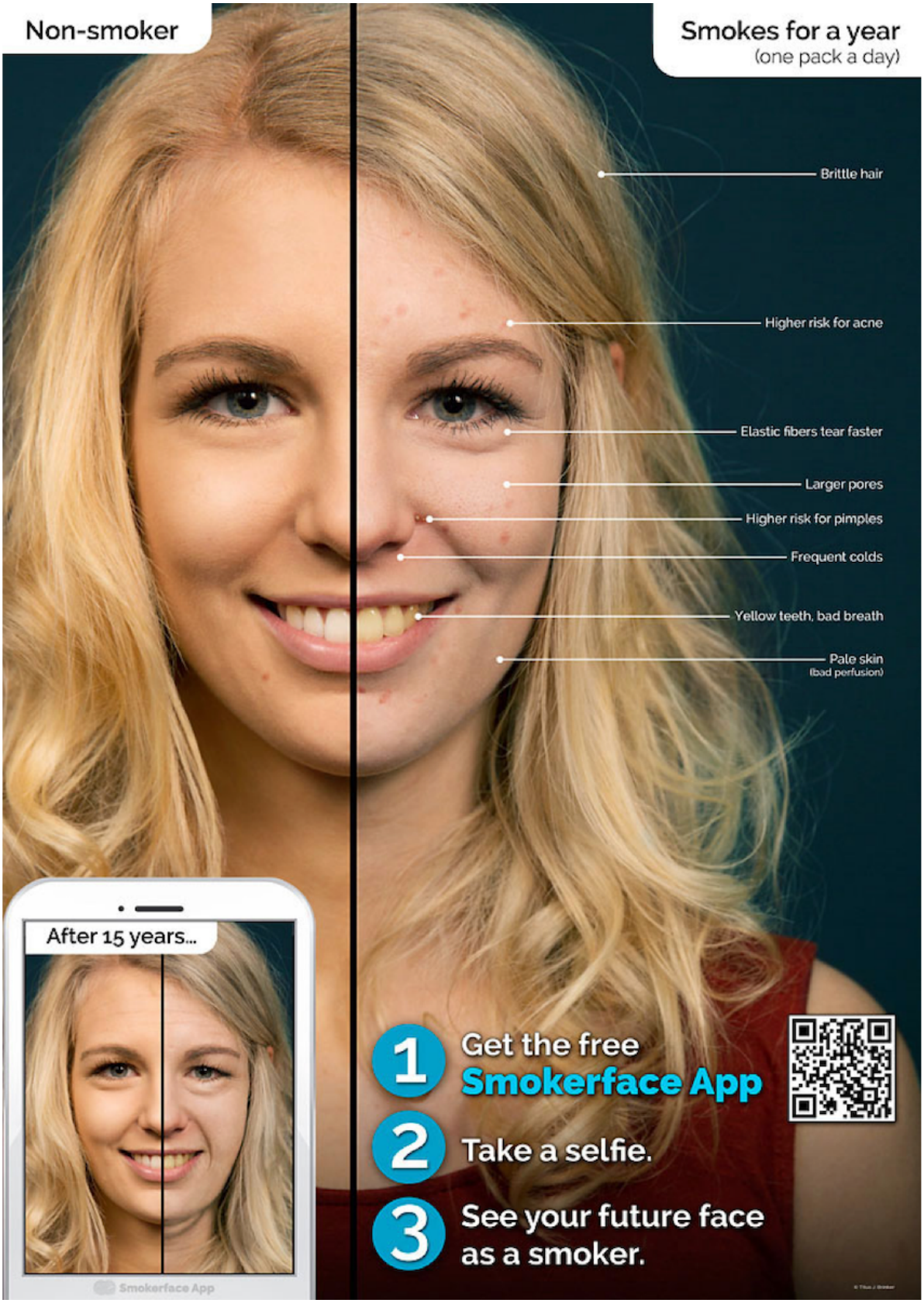

Figure 2. Male poster at baseline.

Figure 3. Female version of post-15 year Smokerface poster at 1 year postintervention.

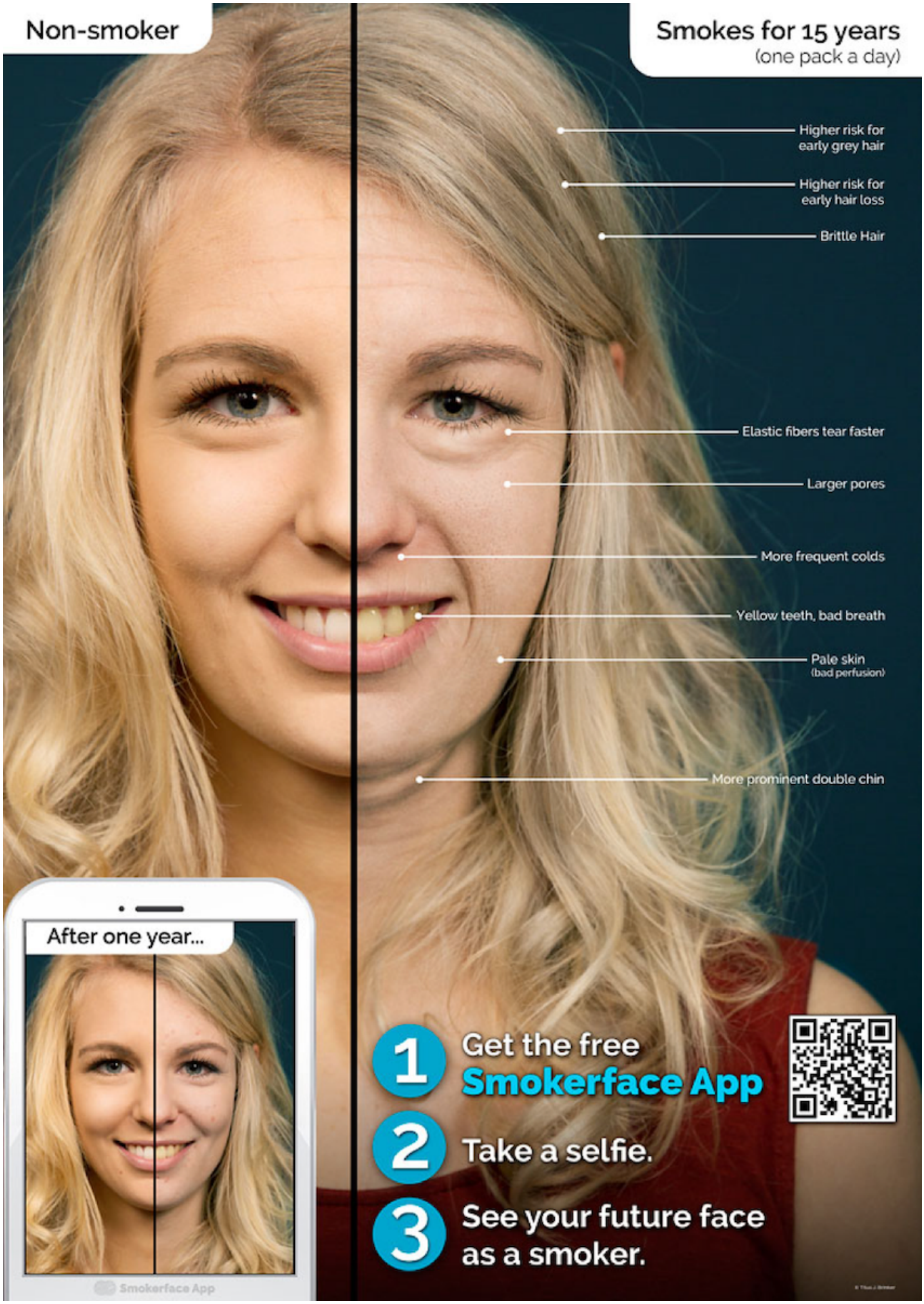

Figure 4. Male version of post-15 year Smokerface poster at 1 year postintervention.

Performance Benefits of Nonsmoking

Performance benefits of nonsmoking (physical performance, stress, and common colds) and understanding the *mechanisms* of *how* tobacco smoking affects the body with age-appropriate examples (eg, occluded vessels lead to loss of connective tissue in women's breasts, which is equivalent to less volume/tightness; impotence in both men and women; pale skin; and mechanisms of acne); this is explained via pencil and paper drafts and interactive questions. In addition, obesity [49,50], lung growth

[51], and body growth impairment in adolescent smokers are discussed using a body model, paper-pencil sketches, and growth curves [50].

Personal Experiences: How Can I Stay Away From Smoking?

The aim of this station is to discuss the students' own experiences with tobacco and how they reacted to peer pressure in the past. The group's knowledge/experience is shared and discussed in a team setting where the medical students take the role of older friends to complement the students' experiences with their own experiences in order to increase students' perceived self-efficacy, which is the most important predictor of future smoking according to the theory of planned behavior [47]. It has been shown to predict both the intention to smoke and actual smoking behavior in a meta-analysis [52].

At the end of the classroom seminar, we will ask for the students' final judgments on smoking to create positive peer pressure and influence students' subjective norm in accordance with the theory of planned behavior [47]. Health consequences are not discussed in great detail, as fear approaches were proven to be ineffective and information on smoking-related diseases can be found on every cigarette pack [25]. As a final exercise, all students breathe through a straw after having physically exercised in the classroom together to learn how lung impairment due to smoking feels with exercising. The medical students hang up the first two self-developed posters of the Smokerface App poster campaign, which has been described in great detail elsewhere [53].

After the Visit

One-year postintervention, the Smokerface App posters showing a 1-year difference of smoking are replaced with a version showing a 15-year difference.

According to a recent Cochrane review [20], smoking parents should be involved and encouraged to stop smoking, as adolescents are twice as likely to start smoking if their parents do [42]. However, increased perceived parental control increases the likelihood of adolescents to choose smoking friends and needs to be avoided [43]. To further increase the use of the apps and to guide smoking cessation among parents within the intervention group, the intervention posters will be complemented by letters to the students and parents (delivered along with the questionnaires at the 9-, 16-, and 24-month follow-ups).

School Involvement

Schools in the intervention group are offered a long-term partnership with their local EAT group, where students also deliver the EAT curriculum to Grade 7 students of the following school years. Inviting the students back is not mandatory. Students taking part in the study do not get a second intervention.

Monitoring

App Stability

The stability of the Smokerface App will be monitored during the study period via the Crashlytics app (San Francisco, CA).

External Data Monitoring Committee

As suggested by the Standard Protocol Items: Recommendations for Interventional Trials guidelines, all primary analyses will be performed externally and the raw datasets will be sent to the Collaboration Center for Clinical Trials in Marburg, Germany, for external monitoring [54].

Participants

Students from Germany attending Grade 7 in all types of regular secondary schools in Germany were eligible. Schools of other types such as special schools for mentally handicapped children or Rudolf Steiner schools, schools in other countries, or schools that had previously participated in an EAT event were not eligible. Schools were contacted by each study center individually, and therefore, only schools in the vicinity of the participating medical schools could enter the study.

Procedure

Data at baseline and follow-up are collected via a published questionnaire developed for and used in our previous investigation in the same age group [53]. All items were based on three established studies declared as high quality by the recent Cochrane review [20] and were either used in their original form or adapted to the specific circumstances of the recent study [55-57]. Data for process evaluation was collected via a newly devised questionnaire asking for feedback on the curriculum, the medical students, and the Smokerface app specifically. Most items were assessed using a 4-point Likert scale.

Data Collection

Teachers will collect the data and hand out a modified protocol, used in the Hutchinson Smoking Prevention Project, which was provided by and discussed with the authors as well as used in our previous investigation [55].

Randomization

Schools were externally and centrally randomly allocated to the control or intervention group by the KKS in Marburg, Germany. This center used permuted-block randomization via a computer with random block sizes. Stratification by a predefined smoking prevalence (≥2.65% or <2.65%) at baseline was used to balance group allocation. Schools were allocated to the control or intervention group in a ratio of 1:1 (except for Bonn, 2:1). A total of 72 schools were randomized into the control group and intervention group.

Outcomes

The primary outcome is the between-group difference of the change in smoking prevalence from baseline to the 24-month follow-up. Secondary outcomes are between-group differences in change in smoking-related attitudes in accordance with the theory of planned behavior and the number of new smokers, quitters, and never-smokers after 24 months. For all outcomes, the number needed to treat will be calculated. Considering the short nature of the intervention, we predefined a number needed to treat below 50 as clinically relevant. Students are defined as smokers if they report having used cigarettes, at least one day in the 30 days preceding the survey, in accordance with the

established National Youth Tobacco Survey definition [58]. Students who report not having smoked cigarettes in the past 30 days were defined as nonsmokers. All participants who report having smoked more than a puff in the past (beyond the past 30 days) were defined as ex-smokers.

Statistical Considerations

Sample Size Calculation

The sample size for the primary outcome was calculated with a two-sided Chi-square test and multiplied by the correction factor design effect (design effect=1 + [cluster size−1]* intraclass correlation coefficient) to adjust for correlation with regard to smoking prevalence within a cluster. We calculated an intraclass correlation coefficient of 0.033, based on the data from our recently published study on smoking behavior in Germany (analysis of variance estimator by Zou and Donner) [11,59].

To detect a between-group difference of 3% change in smoking prevalence from baseline to 24 months of follow-up with an alpha of 5% and a test power of 70%, we calculated a sample size of 5645 to 15,715 participants, depending on the difference in smoking prevalence between the two groups (2% vs 5% up to 9% vs 12%, respectively) and with an assumed dropout rate of 30% during the follow-up. Assuming an average cluster size of 100 participants, approximately 56-157 schools needed to be randomized. The dropout rate of 30% is appropriate for our 24 months of follow-up, as we observed less than 20% dropout in our recent 6-month investigations [10,11].

Data Entry

Data entry will be performed using the current software version of Formic Fusion by the Xerox AG (Kloten, Switzerland) and recommended scanners provided by the Interdisciplinary Centre for Educational Research at the University of Duisburg-Essen.

Analysis

To examine baseline differences in students' characteristics in our experimental design, we will use Chi-square tests for the categorical variables and *t* tests for the continuous variables. To test for differences in baseline and follow-up smoking prevalence between groups, we will use a cluster-adjusted Mantel-Haenszel Chi-square test [60] at a two-sided significance level of 5%. In the main analysis, hierarchical linear models (HLM) will be applied. HLM can handle the nested structure of the data and will be used to test for between-group differences in within-group changes in smoking behavior over time. HLM will also be used to investigate the influence of further covariates (such as gender, cultural background, and social characteristics) and time-dependent behavior in secondary analyses. Statistical analyses will be performed using the newest version of SPSS Statistics (IBM Corp, Armonk, New York).

The potential effects of missing data on the results will be assessed via sensitivity analysis. For this, dropouts (ie, participants who withdraw consent for continued follow-up or who are missing in the classroom during the survey) will be included in the analysis by applying multiple imputations [61].

Results

Baseline Characteristics

Overall, 11,286 students participated in the baseline survey (Table 1). The mean age was 12.32 years (range 9-17) and 50% (5490/10,965) were female. Of the total, 47.2% (68/144) of the schools were grammar schools, which provide general qualification for university entrance at the end; the rest were comprehensive schools, which provide a general certificate of secondary education at the end. At baseline, 2.6% of participants reported smoking within the last 30 days, while 84.5% (9296/11,002) reported never having smoked a cigarette (never-smokers). Current smokers reported having smoked an average of 58.92 cigarettes (SD 158.38) within the last 30 days, amounting to two cigarettes per day on an average. In addition, 4.7% of participants reported having smoked an e-cigarette within the last 30 days, with an average of 6.19 days of use. Tobacco waterpipe smoking was reported by 3.0% of the participants, with an average of 7.30 days of use. Further, 2.2% of participants self-reported using a steam stone waterpipe and cigar/cigarillo (0.6%), chewing tobacco (0.2%), marijuana (1.2%), and other nonspecified tobacco products (0.5%). The survey also identified 3.6% of participants as users of at least two tobacco products. Moreover, 38.5% of participating students reported having at least one smoking parent, 11.2% identified one of their best friends as a smoker, and 11.7% identified an older sibling as a smoker.

Process Evaluation

Our process evaluation is quite extensive, and most of these data are too detailed for publication but help with internal monitoring. The full process-evaluation analysis is provided in Multimedia Appendix 3; only the core parameters are presented in the manuscript.

The process-evaluation surveys were filled out by 324 medical student volunteers ("mentors"), 63 medical student supervisors ("educators"), 4896 students, and 141 teachers. In 59 of the 72 schools in the intervention group, we were allowed to survey the students after the intervention. On an average, 29.5 mentors were educated per medical school by 6.3 educators at the 13 medical schools involved in the study. With an average age of 21.8 years, mentors were about 1 year younger than the average educator (age, 22.7 years), which is reflected by the fact that only 44.1% (142/322) of mentors, as opposed to 82.5% (52/63) of educators, were in the clinical phase of medical school (Table 2).

We received mentor questionnaires from 11 of the 13 medical schools (all except Heidelberg and Düsseldorf) and educator feedback from 10 of the 13 medical schools (all except Giessen, Heidelberg, and Cologne; Table 3). All volunteering medical students for the study received training.

Table 1. Baseline characteristics.

Characteristics	Total	Intervention group	Control group
Students, n (%)	11,286 (100)	5732 (50.8)	5554 (49.2)
Schools, n (%)	144 (100)	72 (50.0)	72 (50.0)
Grammar schools, n (%)	68 (47.2)	36 (50.0)	32 (44.4)
Gender, n (%)	**10,965 (97.2)**	**5584 (97.4)**	**5381 (96.9)**
Female	5490 (48.6)	2777 (49.7)	2713 (50.4)
Male	5475 (48.5)	2807 (50.3)	2668 (49.6)
Age, n (%)	11,054 (97.9)	5624 (50.9), mean 12.32, median 12 (SD 0.67), range 9-17	5430 (49.1), mean 12.33, median 12, (SD 0.64), range 9-17
Current cigarette smoking (at least once in past 30 days), n (%)	**285/11,127[a] (2.6)**	**137/5669[a] (2.4)**	**148/5458[a] (2.7)**
Average number of cigarettes smoked in past 30 days per current smoker (SD)	58.92 (158.38)	56.71 (137.88)	61.013 (176.13)
Average days of use in the past 30 days per current smoker (SD)	**8.68 (10.81)**	**9.14 (11.02)**	**8.25 (10.63)**
1-2 days, n (%), average number of cigarettes per day	145 (1.4), 0.89	63 (1.2), 0.95	82 (1.6), 0.85
3-5 days, n (%), average number of cigarettes per day	30 (0.3), 3.13	18 (0.3), 4.06	1.75 (0.2), 1.75
6-9 days, n (%), average number of cigarettes per day	19 (0.2), 2.45	13 (0.2), 2.27	6 (0.1), 2.83
10-19 days, n (%), average number of cigarettes per day	26 (0.2), 3.33	11 (0.2), 5.18	15 (0.3), 1.97
20-29 days, n (%), average number of cigarettes per day	10 (0.1), 3.90	5 (0.1), 2.50	5 (0.1), 5.30
All 30 days, n (%), average number of cigarettes per day	43 (0.4), 10.12	23 (0.4), 8.52	20 (0.4), 11.95
Not smoked in the past 30 days (nonsmokers), n (%)	10,842 (97.4)	5532 (97.6)	5310 (97.3)
Never tried smoking, not even a puff, n (%)	9458/11,074[a] (85.4%)	4835 (85.7)	4623 (85.1)
Never smoked a cigarette (never-smokers), n (%)	9296/11,002[a] (84.5%)	4754 (85.0)	4542 (84.0)
Ex-smokers who smoked... n (%)			
More than once per week	122 (1.1%)	57 (1.0%)	65 (1.2%)
Less than once per week	122 (1.1%)	66 (1.2%)	56 (1.0%)
Average age of first puff (years), n (%)			
≥8	364 (22.8)	161 (20.5)	203 (25.0)
9-10	238 (14.9)	124 (15.8)	114 (14.0)
11-12	780 (48.9)	389 (49.6)	391 (48.2)
13-14	214 (13.4)	110 (14.0)	104 (12.8)
Intention to smoke cigarettes[b]	0.44	0.45	0.44
Do you intend to quit cigarettes?[c]	0.40	0.43	0.36
Current tobacco waterpipe smoking, n (%), mean days of use in the past 30 days (SD)	330 (3.0), 7.30 (9.36)	163 (2.9), 7.83 (9.84)	167 (3.1), 6.77 (8.87)
Current e-cigarette smoking, n (%), mean days of use in the past 30 days (SD)	519 (4.7), 6.19 (8.60)	250 (4.4), 6.44 (8.63)	269 (5.0), 5.96 (8.57)
Current cigar or cigarillo smoking, n (%), mean days of use in the past 30 days (SD)	72 (0.6), 9.37 (11.87)	30 (0.5), 8.27 (11.52)	42 (0.8), 10.15 (12.19)
Current chewing of tobacco, n (%), mean days of use in the past 30 days (SD)	25 (0.2), 14.90 (12.88)	11 (0.2), 16.32 (13.77)	14 (0.3), 13.79 (12.54)

Characteristics	Total	Intervention group	Control group
Current use of marijuana, n (%), mean days of use in the past 30 days (SD)	128 (1.2), 12.33 (12.68)	64 (1.1), 10.68 (11.97)	64 (1.2), 13.98 (13.25)
Current use of steam stone waterpipe, n (%), mean days of use in the past 30 days (SD)	247 (2.2), 6.32 (8.65)	117 (2.1), 6.07 (8.43)	130 (2.4), 6.54 (8.87)
Current use of other tobacco product, n (%), mean days of use in the past 30 days (SD)	51 (0.5), 9.21 (11.60)	23 (0.4), 10.02 (12.54)	28 (0.5), 8.54 (10.94)
Current use of *at least* two tobacco products, n (%)	402 (3.6)	189 (3.3)	213 (3.9)
Current use of electronic cigarettes and cigarettes, n (%)	145 (1.3)	67 (1.2)	78 (1.4)
Current use of waterpipe with tobacco and cigarettes, n (%)	99 (0.9)	52 (0.9)	47 (0.9)
Smoking in a social environment, n (%)			
I have at least one smoking parent	4278 (38.5)	2188 (38.6)	2090 (38.4)
One of my best friends smokes	1174 (11.2)	567 (10.6)	607 (11.8)
I have an older sibling that smokes	1252 (11.7)	623 (11.5)	629 (12.0)
Migration/socioeconomic background, n (%)			
Both parents born in Germany	6740 (62.6)	3467 (63.2)	3273 (62.1)
One parent born in Germany	1724 (16.0)	877 (16.0)	847 (16.1)
No parent born in Germany	2296 (21.3)	1146 (20.9)	1150 (21.8)
School performance (self-reported point average), n (%), mean (SD)	10,757 (95.3), 2.42 (0.85)	5475 (50.9), 2.40 (0.84)	5282 (49.1), 2.43 (0.86)
Education level of parents[d], score			
Father	3.90	3.90	3.91
Mother	3.84	3.84	3.84
"Do you live in the same household with your parents?", n (%)			
I live with both parents	8430 (76.5)	4320 (77.0)	4110 (75.9)
With mother but not father	1964 (17.8)	994 (17.7)	970 (17.9)
With father but not mother	274 (2.5)	131 (2.3)	143 (2.6)
Neither mother nor father	358 (3.2)	167 (3.0)	191 (3.5)
Survey quality, n (%)			
"Anonymity was explained to me before I filled out the questionnaire."	10,286 (94.0)	5242 (94.1)	5044 (93.9)
"It was made clear that nobody knows that I filled out this questionnaire."	8349 (76.6)	4229 (76.1)	4120 (77.0)

[a]These are valid answers from the questionnaire.

[b]Scale 0-6 (0=I am very sure that I will never smoke to 6=I believe that I will start smoking within the next month).

[c]Scale: 0-3 (0=no to 3=within the next month).

[d]Score: 1-5 (1=not completed school education to 5=completed university).

Table 2. Participant characteristics[a].

Variable	Mentors receive education for classroom visit (n=324)	Educators deliver education to mentors (n=63)
Number of mentors/educators per medical school, mean (SD)	29.5 (16.7)	6.3 (3.4)
Age (years), mean/N (SD); median (range)	**21.8/320 (2.8); 21 (18-32)**	**22.7/63 (1.5); 23 (20-28)**
Female, n/N (%)	217/322 (67.4)	37/61 (60.7)
Male, n/N (%)	101/322 (31.4)	24/61 (39.3)
Preclinical phase of medical school, n/N (%)	180/322 (55.9)	11/63 (17.5)
Clinical phase of medical school, n/N (%)	142/322 (44.1)	52/63 (82.5)
Nonsmokers, n/N (%)	294/322 (91.3)	56/57 (98.2)
Ex-smokers, n/N (%)	24/322 (7.5)	0/63 (0)
Smokers, n/N (%)	4/322 (1.2)	1/57 (1.8)
At least one parent not born in Germany, n/N (%)	152/321 (47.4)	18/62 (29.0)

[a]The denominator for all percentage values is the number of valid cases (number of questionnaires with valid answers).

Table 3. Number of mentors and schools.

Medical school	Number of educated mentors, n/N (%)	Number of visited schools, n/N (%)
Bochum	38/324 (11.7)	5/72 (6.9)
Bonn	36/324 (11.1)	6/72 (8.3)
Düsseldorf	__[a]	11/72 (15.3)
Erlangen	20/324 (6.2)	11/72 (15.3)
Essen	20/324 (6.2)	5/72 (6.9)
Freiburg	40/324 (12.3)	4/72 (5.6)
Hannover	12/324 (3.7)	5/72 (6.9)
Köln	3/324 (0.9)	4/72 (5.6)
Gießen	50/324 (15.4)	5/72 (6.9)
Göttingen	11/324 (3.4)	1/72 (1.4)
Regensburg	48/324 (14.8)	4/72 (5.6)
Tübingen	46/324 (14.2)	5/72 (6.9)
Heidelberg	__[a]	6/72 (8.3)

[a]No questionnaires from mentors were handed in.

When asked about their perception of the training, 99.7% (318/319) of mentors and 100% (63/63) of educators responded positively to whether “overall, the training made sense” for the mentors. A total of 96.6% (311/322) of mentors and 100% (63/63) of educators agreed to the statement, “I feel well prepared,” although only 70.6% (228/323) of the mentors agreed that they were able to train their didactic skills. Furthermore, 94.4% (305/323) of the mentors and 100% (61/61) of educators answered with “fully correct” or “rather correct” to the statement, “It increased my motivation to advise my future patients not to smoke” (Table 4).

General feedback on the curriculum was gathered in surveys for all four viewpoints (Multimedia Appendix 3). Here, 90.6% (4361/4814) of students, 93.9% (123/131) of teachers, 98.4% (311/316) of mentors, and 95.2% (60/63) of educators answered positively to the statement that the intervention “will motivate them (the students) to be non-smokers.” Feedback on the medical students was also very positive, with 95.9% (4642/4819) of students and 97.8% (135/138) of teachers answering positively to the statement, “overall, they (the medical students) left a very good impression.”

Table 4. Participant perceptions. Used scale: 1=fully correct, 2=rather correct, 3=rather not correct, 4=not correct at all.

Variable	Mentors receive education for classroom visit		Educators deliver education to mentors	
	Mean (SD)	Percentage base of valid cases (%[a])	Mean (SD)	Percentage base of valid cases (%)
What influence did the education/training have on yourself?				
Increased my motivation not to smoke	1.5 (0.8)	320 (92.2)	1.5 (1)	63 (85.7)
I learned new things about tobacco as a topic	1.8 (0.9)	324 (76.2)	1.8 (0.9)	63 (73.0)
It increased my awareness about the harms of tobacco	1.8 (0.8)	323 (84.8)	1.8 (1)	61 (85.2)
It increased my motivation to advise my future patients not to smoke	1.3 (0.6)	323 (94.4)	1.2 (0.4)	61 (100)
How did you perceive the training?				
It was fun	1.3 (0.5)	324 (99.1)	1.2 (0.4)	63 (100)
It was interesting	1.3 (0.5)	324 (98.1)	1.3 (0.5)	63 (98.4)
I feel well prepared	1.5 (0.6)	322 (96.6)	1.3 (0.5)	63 (100)
I was able to train my didactic skills	2 (0.9)	323 (70.6)	1.4 (0.5)	63 (98.4)
Global feedback				
Overall, the training made sense	1.2 (0.4)	319 (99.7)	1.2 (0.4)	63 (100)
I would recommend EAT to other medical students	1.1 (0.4)	315 (99.7)	1.1 (0.3)	63 (98.4)

[a]Percent of top two (1 or 2) related to valid cases.

Discussion

Overview

This is the first major randomized trial on a medical student–delivered smoking prevention program in the school setting. Our network previously investigated an early version of the EAT curriculum in a quasi-experimental prospective evaluation with a 6-month follow-up (n=1474) as well as the 2014 EAT curriculum in a smaller randomized controlled trial (n=1504) with a 12-month follow-up and a high loss to follow-up [62]. Chances and synergy effects of a medical student intervention are in need of further evaluation from all angles. The investigated intervention is available in the area around the 13 participating medical schools. The number of schools able to receive this intervention is limited by the capacity of the local EAT group.

Baseline Characteristics

Our baseline survey includes the major predictors of adolescent smoking, as described in the literature [56,57]. The distributions of relevant characteristics over the two groups are balanced, indicating successful randomization. For example, the students in the intervention and control groups are similar with regard to the current smoking prevalence (2.4% and 2.7%, respectively), never-smoking prevalence (85.0% and 84.0%, respectively), and the proportion of those having at least one smoking parent (38.6% and 38.4%, respectively).This large study is conducted in five German federal states. Our definitions for the smoking status of the various monitored tobacco products stem from the National Youth Tobacco Survey by the Center for Disease Control (Atlanta, United States) [57]. Teachers are used as data collectors and were handed out a modified protocol, as used in the Hutchinson Smoking Prevention Project to ensure international comparability.

This is also the first national study to show that current e-cigarette prevalence is higher than cigarette smoking prevalence in Grade 7 students from secondary schools (2.6% use cigarettes and 4.7% use e-cigarettes). More than a quarter of these (1.3% of the total sample) currently use both products at the same time. The epidemiologic data presented here are therefore also valuable, considering that the most cited and most recent surveys in Germany were conducted via telephone interviews, a method showing poor consistency with biochemical validation in our age group [17,63]. We are not using biochemical validation in our study because it would have to take place in the school setting with previous notice on the day the paper questionnaires are given out. This would compromise the comparability of data obtained on that day, since students may answer according to social desirability.

Quality of Data Collection

We monitored the quality of the data collection with the following two items: (1) Was it explained to you that nobody else than the researchers would see your questionnaire? (2) Anonymity was explained to me before filling out the questionnaire.

A total of 76.6% (8349/10,899) of the students remembered at the end of the questionnaire that the data collectors had explained the confidentiality and 94% (10,286/10,943) of the students stated that anonymity was explained to them.

We were obliged to obtain active consent from the parents and students. Of the students in the schools under investigation, who were registered for the study by their responsible teacher, 83.5%

(11,286/13,521) participated in the baseline survey and had obtained parental consent. The teachers are responsible for guaranteeing that only students with parental consent fill out the paper questionnaires; therefore, it is possible that students deliberately or undeliberately failed to present their teachers with a filled out parental consent form and were consequently excluded from data collection.

Process Evaluation

Our process evaluation captures the view of all four participating parties (educators, mentors, students, and teachers) in the preparation and implementation of the intervention. We did not obtain data on the mentors of two of the larger study centers (Düsseldorf and Heidelberg), which makes it more difficult to draw conclusions regarding perceived proficiency in the curriculum beforehand and outcome measured by student's impression of the intervention afterward. The educator's viewpoint is not an individual assessment of each mentor's proficiency but a group evaluation, since mentors were taught in groups of up to four people. Even though this leaves room for inaccuracy in individual assessment, an educator to mentor ratio of 1:1 would have been too time consuming, considering the 3-hour training. Furthermore, mentor training was intentionally designed for mentors to practice supervising a group of listeners and repeating relevant facts in their own words to promote a finer grasp of what the curriculum is trying to accomplish at every step. Accordingly, 96.6% (311/322) of mentors reported "feeling well prepared" for the intervention. Noticeable findings from the process evaluation were derived from comparison of different viewpoints on the general outlook and specific components of the intervention. A total of 94.3% (296/314) of mentors, 96.8% (61/63) of educators, and 93.2% (124/133) of teachers reported that students learned the benefits of nonsmoking that were new to them. However, only 76.1% (3667/4819) of the students agreed to this statement. Considering that the average mentor was only 21.8 years old and graduated not too long ago, we interpret this finding mainly as a sign of increased awareness of tobacco-related health aspects in the younger generation, possibly because it received increased media coverage over the last few years. It is also possible that students overestimate how profound their knowledge was beforehand. We found similar discrepancies in the specific feedback to our Smokerface app. Although 82% (105/128) of teachers, 85% (272/320) of mentors, and 76.2% (48/63) of educators rated the alterations of people's selfies to be "realistic," only 47.3% (2274/4807) of students agreed with this viewpoint. This was especially surprising because at the same station, students were shown pictures of identical twins, one of them being/having been a smoker, during the classroom intervention. When it came to their own face and appearance, students showed reluctance to accept the gravity of skin aging for smokers. When asked which of the presented short-term effects of smoking was most relevant to them, grammar school students reported stunted lung growth most frequently (583/2376, 24.5%), while comprehensive school students most often reported pimples as their primary concern (440/1891, 23.3%). The curriculum should be adapted to cater to these concerns (focus on appearance vs noxious effects), depending on which type of school is receiving the intervention. Only 49.1% (2338/4765) of students made a selfie with the provided tablet during the great hall presentation, even though everyone was supposed to be given the opportunity. Feedback by study centers suggests that time management was an issue: 45 minutes of presentation did not leave much buffer time for delay, so students arriving late or great halls not being prepared by janitors ultimately resulted in several cases of time management issues. A discussion of whether the presentation will be slimmed down or formally extended to 60 minutes will take place in the near future. The short time frame may also be the reason why 89.3% (92/103) of teachers considered the presentation to be "very good" compared to 98.5% (128/130) for the classroom intervention, where time management was not reported to be an issue.

Generalizability

As this study is conducted only in Germany, the results might not be generalizable to other cultural or national settings. However, the EAT network is quickly expanding to other countries such as Brazil, and research is also conducted there using part of the EAT curriculum [64]. Participating schools are mostly located in urban areas close to larger cities with medical schools. Therefore, the results might not be generalizable to schools in rural areas. However, since medical student–delivered interventions are unlikely to be widely available there, these concerns might be negligible.

Part of the investigated intervention is easy to implement and can be added to existing school-based programs. We provide original posters in high resolution for offset print on our website [65].

Conclusions

Our research provides a great opportunity to evaluate the curriculum of a multinational medical student network. Involving and engaging medical student volunteers in interactions with young students can sensitize them toward the current trends in and danger of smoking. Our baseline analysis shows good comparability between the groups at baseline after randomization and provides new insights into the prevalence of smoking and the use of e-cigarettes among students in the seventh-grade in Germany. With our process evaluation, we were able to ensure the quality of the intervention as well as the medical student training and receive positive feedback on the curriculum and medical students' performance. The feedback will help further optimize the intervention with regard to the type of school receiving the intervention and the organizational structure, especially the great hall presentation. We are looking forward to sharing our final report on the follow-up results and changes implemented, as EAT is an ongoing project expanding in size and availability.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Video introduction to Education Against Tobacco.

[MP4 File (MP4 Video), 7MB - resprot_v8i4e13508_app1.mp4]

Multimedia Appendix 2

Animated touch-effect "cough" of the Smokerface App.

[MP4 File (MP4 Video), 2MB - resprot_v8i4e13508_app2.mp4]

Multimedia Appendix 3

Detailed process evaluation.

[DOCX File, 34KB - resprot_v8i4e13508_app3.docx]

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Abbreviations

EAT: Education Against Tobacco
e-cigarettes: electronic cigarettes
HLM: hierarchical linear models

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Protocol

The Effect of Vitamin D Supplements on Clinical and Para-Clinical Outcomes in Patients With Multiple Sclerosis: Protocol for a Systematic Review

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Abstract

Background: Multiple sclerosis (MS) is an inflammatory disease, which has a wide range of effects on patients. There are controversies regarding the role of vitamin D in clinical and laboratory improvements in MS patients.

Objective: The aim of this systematic review protocol is to evaluate the efficacy of vitamin D supplements on relapse rate, gadolinium-enhancing lesions of magnetic resonance imaging (MRI), and cytokine profiles.

Methods: We will search PubMed, Scopus, EMBASE, CINAHL, Web of Science, Ovid, ProQuest, American College of Physicians Journal Club database, Health Technology Assessment Database (The Cochrane Collaboration), and National Health System Economic Evaluation Database (The Cochrane Collaboration) and gray literature including reference of included studies and conference abstracts. Clinical trials reporting the effect of any doses of vitamin D on relapse rate, gadolinium-enhancing lesions of MRI, and cytokine profiles will be included. In total, 2 independent researchers will independently assess the studies, extract data, and evaluate the quality of primary studies.

Results: This systematic review was started in September 2017 and the process is continuing. The included articles are evaluated and researchers are going to extract the data.

Conclusions: To our knowledge, this will be the first comprehensive systematic review aiming to assess the effect of vitamin D supplements on clinical and para-clinical outcomes in patients with multiple sclerosis.

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KEYWORDS

multiple sclerosis; systematic review; relapse; magnetic resonance imaging; chemokines

Introduction

Background

Multiple sclerosis (MS) is an inflammatory progressive disorder of the central nervous system, which affects women more than men [1]. The annual incidence of the disease has increased, and environmental and genetic factors are considered important in disease development [2-4].

Smoking, Epstein-Barr virus infection, habitat latitude, and vitamin D status are among the environmental factors associated with disease risk [5,6].

Previous studies have demonstrated that a longer duration of sunlight exposure, decreasing latitude of residence, and a vitamin-rich diet are associated with a lower risk of developing MS [7-9].

Vitamin D, which is a modulator of calcium and phosphorus, plays an important role in bone formation and maintenance as well as having anti-inflammatory, antiproliferation, and immune intonation functions [10]. The regulation of gene expression in immune cells is thought to explain vitamin D's immune effects on cells [11].

Experimental studies have shown that vitamin D administration could slow down experimental autoimmune encephalomyelitis progression [12,13]. In humans, lower vitamin D status has been reported at the time of relapse in MS patients as compared with the relapse-free period [14-16]. Some previous studies showed that vitamin D supplements were not effective in reducing MS-related relapses [17,18], whereas others revealed that vitamin D supplements were helpful in reducing relapse rates and MRI lesions in MS patients [19,20].

A systematic review and meta-analysis conducted previously showed that vitamin D supplementation was not beneficial to control MS relapses (odds ratio 0.98, 95% CI 0.45-2.16) by including 5 randomized clinical trials (RCTs) [21].

The main goal of this systematic review and meta-analysis will be to evaluate the effectiveness of vitamin D supplementation on clinical and para-clinical outcomes in patients with multiple sclerosis

Objectives

Primary Objective

The primary objective was to identify the efficacy of vitamin D supplement administration in patients with MS on relapse rates.

Secondary Objectives

The secondary objectives were the following:

1. Identify the efficacy of vitamin D supplement administration in patients with MS on gadolinium-enhancing lesions.
2. Identify the efficacy of vitamin D supplement administration in patients with MS on cytokine profiles.
3. Identify the efficacy of vitamin D supplement administration in patients with MS on disability.

Methods

Study Characteristics

We will include RCTs, being single-blinded or double-blinded or open-label trials in which relapse rate was one of the main outcomes after vitamin D supplement therapy. The articles that had been published in the English language will be included.

Cohort studies, case-control studies, and any other types of studies will be excluded.

Types of Participants

We will include studies with adult participants (aged more than 18 years) with the relapsing-remitting (RR) form of the disease (as we want to assess the effect of the intervention on relapse rate).

Control Group

The control group should be patients who received placebo (color, shape, and smell similarity with the vitamin D supplements).

Types of Intervention

We considered interventions as vitamin D supplements (any doses) whereas controls should have received placebos.

Outcome Assessment

The primary outcome assessment will be carried out by a report of relapse, which is characterized by attacks of new or increasing neurologic symptoms (such as double vision, blurred vision, numbness, the lack of balance, memory loss, muscle cramping secondary to spasticity, bladder, bowel, and sexual dysfunction, bilateral facial weakness or trigeminal neuralgia, nystagmus, and intention tremor, and heat intolerance). The secondary outcomes will be assessed by comparing the number of gadolinium-enhanced plaques before and after the treatment, level of cytokines (tumor necrosis factor and interleukins) before and after the treatment, and progression of disability measured with the Expanded Disability Status Scale (EDSS).

Information Sources

We will search PubMed, Scopus, EMBASE, CINAHL, Web of Science, Ovid, ProQuest, American College of Physicians Journal Club database, Health Technology

Assessment Database (The Cochrane Collaboration), and National Health System Economic Evaluation Database (The Cochrane Collaboration) and gray literature including reference of included studies and conference abstracts.

Search Strategy

A search strategy was developed, and it will be used to search in all databases. The search keywords are as following:

1. Multiple sclerosis
2. MS
3. Relapsing-Remitting
4. RR
5. Multiple Sclerosis, Relapsing-Remitting
6. Remitting-Relapsing Multiple Sclerosis
7. Multiple Sclerosis, Remitting-Relapsing

8. Remitting Relapsing Multiple Sclerosis
9. Relapsing-Remitting Multiple Sclerosis
10. Relapsing -Remitting Multiple Sclerosis
11. Multiple Sclerosis, Acute Relapsing
12. Acute Relapsing Multiple Sclerosis
13. Vitamin D
14. 25 Hydroxyvitamin D 2
15. 25-Hydroxyergocalciferol
16. 25 Hydroxyergocalciferol
17. 25-Hydroxyvitamin D2
18. 25 Hydroxyvitamin D2
19. Ercalcidiol
20. 25-Hydroxycalciferol
21. 25 Hydroxycalciferol
22. Dietary Supplement
23. Supplements, Dietary
24. Dietary Supplementations
25. Supplementations, Dietary
26. 1 or 2
27. 3 or 4
28. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
29. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
30. 22 or 23 or 24 or 25
31. 26 and 27 and 28 and 29 and 30

Study Records

In total, 2 independent researchers will independently assess the articles. All obtained articles will be screened by title and abstract, and selected articles will be considered as eligible, not eligible, or may be eligible.

Articles that are considered as not eligible by both researchers will be excluded and others will be searched for by obtaining the full text. Eligible and may be eligible articles will be assessed independently, and in the case of a disagreement, a session for solving the disagreement will be held. The researchers will extract the data from papers and in the case of incomplete/unclear information, surveys will be sent to the authors.

Data Items

Data regarding the name of authors, year of publication, number of patients, journal title, date, demographic data, method of intervention, dose of vitamin D supplement, duration of the study, frequency of relapses during the study, mean vitamin D levels at baseline and at the end of the study, type of control, number of baseline and final gadolinium enhanced plaques in MRI, and mean levels of cytokines and EDSS at baseline and the end of the study will be extracted by 2 independent researchers and will be recorded.

Assessment of Risk of Bias in Included Studies

On the basis of the Cochrane Collaboration Risk of Bias assessment tool, 2 researchers will assess the risk of bias in each study [22]. Thus, each article will be categorized into low risk, high risk, and unclear risk. In the case of a disagreement, a discussion to reach an agreement will be held.

Data Synthesis

When adequate studies are included, the meta-analysis will be performed by considering the relapse, the number of gadolinium-enhanced plaques, and the level of cytokines and disability (which is assessed by means of EDSS) as the main outcome. For all of the main outcomes, mean differences and standardized mean differences will be applied. In the case of missing SD or SE, it will be calculated directly using the data where possible. If adequate studies are retrieved, a subgroup analysis will be carried out.

Subgroup Analysis

A subgroup analysis will be carried out according to sex, age, and EDSS.

Results

This systematic review was started in September 2017, and the search process is completed. The articles are retrieved and are under review by 2 independent researchers. The findings of this systematic review will determine the effectiveness of vitamin D supplements on the prevention of MS relapses, MRI findings, and cytokines. The results of this systematic review will be published in a peer-reviewed journal.

Discussion

MS is a disabling disease and nearly 85% of patients present with the RR form [23]. Relapses are not predictable and have negative impacts on a patient's quality of life [24].

Since 1970, vitamin D has been considered as an important factor in MS development. Studies showed that the prevalence of MS is higher in regions with less exposure to ultraviolet light [25]. Other studies demonstrated that higher levels of serum vitamin D levels are associated with less disease activity in patients and by each doubling of serum level of this vitamin, the risk of relapse decreased by 27% [16]. Vitamin D supplements were considered to be useful for the reduction of disease-related MRI lesions, disability, and reduced relapse rates during the study period [17], but there is no consistent finding on the effectiveness of vitamin D supplements in all those studies. This may be because different studies administered different doses of supplements and they assessed the effects on different outcomes.

The results of this systematic review could be helpful for clinicians to understand the best dose of vitamin D supplement for patients with MS.

Conflicts of Interest

None declared.

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Abbreviations

EDSS: Expanded Disability Status Scale
MRI: magnetic resonance imaging
MS: multiple sclerosis
RCT: randomized clinical trial
RR: relapsing-remitting

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Protocol

Text Messaging Interventions for Reducing Alcohol Consumption Among Harmful and Hazardous Drinkers: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Mobile phone-based interventions have become popular for lifestyle behavior change, particularly the use of text messaging as it is a technology ubiquitous in mobile phones. Reviews and meta-analyses of digital interventions for reducing harmful and hazardous use of alcohol have mainly focused on Web-based interventions; thus, there is a need for a body of evidence to guide health practitioners, policy makers, and researchers with respect to the efficacy of available text messaging interventions.

Objective: The aim of this systematic review and meta-analysis is to assess the effectiveness of text messaging interventions for reducing the amount of alcohol consumed among harmful and hazardous drinkers; this is compared to receiving no, minimal, or unrelated health information. Specifically, we ask the following questions: (1) Can interventions consisting of only text messages be effective in reducing alcohol consumption compared to no intervention or a minimal or unrelated intervention? (2) Can interventions consisting of only text messages be effective in reducing the prevalence of risky drinking compared to no intervention or a minimal or unrelated intervention?

Methods: Several databases will be searched, including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PsycINFO, the Conference Proceedings Citation Index, ClinicalTrials.gov, OpenGrey, among others. Reports of studies that evaluate text messaging interventions for reducing the amount of alcohol consumed will be included. Primary outcomes of interest will be weekly alcohol consumption and frequency of heavy episodic drinking. The Cochrane Collaboration Risk of Bias tool will be used to assess bias in reports, and the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach will be used to assess the quality of the body of evidence. A narrative review will be presented, and a meta-analysis will be conducted in case of homogeneity among included studies.

Results: The systematic review has not yet begun but is expected to start in May of 2019; publication of the final review and meta-analysis is expected at the end of 2019.

Conclusions: The technology for text messaging is ubiquitous in mobile phones; thus, the potential reach of interventions utilizing this technique is great. However, there are no meta-analyses to date that limit the scope to the use of text messaging interventions for alcohol consumption reduction. Therefore, the proposed systematic review and meta-analysis will help health practitioners, policy decision makers, researchers, and others to better understand the effects of these interventions.

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KEYWORDS

text messaging; SMS; risky drinking; harmful drinking; hazardous drinking; intervention; systematic review; meta-analysis

Introduction

Rationale

Hazardous drinking, defined as a quantity or pattern of consumption that places an individual at risk for adverse health events [1], is a modifiable behavior that increases the risk of noncommunicable diseases [2]. Noncommunicable diseases are responsible for 70% of deaths globally each year, of which cardiovascular diseases, cancer, respiratory diseases, and diabetes account for over 80% [3,4]. Recent evidence suggests that alcohol consumption at any level increases the risk of stroke, heart failure, fatal hypertensive disease, fatal aortic aneurysm, and coronary disease, excluding myocardial infarction, but may on the other hand have a protective effect on myocardial infarction [5].

Harmful drinking, defined as consumption of alcohol that results in physical or psychological harm [1], may lead to injury, road traffic accidents, violence, and social and economic burdens, as well as having a causal relationship with a range of mental and behavioral disorders [6]. Harmful use of alcohol contributes to 5.9% of deaths globally, and as much as 25% of total deaths in the age group 20-39 years are attributable to harmful drinking [2,7]. Furthermore, harmful use of alcohol is the seventh-leading risk factor for disability-adjusted life years and is the leading risk factor of death among those aged 15-49 years [8].

mHealth and Text Messaging

The World Health Organization (WHO) defines eHealth as the use of information and communication technologies for health, including electronic health records, patient management systems, ecological monitoring, robotics, lab systems, informatics, etc. By extension, eHealth interventions can be understood as interventions that promote health using information and communication technologies. With the global growth of mobile phone subscriptions—in 2016, it was estimated that 95% of the global population resided in an area with a mobile-cellular network [9]—a subfield of eHealth called mHealth (ie, mobile health) has emerged [10]. Continuous contact with individuals, interactivity, and cost reductions are only some of the benefits that mHealth interventions may be associated with.

Text messaging, more formally known as short message service (SMS), is a technology ubiquitous in mobile phones. The technology does not rely on data networks such as 3G or 4G, which usually incur extra costs for end users and may be unavailable in certain areas, but runs on networks utilizing earlier standards such as Global System for Mobile communications (GSM), which are generally more available and cheaper. Thus, there is potentially a great reach for lifestyle interventions that utilize text messaging.

Trials of text messaging for smoking cessation have shown positive results [11-13], and a Cochrane review reported a beneficial impact of mobile phone-based smoking cessation programs [14], most of which were text message based. However, while there have been evaluations of text messaging interventions for alcohol consumption reduction [15-19], there have been no meta-analyses regarding the use of text messaging programs for reducing alcohol consumption, despite the need to collect evidence and provide guidance on these types of interventions.

Digital Interventions for Alcohol Reduction

Previous meta-analyses of digital interventions targeting harmful and hazardous use of alcohol have mainly focused on trials of electronic screening and brief interventions [20-23]. Commonly, individuals engaging with this type of intervention respond to a series of questions, after which a summary of their alcohol habits is presented; feedback is then given with respect to recommended drinking levels, alongside some advice on behavior change. The focus was broadened in a Cochrane review to include all digital interventions [24], which identified moderate-quality evidence that digital interventions may lower alcohol consumption; however, the authors emphasize that "Most included trials tested Web - based interventions, so the effectiveness of other types of interventions such as smartphone apps or SMS messages is less clear." Thus, there still exists a knowledge gap with respect to the efficacy of text messaging interventions. A recent systematic review [25] supported the use of mHealth interventions to address substance use; however, while included trials of interventions were delivered in a variety of formats (eg, Web based, text messaging, and mobile phone apps), overall effectiveness in a meta-analysis was not quantified.

Objectives

The aim of this systematic review and meta-analysis is to assess the effectiveness of text messaging interventions for reducing the amount of alcohol consumed among harmful and hazardous drinkers; this is compared to receiving no, minimal, or unrelated health information. Specifically, we ask the following questions:

1. Can interventions consisting of only text messages be effective in reducing alcohol consumption compared to no intervention or a minimal or unrelated intervention?
2. Can interventions consisting of only text messages be effective in reducing the prevalence of risky drinking compared to no intervention or a minimal or unrelated intervention?

Methods

Protocol Registration and Development

In accordance with the guidelines, this systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on April 3, 2019 (registration number: CRD42019117431). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement [26] has been followed when developing this protocol. The execution and reporting of the described systematic review and meta-analysis will be done in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [27].

Eligibility Criteria

Study Design

We will include randomized controlled trials (RCTs), including cluster RCTs.

Participants

Studies examining harmful or hazardous drinkers identified by a screening tool in any population (eg, students, general population, and primary care patients) will be included. No restriction on age or population will be made, as the review attempts to assess the effect of text messaging among any harmful or hazardous drinkers. However, studies that include participants who are obviously receiving care for their alcohol consumption (eg, patients in a treatment program) will not be included. The aim is to assess the effect of text messaging interventions as the main intervention, not as a cointervention to other treatment programs. Recruitment can be done through different means (eg, through email, workplaces, at emergency rooms, and in primary care settings). However, studies will be excluded if participants were mandated to take part in the trial.

Interventions

Interventions of interest should consist of a series of text messages sent to participants' mobile phones over a number of weeks. For an intervention to be included, at least two messages should be sent per week, on average. The content of the messages should be focused on behavior change, thus excluding studies where text messages are used only to schedule or remind participants of other activities. Only studies where a text message intervention is the sole intervention will be considered; therefore, studies of interventions where text messages are combined with other interventions (eg, therapy or pharmaceutical treatment) will be excluded.

In cases where the intervention targets multiple behaviors or conditions (eg, smoking and depression), the study report will be included if participants were screened into the trial (ie, nonharmful and nonhazardous drinkers were excluded) and alcohol consumption outcomes are available.

Comparators

Four types of control settings will be considered:

1. Minimal contact and potentially put on a waiting list. For instance, this includes participants allocated to the control setting that were told they would not be given access to the novel intervention, and possibly that they would be given access once the trial was finished.
2. Basic health information. For instance, this includes participants allocated to the control setting that were given basic information about the risks of alcohol at the time of randomization and possibly contacted with similar information at intervals throughout the period, however, at a lower frequency than twice a week, on average.
3. Referred to self-help. For instance, this includes participants allocated to the control setting that were told that they should access a website for more information and help or that they should contact their primary health care provider, etc. Additional contact in the form of reminders at a lower frequency than twice a week, on average, is acceptable.
4. Intervention focusing on something other than alcohol consumption. For instance, this includes participants in the control setting that were given an intervention with content about physical activity, smoking, nutritional intake, etc.

Outcomes

Studies will be included if they measured one of two common alcohol consumption outcomes:

1. Weekly alcohol consumption measured in grams of alcohol. If the outcome is reported in terms of standard units, then it will be converted to grams of alcohol based on the definition reported in the study, or inferred based on the country in which the trial was run.
2. Number of episodes of heavy drinking during the past month. Cutoff points for heavy episodic drinking may differ; however, cutoff points commonly sit at 3 (female) or 4 (male) standard units of alcohol on a single occasion. We will adopt the cutoffs used in the respective studies.

Timing

Length of follow-up will be defined based on time elapsed since randomization. Studies will not be excluded based on the timing of follow-up.

Language

We will include reports in English.

Information Sources

We will search for literature in PubMed, including MEDLINE and PubMed Central; Cochrane Central Register of Controlled Trials (CENTRAL); Cochrane Database of Systematic Reviews (CDSR); Database of Abstracts of Reviews of Effects (DARE); National Health Service Economic Evaluation Database (NHS-EED); Scopus; PsycINFO; PsycARTICLES; Cumulative Index to Nursing and Allied Health Literature (CINAHL); Science Citation Index (ie, Web of Science); Social Sciences Citation Index (ie, Web of Science); and Conference Proceedings Citation Index (ie, Web of Science). Journals in which included literature from the electronic databases are published will be searched, and reference lists of the included studies will be scanned for additional literature.

The following clinical trial registries will be searched: International Standard Randomised Controlled Trial Number (ISRCTN) registry; ClinicalTrials.gov; and the WHO International Clinical Trials Registry Platform (ICTRP). Grey literature will be sourced from the OpenGrey database. PROSPERO will also be searched to identify completed, ongoing, or planned systematic reviews and meta-analyses of relevance. Reports included in any relevant systematic reviews and meta-analyses will also be searched. Finally, authors' personal files will be consulted.

Review Team

MB is the guarantor. A review team consisting of at least three researchers, including MB, will be put together before the search stage begins. The review team will consist of individuals with extensive experience in the development and evaluation of lifestyle interventions.

Textbox 1. Draft of search strategies for PubMed.

Search strategies for PubMed articles:

Strategy 1: (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab])

Strategy 2: (animals [mh] NOT humans [mh])

Strategy 3: (Alcohol* OR Risky Drink* OR Harmful Drink* OR Hazardous Drink* OR Heavy Episodic Drink*)

Strategy 4: mobile* OR mobile phone* OR cell* OR cell phone*

Strategy 5: Text Messaging [mh] OR Text Messag* OR Mobile Messag* OR SMS OR Short Messag* OR Texts

Strategy 6: Strategy 1 NOT Strategy 2

Strategy 7: Strategy 3 OR Strategy 4 OR Strategy 5

Strategy 8: Strategy 6 AND Strategy 7

Search Strategy

A strategy for PubMed will be developed. Once this strategy is finalized, it will be translated to the syntax for the other databases. Medical Subject Headings (MeSH) terms and text words related to alcohol, harmful and hazardous drinking, text messaging, etc, will be used in the search strategies. The Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision) [28], will be used to filter RCTs. A draft of the search strategies can be found in Textbox 1.

Study Records

Data Management and Selection Process

Search results will be input into Mendeley, the reference management software. Initially, the guarantor (MB) will screen the titles and abstracts for duplicates and will also remove reports of studies that are clearly deemed irrelevant for the objective. Reports of studies for which uncertainty exists regarding their relevance will be kept at this stage; removed reports will be shown to the rest of the research team to confirm that nothing has been removed that should be considered for inclusion. Each member of the research team will then independently analyze the full text of the retained studies, deciding which studies to include using the eligibility criteria. If necessary, report authors will be contacted for further information. Disagreements that cannot be resolved will be arbitrated by the guarantor. Excluded and removed studies will be stored for future reference along with an explanation for why they were not included.

Data Collection Process

A data form in MS Excel will be used to record extracted data for each included trial. Each member of the research team will extract data independently. Differences will be discussed among team members and arbitrated by the guarantor, possibly after contacting report authors for further details.

Data Items

Overview

The following quantitative items will be extracted from the trials:

1. Alcohol consumption measures at baseline and follow-up: mean or median and dispersion for weekly alcohol consumption and heavy episodic drinking. Prevalence of risky drinking according to national guidelines.
2. Characteristics of the randomized individuals: for example, age and gender.
3. Trial procedures: for example, number randomized, group sizes, number of responses, trial design, and duration of follow-up.
4. Details of intervention: for example, number of weeks the intervention lasted and average weekly frequency of text messages.

The following qualitative items will be extracted from the trials:

1. Control: the type of control setting used in the trial.
2. Support: the type and source of financial support.

If necessary, outcomes will be extracted or approximated from figures in the reports. We will, as far as possible, extract data from intention-to-treat analyses and remark on trials that do not report on these.

Data Simplifications

Some trials may consist of more than two arms (eg, comparing variations of a text messaging intervention with a single control group). If only one arm fit the eligibility criteria for the proposed review, then we will extract only this arm and the control group. If multiple arms fit the criteria, then they will be combined into one arm, so as to avoid multiple comparisons with the same control group. Likewise, if multiple control groups are utilized with very similar control settings, then they will be combined (ie, weighted mean for continuous outcomes and summing dichotomous outcomes).

Outcomes and Prioritizations

Primary Outcomes

There are two primary outcomes: weekly alcohol consumption and heavy episodic drinking.

Weekly Alcohol Consumption

Reports of weekly alcohol consumption will likely be self-reported via questionnaires or interviews. We expect that two modes of assessing alcohol consumption will be in the majority: either a look-back period approach or a

frequency-intensity approach. Regardless of the method used, we will convert the units to grams per week for each study, an approach used in previous meta-analyses where weekly alcohol consumption has been an outcome.

Heavy Episodic Drinking

Heavy episodic drinking will also likely be self-reported, however, there is usually more homogeneity in how this is collected. Typically, individuals are asked to report the number of times they drank more than 3 (female) or 4 (male) standard units of alcohol on the same occasion over the past month. Some countries include a time period during which the units should have been consumed, however, we will not take any action to account for this difference. What also may differ is the use of fixed-response options (eg, *Once or twice a week*) or a numerical measure. We will convert all data to monthly assessments, converting fixed-response options to numerical measures by taking mean values and multiplying appropriately, for example, *Once or twice a week* would be $(1 + 2)/2 \times 4 = 6$.

Secondary Outcome

The single secondary outcome is prevalence of risky drinking. Definitions vary between countries; however, risky drinking is typically defined as drinking in excess of 7 (female) or 14 (male) standard units of alcohol per week or one or more heavy episodes of drinking per month. The definition of a standard unit differs between countries and typically ranges from 8 to 14 grams of ethanol per unit. We will adopt the definition used in each respective trial.

Risk of Bias in Individual Studies

To assess the risk of bias in each trial, two team members will independently collect information using the Cochrane Collaboration's tool for assessing risk of bias [28,29]. Differences will first be discussed; if no consensus is found, then a third team member will arbitrate. The tool assesses several sources of bias, including selection, performance, detection, attrition, and reporting. This is done by judging the sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, etc. The assessment will result in a *low risk*, *high risk*, or *uncertain risk* classification of each included trial.

The publication in which each included trial was initially published will be scrutinized for predatory behavior, since predatory publications usually apply less rigor in their review practices. If a publication is found to be predatory, either through Cochrane's list of predatory publications or the website Stop Predatory Journals [30], then we will consider removing the trial completely or classifying the trial as *high risk*.

Data Synthesis

Overview

A systematic narrative synthesis will be presented in line with the guidance from the Centre for Reviews and Dissemination [31]. A meta-analysis will be conducted using a random-effects model if at least two included trials are found to be sufficiently homogenous with respect to trial design, intervention, and comparator.

1. The two primary continuous outcomes—weekly consumption and heavy episodic drinking—will be analyzed using weighted mean differences with 95% CI. Transformed data will be back-transformed, and reports of medians will be taken as the best approximator of the mean; ranges will be converted to standard deviations, as described in the Cochrane Handbook for Systematic Reviews [28].
2. The secondary dichotomous outcome will be analyzed in terms of relative risk with 95% CI and pooled in a meta-analysis using Mantel-Haenzel weighting.

Since individuals randomized is the primary unit of analysis, the interclass correlation coefficient will be extracted from reports on cluster randomized trials and results modified according to the Cochrane Handbook for Systematic Reviews.

In studies where outcomes have been assessed more than once, we will use data from the first postintervention analysis. For instance, an intervention might last for 12 weeks and have assessments at 6, 12, and 18 weeks. In this case, the 12-week assessment will be the primary assessment in the meta-analysis. However, all data will be extracted, since subgroup analyses will be conducted for different time frames.

Subgroup and Sensitivity Analyses

If outcome data are available, subgroup analyses will be conducted with respect to age, creating three equal-width categories, and gender. Also, separate analyses will be created for pragmatic groupings of follow-up periods; for instance, we may find that we can define three periods, such as 0-3 months (short), 4-6 months (mid), and 7+ months (long); however, we will leave the exact time frames undefined at this stage.

Sensitivity analyses will be conducted by exploring the effect of removing trials that do not report intention-to-treat analyses, are at high risk of bias due to follow-up attrition or otherwise missing data, have been classified as having a high or uncertain risk of bias due to allocation concealment, have had standard deviation imputed, or employ cluster randomization.

Assessment of Heterogeneity and Publication Bias

Heterogeneity magnitude among trials will be assessed using the I^2 statistic, and significance will be assessed using χ^2 tests (significance level .1). If heterogeneity is found using the Cochrane recommended cutoffs for the I^2 statistic [28], we will explore sources for the heterogeneity. Publication bias assessment using funnel plots will only be considered if at least 10 studies are included. Trial registration databases and protocols will be consulted to ensure that recruitment began after registration and publication of protocols and that the trial conformed to the study design and analysis planned.

Confidence in Cumulative Estimate

By only including RCTs, we will aim for the highest-quality rating according to the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach [28,32]. The highest grade should be given to bodies of evidence that instill confidence that an estimate of effect is close to the quantity of interest. However, downgrading this rating will be necessary after evaluating quality ratings of each outcome, which includes assessment of factors such as imprecision of results and

unexplained heterogeneity. We will report on a final grade of the evidence collected.

Results

The systematic review has not yet begun but is expected to start in May of 2019; publication of the final review and meta-analysis is expected at the end of 2019.

Discussion

The technology for text messaging is ubiquitous in mobile phones; thus, the potential reach of interventions utilizing this technique is great. However, there are no systematic reviews to date, as far as the authors are aware, that limit the scope to the use of text messaging interventions for alcohol consumption reduction. Therefore, the proposed systematic review and meta-analysis will help health practitioners, policy decision makers, researchers, among others, to better understand the effects of these interventions.

Due to the narrowness of the research question, it is likely that only a few studies will be available for inclusion in the proposed review. However, the final review should be interpreted as a summary of current evidence and will be updated when new evidence is made available. The narrative review and meta-analysis is planned to be updated every 2 years.

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Authors' Contributions

MB drafted the manuscript, developed the search and bias assessment strategy and selection criteria, and provided statistical expertise. All members of the systematic review team will contribute to the screening, selection, data extraction, bias assessment, and reporting stages.

Conflicts of Interest

MB owns a private company that develops and distributes lifestyle interventions to be used in health care settings.

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Abbreviations

CDSR: Cochrane Database of Systematic Reviews
CENTRAL: Cochrane Central Register of Controlled Trials
CINAHL: Cumulative Index to Nursing and Allied Health Literature
DARE: Database of Abstracts of Reviews of Effects
GRADE: Grades of Recommendation, Assessment, Development, and Evaluation
GSM: Global System for Mobile communications
ICTRP: International Clinical Trials Registry Platform
ISRCTN: International Standard Randomised Controlled Trial Number
MeSH: Medical Subject Headings
NHS-EED: National Health Service Economic Evaluation Database
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PROSPERO: Prospective Register of Systematic Reviews
RCT: randomized controlled trial
SMS: short message service
WHO: World Health Organization

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Protocol

A Patient-Centered PaTH to Address Diabetes: Protocol for a Study on the Impact of Obesity Counseling

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Abstract

Background: Overweight and obesity are America's number one health concern. The prevalence of obesity in the United States is greater than 36%, a rate that has doubled since 1970. As the second most preventable cause of death, obesity is a risk factor for diabetes, cardiovascular disease, stroke, and cancer, all major causes of death. Primary care clinics may be an ideal setting for weight control interventions to help manage and prevent diabetes. For this reason, the Centers for Medicare and Medicaid Services (CMS) implemented a health care procedure coding system code for intensive behavioral therapy (IBT) for obesity within primary care in 2012 to facilitate payment for addressing obesity, which was followed by broader coverage by most insurers for IBT for adults in 2013. However, the impact of this coverage on patient-centered outcomes is largely unknown.

Objective: The overarching goal of this study is to understand the comparative effectiveness of obesity counseling as covered by CMS and other insurers in improving weight loss for adults either with or at increased risk for type 2 diabetes.

Methods: This study leverages the novel infrastructure of the Patient-Centered Outcomes Research Institute–funded PaTH Clinical Data Research Network. The PaTH network is comprised of Geisinger Health System, Johns Hopkins University, Johns Hopkins Health System, Lewis Katz School of Medicine at Temple University, Temple Health System, Penn State College of Medicine, Penn State Milton S Hershey Medical Center, University of Pittsburgh, UPMC and UPMC Health Plan, and the University of Utah. Electronic health record (EHR) data will originate from the 6 PaTH health systems. Specifically, we will (1) evaluate the impact of broader preventive service coverage for obesity screening and counseling on weight loss, diabetes incidence, and diabetes outcomes in patients with diabetes or at increased risk for diabetes (defined by body mass index [BMI] ≥25). We will determine how the annual probability of receiving obesity and/or nutritional counseling changed pre- and postpolicy across all insurers in a cohort of patients with diabetes and at high risk for diabetes. We will (2) compare patient weight loss and diabetes-related outcomes among those who receive obesity screening and counseling with those who do not, following implementation of preventive service coverage. We will examine postpolicy impact of obesity screening and counseling in a cohort of patients with diabetes and at increased risk for diabetes. Specific outcomes to be examined include weight loss, diabetes incidence, and diabetes outcomes. Exploratory outcomes will include patient-reported outcomes. Furthermore, we will determine patient characteristics, including demographics, and practice characteristics, including provider type.

Results: Our PCORI-funded study is underway. To date, we have obtained our second data extraction from the PaTH CDRN and are performing data editing and cleaning. Next steps include analysis of early policy change.

Conclusions: Given patients who are overweight are at highest risk for diabetes, improved weight management services could prevent diabetes and its negative health outcomes. Comparing weight and diabetes outcomes in 3 states using EHRs and claims data before and after this policy was implemented using the PaTH Network will allow important insight into policy effectiveness.

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KEYWORDS

diabetes complications; obesity; electronic medical record

Introduction

Background

Overweight and obesity are America's number one health concern. The prevalence of obesity in the United States is greater than 36% [1], which is far above the Healthy People 2020 objective of less than 30.5% [2]. Perhaps, the most concerning is the rate in which obesity has increased, having doubled since 1970 [3]. As the second most preventable cause of death [4], obesity is a risk factor for diabetes, cardiovascular disease, stroke, and cancer, all major causes of death in the United States [5]. Addressing obesity through lifestyle interventions decreases the risk of developing type 2 diabetes, a disease which affects over 29 million people (9.3% of the US population) [6]. Diabetes is associated with serious complications, including cardiovascular disease, blindness, renal failure, and lower extremity amputation. Although complications are preventable with proper medical and lifestyle management, including weight loss, nearly half of the patients with diabetes do not maintain adequate glycemic control [7].

Primary care clinics may be an ideal setting for weight control interventions. More than 80% of Americans see a primary care physician (PCP) regularly, and access to primary care is expected to increase with health care reform [8]. Furthermore, as PCPs identify and treat a multitude of conditions affected by being overweight, including diabetes, they are ideally positioned to best engage their patients in weight management. In 2012, the Centers for Medicare and Medicaid Services (CMS) implemented a health care procedure coding system code for intensive behavioral therapy (IBT) for obesity within primary care settings to facilitate payment for addressing obesity, which was followed by universal coverage among nongrandfathered private plans without cost sharing for adults of all ages in 2013, a key provision of the Affordable Care Act [9-11]. The rate of uptake of the Medicare obesity benefit within the first 2 years of implementation was small (0.10% and 0.17%, respectively) among beneficiaries. However, the updated impact of this policy coverage on patient-centered outcomes across insurers remains largely unknown.

This study leverages the novel infrastructure of the Patient-Centered Outcomes Research Institute (PCORI)–funded PaTH Clinical Data Research Network (CDRN), a partnership of 4 mid-Atlantic academic health systems (Penn State Hershey Medical Center, University of Pittsburgh Medical Center, Temple Health System, and Johns Hopkins Health System) that has established governance to operate as an integrated research network. In 2015, the University of Utah and Geisinger Health System also joined PaTH, creating an electronic health record (EHR)–based data infrastructure across 3 states (Maryland, Pennsylvania, and Utah).

This study is significant for several reasons. First, diabetes is a leading public health concern and is associated with significant economic burden. Recent health policy changes (eg, CMS coverage) are expected to impact diabetes outcomes, and this study will capture differences in these outcomes through varied state implementation. Understanding effects on diabetes outcomes can inform future policies to improve overall diabetes care for patients. Second, this study focuses on the influence of policy-level factors for diabetes management. Poor outcomes are preventable but require complex medical and lifestyle management, including careful diet modification, medication use including oral pills and/or insulin injections, blood glucose self-monitoring, frequent medical visits and laboratory testing, cholesterol management, weight management, and physical activity. The ability of individuals with diabetes to effectively manage their diabetes is multifactorial, influenced by individual-, social-, and policy-level factors [12]. Finally, we have an additional focus on rural/urban differences in provision of obesity screening and counseling and the resultant impact on weight loss and diabetes incidence.

Objectives

The overarching goal of this study was to understand the comparative effectiveness of obesity counseling as covered by CMS in improving weight loss for adults either with or at increased risk for type 2 diabetes. CMS and most insurers now include obesity screening and counseling benefits, with no cost sharing to patients [9]. As patients who are overweight are at highest risk for diabetes, improved weight management services could prevent diabetes and its negative health outcomes. CMS beneficiaries with obesity are eligible for up to 20 face-to-face visits for weight counseling in the primary care setting, although total visits may vary for other insurers. We will compare weight and diabetes outcomes in 3 states using EHRs and claims data before and after this policy was implemented. Using the PaTH CDRN infrastructure, the study will aim to do the following:

- Aim 1: The study will evaluate the impact of broader preventive service coverage for obesity screening and counseling on weight loss, diabetes incidence, and diabetes outcomes in patients with diabetes or at increased risk for diabetes (defined by body mass index [BMI] ≥25). We will

determine how the annual probability of receiving obesity counseling (as defined by Common Procedural Treatment [CPT] codes G0447, G0473, S9470, and/or S9449) changed pre- and postpolicy across all insurers in a cohort of patients with diabetes and at increased risk for diabetes. We hypothesize that individual patients are more likely to receive counseling following coverage implementation. Furthermore, we hypothesize that patients who receive a greater number of face-to-face visits will have greater weight loss compared with those who receive fewer visits. Exploratory outcomes will include patient-reported outcomes (PROs).

- Aim 2: The study will compare patient weight loss and diabetes-related outcomes among those who receive obesity screening and counseling with those who do not, following implementation of preventive service coverage. We will examine postpolicy impact of obesity screening and counseling in a cohort of patients with diabetes and at increased risk for diabetes. Specific outcomes to be examined include weight loss, diabetes incidence, and diabetes outcomes (including hemoglobin A_{1c} [HbA_{1c}], controlled blood pressure, and use of a statin medication). Exploratory outcomes will include PROs. Furthermore, we will determine patient characteristics, including demographics (age, race/ethnicity, and rurality), and practice characteristics, including provider type, and their impact on receiving/providing obesity screening and counseling. Understanding patient and practice characteristics most likely to engage in obesity counseling can identify best practices and inform how to increase engagement by both patients and providers.

Methods

Preliminary Studies

PaTH Clinical Data Research Network

The PaTH CDRN provides an infrastructure for pragmatic clinical trials and observational studies that require populations beyond a single health system to answer important patient-centered clinical and health services questions [13]. Funded by the PCORI in March 2014, the PaTH CDRN is one of 11 CDRNs across the country. Along with 18 Patient-Powered Research Networks, these 11 CDRNs form the National Patient-Centered Clinical Research Network (PCORnet)—a national network for conducting clinical outcomes research [14]. The goal of PCORnet is to improve the nation's capacity to conduct comparative effectiveness research by creating a large, highly representative network from which to draw data, while protecting patient privacy and ensuring data security.

The patients in the PaTH network are diverse—22% are aged 17 years or younger and 20% are aged 65 years or older. Over 25% are nonwhite and 20% have public insurance (excluding Medicare) or no insurance. The organizations are also diverse and are affiliated with community-based hospitals and outpatient practices in addition to their academic hospitals. Other facilities include rehabilitation hospitals, dialysis centers, fitness and wellness centers, psychiatric hospitals, ambulatory surgery centers, and home health care support.

PaTH leverages health-related data from (1) EHRs, (2) PROs, (3) insurance claims data, and (4) biospecimen data. The PaTH data that will be used in the study will be limited to EHR data and claims data.

The PaTH network has also established a centralized process for institutional review board (IRB) reviews. Creating separate IRB protocols with different formats and procedures to be reviewed by separate IRBs would be an inefficient and ineffective process. This problem has been recognized by the National Institutes of Health, which promotes use of a single IRB in multisite clinical research studies to reduce duplication of effort, speed-up the initiation of important research, and save time and resources [15]. To this end, the PaTH network has established a reliance agreement naming Johns Hopkins' IRB as our central IRB of record. Under the reliance agreement, the other institutions agree to allow the Johns Hopkins' IRB to review the study protocol and to honor the approval of the protocol. To ensure that each PaTH institution would have input into the review process, we convened the PaTH Network Protocol Review Committee (PNPRC). A total of 2 IRB members from each institution serve on the PNPRC, an IRB member and a community member, currently totaling 8 members. After the PNPRC approves a PaTH protocol, it is then submitted to the Johns Hopkins' IRB for centralized review.

Data Sources for All Aims

Electronic Health Records/PaTH Clinical Data Research Network

EHR data will originate from the 6 PaTH health systems. These health systems have greater than 13 million patients with at least one encounter and 5 million active patients in their EHR systems (see Table 1).

PaTH has united previously disconnected health care systems with a common, scalable data architecture. Our health systems employ the 2 most commonly used EHR systems nationwide—Epic and Cerner. Penn State uses Cerner; University of Pittsburgh Medical Center (UPMC) uses Epic for its outpatient EHRs and Cerner for its inpatient EHRs; and Temple, Johns Hopkins, Geisinger, and the University of Utah use Epic. The health systems also incorporate data from ancillary Information Technology (IT) systems including Eclipsys, General Electric, AllScripts, and Phillips. Each EHR system has undergone extensive customization during their lifetimes, creating disparate systems with inherent interoperability gaps across all areas including diagnosis, lab results, and patient demographic data.

All health systems are using, or will use, the following standards to achieve semantic interoperability for their EHRs and ancillary systems: LOINC for encoding laboratory tests; Systematized Nomenclature of Medicine (SNOMED) for medical terminologies; CPT and International Classification of Diseases (ICD)-9 and ICD-10 for encoding problems, diagnoses, and procedures; RxNORM for encoding medications; and DICOM for transmitting radiologic images. Given the heterogeneity of

the EHRs, the PaTH network sought an existing solution that permits intersystem syntactic interoperability and leverages previous investments and expertise.

Table 1. Patient population overview at individual clinical sites.

Clinical Site Criteria[a,b]	Penn State Hershey	Pitt/UPMC[c]	TUHS[d]	Hopkins	University of Utah
EHR[e] platform	Cerner	Cerner (inpatient); Epic (outpatient)	Epic	Epic	Epic
Distinct patients with at least 1 encounter or record in HER, n	615,012	5,537,583	457,388	4,800,000	1,602,245
Active patients with data in EHR, n	520,310	1,880,457	323,682	1,764,221	581,568

[a]Geisinger Health System was added to the PaTH Clinical Data Research Network (CDRN) after submission of this proposal.

[b]Data pulled in 2015 from i2b2 at each site.

[c]UPMC: University of Pittsburgh Medical Center.

[d]TUHS: *Temple University Health System.*

[e]EHR: electronic health record.

Each health system's efforts to utilize standard vocabularies and formats can significantly narrow the gap of interoperability, but the final bridge is the PCORnet-specified Common Data Model (CDM) [16]. The PCORnet CDM enables us to transform each health care system's dialect into a common language standardized on the meaningful use–recommended vocabularies (SNOMED, RxNORM, and LOINC). The PCORI CDM provides specifications for what common data elements each CDRN must include at a minimum and standardizations for how they are to be named and mapped in a consistent format (eg, with the same variable name, precision, and other metadata) within standard health care terminologies to ensure interoperability within sites and between networks. The PaTH network is in compliance with PCORnet CDM version 1.0 and is moving to conform to the recently released CDM version 2.0. All of the 11 PCORnet CDRNs are required to define at least 1 million patients by Fall 2015, which includes patients with complete data and data specifications in compliance with the latest update of the PCORnet CDM creating a large network of networks, all with data mapped to a consistent format.

Once the PaTH research team cooperatively identifies data elements appropriate for the prespecified research questions, extract, transform, load teams at each site extract these data elements from their EHRs or ancillary systems, deidentify the data, map these data to standard vocabularies as specified by the PCORnet CDM and any additional PaTH data element specifications, and load the data to Pittsburgh's Comparative Effectiveness Research Core Data Center (CERC-DC), which provides secure data storage and high-throughput computing.

The informatics design of PaTH has 2 main features: (1) the ability to support researchers to easily perform exploratory research queries (ie, counts) through the distributed data network and (2) the ability to support use of aggregated deidentified data that conform to our shared PaTH information model. Currently, the PaTH network uses the University of Pittsburgh CERC-DC to house these aggregated datasets. One important feature in this model is that it incorporates authorization and audit mechanisms to ensure that each site retains adequate control and logs of their data. The additional data integration with contextual data and the associated data flow for this study is described in Figure 1.

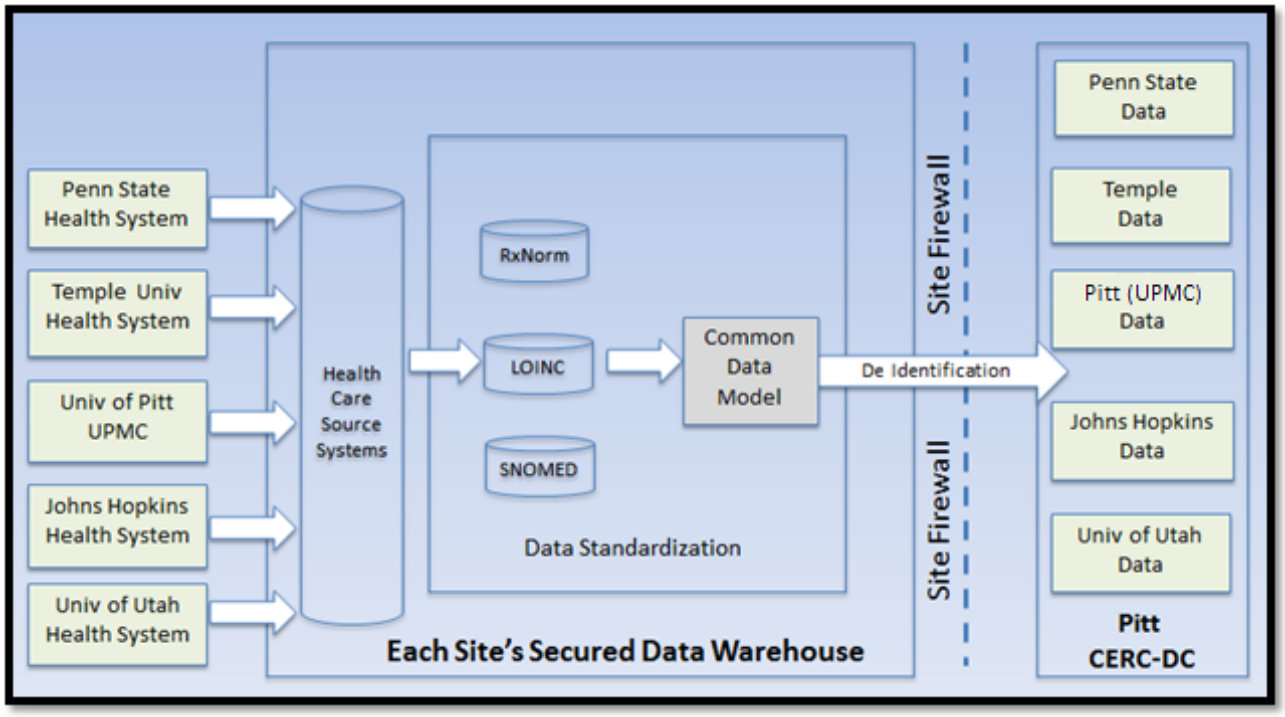
Claims Data

A limitation of EHR data is the uncertainty of its completeness, that is, when a patient receives medical care outside of the health system or is hospitalized while away on vacation. However, claims data can capture clinical encounters that occur outside of our 6 health systems. Claims data also provide other supplementary information—for example, the EHR only tells us a patient was prescribed a statin medication but not whether the patient picked it up from the pharmacy. The insurance data can verify whether a pharmacy claim for the medication was processed, indicating the patient received the medication.

Secure Sharing of Deidentified Integrated Patient Data for Analysis

The PaTH network has established an operational data infrastructure with the necessary technical safeguards as agreed upon in the PaTH Data Use Agreement for sharing and analyzing data while addressing data confidentiality and security concerns. PaTH has deployed 2 mechanisms for storing, protecting, and sharing data (as described previously under PaTH governance and regulatory issues): (1) data with protected health information (PHI) are stored and protected behind each institution's firewall in the distributed data network and (2) deidentified data are sent to the PaTH data center at the University of Pittsburgh (CERC-DC). Once data integration is accomplished at each site, sites will remove all PHI and send the deidentified version of the integrated data to the CERC-DC through PaTH's virtual private network/secure file transfer protocol, which has been operational for data transmission since November 2014. Data analysis will then be performed via secure remote computing using standard statistical software packages (eg, SAS developed by the SAS Institute).

Figure 1. PaTH network data integration scheme for the proposed project. CERC-DC: Comparative Effectiveness Research Core Data Center; SNOMED: Systematized Nomenclature of Medicine; UPMC: University of Pittsburgh Medical Center.



PaTH Patients With Diabetes and At Increased Risk for Diabetes

The PaTH CDRN data infrastructure is designed to support a broad range of research topics, with the ability to define specific patient cohorts when needed to support specific use case research questions. This study utilizes 2 patient cohorts: (1) diabetes cohort and (2) at increased risk for diabetes cohort. As demonstrated in Tables 2 and 3, the PaTH network includes over 328,000 patients with a diagnosis of diabetes (defined as aged 18 years and older with a diagnosis of diabetes mellitus—ICD-9 250.xx) and over 2 million patients at increased risk for diabetes (defined as aged 18 years and older with a BMI of ≥25). We recognize use of BMI ≥25 is a limited definition for patients at increased risk for diabetes, particularly when used across all racial and ethnic groups. However, given that only patients with obesity (BMI ≥30) would be eligible for IBT, this threshold allows for appropriate inclusion of patients with future opportunity for narrowing the definition. In addition, we have demonstrated our preliminary results of several of the Healthy People 2020 objectives, which will serve as outcomes for the study (see Table 4), indicating the feasibility and accessibility of these data. For this study, receipt of IBT will include the presence of the G0447, G0473, S9470, and/or S9449 CPT codes with a diagnosis of obesity (278.00, 278.01, 278.03, and 278.01, respectively; V85.3-V85.4) consistent with regulatory requirements.

Table 2. Preliminary data of PaTH patients with diabetes.

Patient characteristics[a,b]	Penn State University (N=25,219), n (%)	University of Pittsburgh (N=150,589), n (%)	Johns Hopkins University (N=60,324), n (%)	Temple University (N=40,536), n (%)	University of Utah (N=51,787), n (%)	PaTH total (N=328,455), n (%)
Insurance type						
Private	9874 (38)	60,223 (40)	32,371 (54)	5261 (13)	21,264 (41)	128,993 (39)
Medicaid	1890 (8)	10,165 (7)	727 (1)	21,759 (54)	4189 (8)	38,730 (12)
Medicare	12,998 (52)	54,675 (36)	22,826 (38)	10,916 (27)	23,997 (46)	125,412 (38)
Uninsured	457 (2)	11,625 (8)	485 (1)	2599 (6)	2337 (5)	17,503 (5)
Race						
White	21,780 (86)	116,056 (77)	32,544 (54)	14,347 (35)	39,580 (76)	224,307 (68)
African American	1679 (7)	15,336 (10)	20,053 (33)	14,656 (36)	944 (2)	52,668 (16)
Other	1760 (7)	19,197 (13)	7727 (13)	11,533 (29)	11,263 (22)	51,480 (16)
Hispanic ethnicity	1054 (4%)	697 (0.5)	2002 (3)	7356(18)	6077 (12)	17,186 (5)
Female gender	12,014 (48)	70,623 (47)	30,912 (51)	22,485 (55)	25,727 (50)	161,761 (49)

[a]Geisinger Health System was added to the PaTH Clinical Data Research Network (CDRN) after submission of this proposal.

[b]Data pulled in 2015 from i2b2 at each site.

Table 3. Preliminary data of PaTH patients at increased risk for diabetes.

BMI[a,b,c]	Penn State University (N=167,799), n (%)	University of Pittsburgh (N=950,020), n (%)	Johns Hopkins University (N=471,860), n (%)	Temple University (N=212,314), n (%)	University of Utah (N=260,506), n (%)	PaTH total (N=2,062,499), n (%)
25-29.9	69,353 (30)	433,799 (31)	226,113 (32)	92,807 (31)	122,583 (31)	944,655 (32)
30-34.9	48,353 (21)	268,236 (19)	128,799 (18)	60,330 (20)	87,023 (22)	592,741 (20)
35-39.9	25,388 (11)	128,113 (9)	58,072 (8)	29,930 (10)	70,774 (18)	312,277 (10)
40+	24,705 (11)	94,550 (7)	43,377 (6)	23,321 (8)	25,410 (7)	211,363 (7)

[a]Geisinger Health System was added to the PaTH Clinical Data Research Network (CDRN) after submission of this proposal.

[b]Data pulled in 2015 from i2b2 at each site.

[c]BMI: body mass index.

Table 4. Preliminary data of Healthy People 2020 objectives for PaTH patients with diabetes (N=328,455) and at increased risk for diabetes (N=2,062,499).

Patient characteristics[a,b]	Across PaTH, n (%)	Healthy People 2020	
		Baseline (%)	Goal (%)
Patients with diabetes			
With controlled diabetes (ie, HbA_{1c}[c]<7)	80,486 (25)	53.5	58.9
With uncontrolled diabetes (ie, HbA_{1c}>9)	47,701 (15)	17.9	16.1
With controlled blood pressure (ie, <140/90)	123,038 (38)	51.8	57
On a statin medication	132,841 (40)	__[e]	__[e]
With annual urinary microalbumin	65,180 (20)	33.6	37
With ≥2 HbA_{1c} values during past year	67,797 (21)	64.6	71.1
Patients at increased risk for diabetes			
BMI[d]			
18.5-24.9	934,664 (31)	30.8	33.9
25-29.9	944,655 (32)	—	—
30+ (obese)	1,116,381 (37)	33.9	30.5
Percentage obese (BMI ≥30) who receive nutrition counseling (CPT[f] codes 97802, 97803, 97804, G0270, G0271)	10,717 (1)	—	—
Percentage without diagnosis of diabetes (ICD-9[g] 250.xx) but with ≥1 A_{1c}	179,412 (16)	—	—
Percentage with diagnosis of hypertension (ICD-9 401) who receive nutrition counseling (CPT codes 97802, 97803, 97804, G0270, G0271)	6747 (<1)	—	—

[a]Does not include data from Geisinger.

[b]Data pulled in 2015 from i2b2 at each site.

[c]HbA_{1c}: hemoglobin A_{1c}.

[d]BMI: body mass index.

[e]Not applicable.

[f]CPT: Common Procedural Treatment.

[g]ICD-9: International Classification of Diseases, Ninth revision.

Research Design

The overarching goal of this research was to understand the comparative effectiveness of obesity counseling as covered by CMS in improving weight loss for adults either with or at increased risk for type 2 diabetes**.** Using the PaTH Network infrastructure, we will examine the impact of the policies on a population of more than 328,000 patients with diabetes, as well as an additional 2,000,000 patients at increased risk for the development of diabetes.

Aim 1: Overview

Evaluate the impact of broader preventive service coverage for obesity screening and counseling on weight loss, diabetes incidence, and diabetes outcomes in patients with diabetes or at increased risk for diabetes (defined by BMI ≥25). We will determine how the annual probability of receiving obesity and/or nutritional counseling (as defined by CPT code) changed pre- and postpolicy across all insurers in a cohort of patients with diabetes and at increased risk for diabetes. We hypothesize that individual patients are more likely to receive counseling following coverage implementation. Furthermore, we hypothesize that patients who receive a greater number of face-to-face visits will have greater weight loss compared with those who receive fewer visits. Exploratory outcomes will include PROs, as outlined in Table 5.

Weight loss is an important patient-centered outcome, as nearly every patient with overweight/obesity desires weight loss and assistance from their physician but few currently receive it [17-21]. Furthermore, our CDRN patient partners indicated that weight loss and diabetes incidence are significant patient-centered outcomes.

HbA_{1c} also remains an important patient-centered outcome, given it is well-established that improved glycemic control results in prevention of serious complications (cardiovascular disease, blindness, renal failure, and lower extremity amputation) and is appropriate for the timeframe of the study. In addition, we will examine blood pressure control, use of a statin medication, and appropriate diabetic screening, given the importance of these guideline-recommended measures in diabetes care. Exploratory outcomes will include PROs (including *Patient-Reported Outcomes Measurement Information System*, Short Form-12, and Patient Heath Questionnaire) listed in Table 5, which are available at some of our sites across the CDRN.

Table 5. Outcomes for the diabetes and at increased risk for diabetes cohorts.

Outcomes	Definition	Notes
Diabetes cohort		
Weight loss during counseling	Weight lost from first intensive behavioral therapy (IBT) visit to final IBT visit	Available at all PaTH sites
Weight loss maintenance	Percentage of weight lost during program and maintained over remaining time period, reported by year	Available at all PaTH sites
Patient-reported outcomes (PROs)	Short Form-12 (SF-12); Patient Health Questionnaire (PHQ-2, PHQ-8, PHQ-9; physical function; Sleep; Fruit and vegetable consumption; Social support; Physical activity; *Patient-Reported Outcomes Measurement Information System(* PROMIS; PROMIS 29, physical function, depression); Healthy lifestyles; Patient-reported medication reconciliation	Available at some sites—formal inventory of PROs will be collected at each institution at the beginning of the project, to be included as secondary outcomes
Uncontrolled diabetes	Average A_{1c}>9 or no A_{1c}	Available at all PaTH sites
Controlled blood pressure	Systolic blood pressure <140, diastolic blood pressure <90, averaged across values over a year	Available at all PaTH sites
On a statin medication	Evidence of a statin medication on current electronic health record medication list	Available at all PaTH sites
Receiving annual eye exam	Documentation of eye exam once in past year	Available at all PaTH sites
Receiving annual urinary microalbumin test	Documentation of lab testing for urinary microalbumin at least once in past year	Available at all PaTH sites
Lower extremity amputations	Documentation of procedure for lower extremity amputation or billing code through health plans in past year	Available at all PaTH sites
Diabetes Service Use	-Clinic visit with primary or secondary diagnosis of diabetes; Emergency department visit with primary or secondary diagnosis of diabetes; Hospitalization with primary or secondary diagnosis of diabetes	Available at all PaTH sites
At increased risk for diabetes cohort		
Weight loss during counseling	Weight lost from first IBT visit to final IBT visit	Available at all PaTH sites
Weight loss maintenance	Percentage of weight lost during program and maintained over remaining time period, reported by year	Available at all PaTH sites
Diabetes incidence	Percentage of patients who develop diabetes per year following weight counseling	Available at all PaTH sites
PROs	-SF-12; PHQ-2, PHQ-8, PHQ-9; Physical function; Sleep; Fruit and vegetable consumption; Social support; Physical activity; PROMIS (PROMIS 29, physical function, depression); Healthy lifestyles; Patient-reported medication reconciliation	Available at some sites—formal inventory of PROs will be collected at each institution at the beginning of the project, to be included as secondary outcomes
Exposure variables		
Individual level	-Sociodemographics (eg, age, sex, race, insurance status, and rural vs urban); Medical comorbidities	Available at all PaTH sites
Provider/practice level	-Practitioner type (advanced practice vs MD/DO); Practitioner specialty; Practice size (number of providers); Practice type (multispecialty, academic); Practice setting (rural vs urban)	To be determined

Diabetes Cohort Definition

During year 1 of the proposed project, the investigative team, in collaboration with the PaTH Network, will identify a valid cohort of patients with type 2 diabetes. The cohort of patients under study will be defined as all patients aged 18 years and older with an indication of type 2 diabetes during the proposed study timeframe. Patients will be classified as having diabetes using a clinically validated algorithm: type 2 diabetes mellitus on the problem list, diabetes-specific medications, HbA_{1c} results >7.0%, or 1 inpatient diagnosis code or 2 out-patient diagnosis codes for type 2 diabetes (ICD-9 codes 250.xx). This algorithm has been shown to have 98% sensitivity and 98% specificity for diabetes when compared with the gold standard of manual chart review by a trained research nurse [22]. The diabetes cohort will be further limited to patients who will likely be captured in the PaTH EHRs or claims data so that outcome assessments can occur. Thus, we will further limit the diabetes cohort to patients who have either (1) had at least 2 outpatient primary care visits in 1 of the PaTH health systems in the past

3 years (since January 1, 2012) or (2) for whom claims data are available. The cohort will be dynamic, with new patients added into the cohort after 2015 as they meet the diabetes cohort definition prospectively. The observational period for the outcome variables will be for the 10-year period from 2009 to 2019, thus including 3 years of data before the first policy change (CMS instituting coverage for IBT for obesity) and 3 years after the last policy change (Pennsylvania Medicaid expansion) under study (Figure 2).

Definition and Measurement of Key Diabetes Outcomes and Covariates

Key individual-level diabetes outcomes relate to the Healthy People 2020 diabetes objectives (Table 6). Diabetes outcomes will be assessed through PaTH EHRs and supplemented by claims data when available. Key exposure variables will include individual-level variables (sociodemographics and medical comorbidities) and state of residence (to capture state-specific variation in policy implementation).

Following the definition of the diabetes cohort and key diabetes outcomes and covariates as described above, an initial extraction of variables will be conducted in year 2 of the proposed project for years 2009 to 2015. This early data extraction from the PaTH Network will allow for cohort validation and data cleaning and editing, as well as required programming and determination of the analysis models. We will utilize this initial data extraction in years 2 and 3 to analyze the impact of broader coverage for intensive behavioral counseling. The final data extraction will occur during the final quarter of year 4 of the proposed project, allowing for completion of a 10-year time period (2019).

As older adults have various degrees of comorbidity conditions, the American Diabetes Association (ADA) developed a framework (Table 7) considering treatment goals for glycemic control, blood pressure, and dyslipidemia in older adults with diabetes [23,24]. Therefore, we will conduct subgroup analysis in older adults according to these recommendations. In this population, individualized A_{1c} targets were recommended by ADA: <7.5%, 8%, and 8.5% for healthy, complex/intermediate, and very complex/poor health patients, respectively. However, the classification of health status was subjective, and not every patient will clearly fall into a specific category (eg, cognitive function and functional limitations). For the purpose of this study, we will conduct subgroup analysis in older adults using individualized A_{1c} targets based on presence of complications: individuals without diabetic-related complications (A_{1c} level, <7.5%) and those with diabetic-related complications (A_{1c} level, <8.0%). Complications may include arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, stroke, oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer. Those conditions may cause significant symptoms or impairment of functional status and significantly reduce life expectancy.

Figure 2. Timeline for Affordable Care Act and Centers for Medicare and Medicaid Services policy changes. ACA: Affordable Care Act; CMS: Centers for Medicare and Medicaid Services.

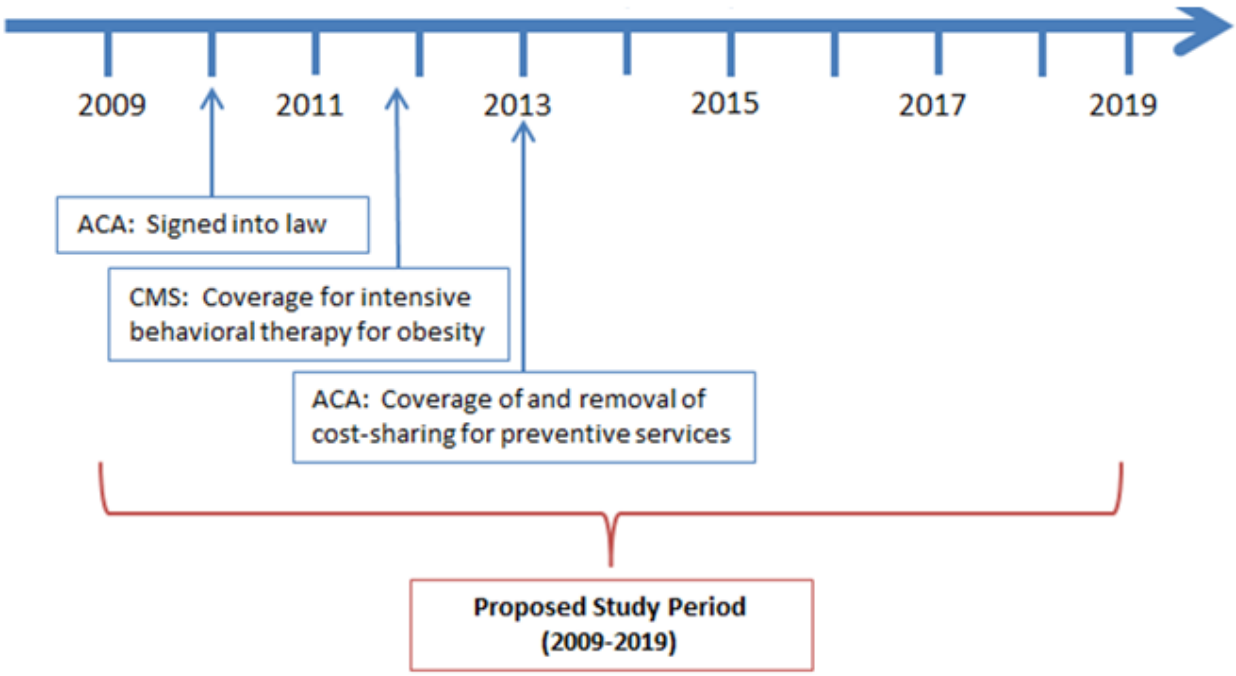


Table 6. Aim 1: key diabetes outcomes and covariates.

Diabetes outcomes (extracted annually)	Definition
Individual-level outcomes	
Controlled diabetes (HP obj D-5)	Average A_{1c}<7 (LOINC: 4548-4)
Uncontrolled diabetes (HP obj D-5)	Average A_{1c}>9 or no A_{1c} measurement in past year (LOINC: 4548-4)
Controlled blood pressure (HP obj D-7)	SBP[a]<140, DBP[b]<90, averaged across values over year
On a statin medication (HP obj D-6)	Evidence of a statin medication on current EHR[c] medication list
Receiving annual eye exam (HP obj D-10)	Documentation of eye exam once in past year
≥2 A_{1c} tests each year (HP obj D-11)	Documentation of lab testing for A_{1c} (LOINC: 4548-4)
Receiving annual urinary microalbumin test (HP obj D-12)	Documentation of lab testing for urinary microalbumin at least once in past year (LOINC: 14957-5)
Lower extremity amputations (HP obj D-4)	Documentation of procedure for lower extremity amputation or billing code through health plans in past year
Exposure variables	
Individual level	Sociodemographics (eg, age, sex, race, and insurance status); Medical comorbidities
Policy level	CMS[d] and other insurer implementation

[a]SBP: systolic blood pressure.

[b]DBP: diastolic blood pressure.

[c]EHR: electronic health record.

[d]CMS: Centers for Medicare and Medicaid Services.

Table 7. American Diabetes Association Framework for considering treatment goals in older adults with diabetes.

Patient characteristics	ADA[a] rationale	Reasonable A_{1c} goal[b] (%)	Blood pressure (mmHg)
Healthy (few coexisting chronic illnesses[c])	Longer remaining life expectancy	<7.5	<140/90
Complex/intermediate (3+ coexisting chronic illnesses[c])	Intermediate remaining; life expectancy, high treatment burden, hypoglycemia, vulnerability, and fall risk	<8.0	<140/90
Very complex/poor health (long-term care or end-stage chronic illnesses[d]	Limited remaining life expectancy makes benefit uncertain	<8.5	<150/90

[a]ADA: American Diabetes Association.

[b]A lower A_{1c} goal may be set for an individual if achievable without recurrent or severe hypoglycemia or undue treatment burden.

[c]Coexisting chronic illness are conditions serious enough to require medications or lifestyle management and may include arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke.

[d]The presence of a single end-stage chronic illness, such as stages 3 and 4 congestive heart failure or oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer.

Aim 2: Overview

Compare patient weight loss and diabetes-related outcomes among those who receive obesity screening and counseling to those who do not, following implementation of preventive service coverage. We will examine postpolicy impact of obesity screening and counseling in a cohort of patients with diabetes and at increased risk for diabetes. Specific outcomes to be examined include weight loss, diabetes incidence, and diabetes outcomes (including HbA_{1c}, controlled blood pressure, and use of a statin medication). Exploratory outcomes will include PROs. Furthermore, we will determine patient characteristics, including demographics (age, race/ethnicity, and rurality), and practice characteristics, including provider type, and their impact on receiving/providing obesity screening and counseling. Understanding patient and practice characteristics most likely to engage in obesity counseling can identify best practices and inform how to increase engagement by both patients and providers.

At Increased Risk Cohort Definition

The cohort of patients under study will be defined as patients aged 18 years and older who are at increased risk for the development of diabetes based on being overweight. Patients seen at one of the PaTH institutions will be included in the at increased risk cohort if they have a BMI ≥25 kg/m^2, based on most recent recorded weight and at least one recorded height. The at increased risk cohort will be further limited to patients who will likely to be captured in the PaTH EHRs or claims data

so that outcome assessments can occur. Thus, we will further limit the at increased risk cohort to patients who have either (1) had at least 2 outpatient primary care visits in one of the PaTH health systems in the past 3 years (since January 1, 2012) or (2) for whom claims data is available. The cohort will be dynamic, with new patients added into the cohort after 2015 as they meet the at increased risk cohort definition prospectively. Patients will not be removed from the cohort even if they are no longer overweight. The observational period for the outcome variables will be for the 10-year period from 2009 to 2019, thus including 3 years of data before the first policy change (CMS instituting coverage for IBT for obesity) under study (see Figure 2).

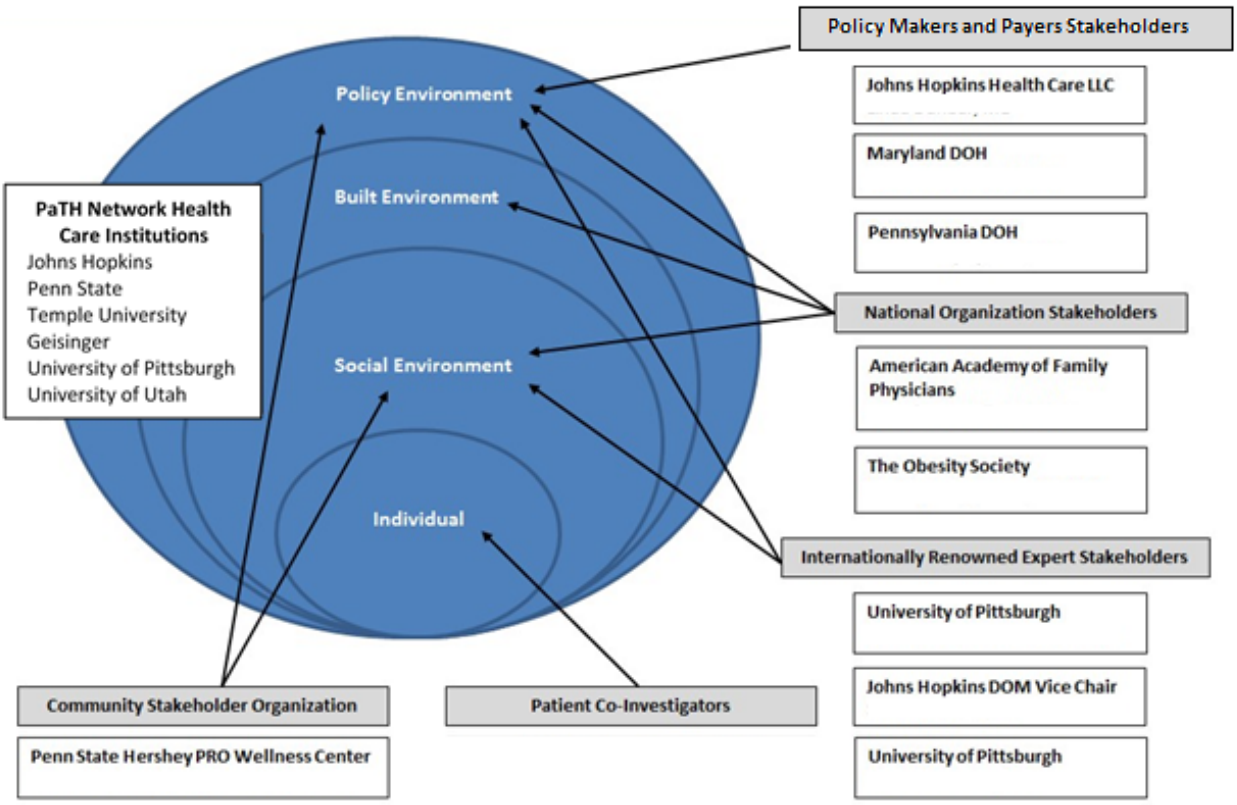
Definition and Measurement of Key Diabetes Outcomes and Covariates

The key diabetes prevention outcomes in this aim will be assessed on the population level. Specifically, we will examine (1) the impact of broader coverage for intensive behavioral counseling for obesity on counseling receipt in patients aged ≥65 years and (2) the impact of intensive behavioral counseling for obesity on counseling receipt in patients aged <65 years. Receipt of counseling for obesity will be assessed through PaTH EHRs and supplemented by claims data when available, utilizing G0447, G0473, S9470, and/or S9449 CPT codes in combination with a diagnosis of obesity (278.00, 278.01, 278.03, and 278.91, respectively; V85.3-V85.4). Key exposure variables will include individual level variables (sociodemographics and medical comorbidities). Medical comorbidities will be assessed using a modified Charlson Comorbidities Index adapted for use with the EHR.

Stakeholder Engagement

We have created this research study with a focus on patient centeredness in all aspects of the research design. The following model (Figure 3) takes the conceptual framework and overlays the Stakeholder Advisory Board members' expertise and their reach on both a regional and national level. As demonstrated, we have focused stakeholders on every layer of the model, ensuring successful engagement in all aspects necessary for the project. For example, we have 3 stakeholders with expertise and reach into the policy environment, including the Departments of Health from both Maryland and Pennsylvania. Representation from National Professional Organizations, including the American Academy of Family Physicians and The Obesity Society, offers expertise in policy, built, and social environments, in addition to networks for dissemination. Our engagement of internationally renowned diabetes researchers will offer important insight into shaping the research in all aspects and offering important assistance in dissemination. The tremendous reach of the Penn State Hershey PRO Wellness Center's state-wide Advisory Board allows further expertise from patient-centered organizations and avenues for future dissemination. We will also include 6 PCPs who serve on the frontlines of this policy change.

Figure 3. Conceptual framework and stakeholder advisory board members' expertise. DOH: department of health; DOM: department of medicine.



Finally, we maintain patients at the very center, as evidenced by our patient coinvestigators, individuals experienced with diabetes and at increased risk for diabetes as both patients and caregivers. Our patient coinvestigators are ready to serve as the voices of patients afflicted with these diseases and feel equally committed to being involved in research:

> *It is vitally important for patients [to be involved in research]! Understanding more about diabetes and providing input to researchers about my personal experiences is mutually beneficial to the patient and the research.* [Patient coinvestigator]

Statistical Analysis Plan

Descriptive statistics will be generated to describe the characteristics of different cohorts of interest. The diabetes-related outcomes will be summarized at the individual level on a yearly, quarterly, or monthly basis depending on the availability of the data within the data source. There will be binary outcomes (Yes/No) such as receiving obesity and/or nutritional counseling, controlled diabetes, controlled blood pressures, receiving annual eye exam, and count outcomes, such as numbers of clinic visits, emergency department visits, and hospitalization, and continuous outcomes, such as weight and HbA_{1c}. The distributions of outcome measures will be examined by using minima, maxima, ranges, medians, quartiles, means, and SDs for continuous variables and frequency and contingency tables for categorical variables.

To evaluate the impact of policy changes on these outcomes (Aim 1), we will examine how these outcomes change over time, in response to the policy changes. As descriptive analyses, we will plot the mean trajectory of each outcome over time at the clinic level, health system level, and state level. Outcomes will be at least annually, but possibly monthly or quarterly, depending on variable availability from the data source. The statistical modeling of patterns of changes in individual-level outcomes will be carried out through multilevel mixed-effects models [25-28]. The mixed-effects model is a common and popular modeling technique for longitudinal data. A mixed-effects model can accommodate within- and between-subjects variability, as well as serial correlations. In addition, it has the flexibility to incorporate time-dependent covariates, incomplete data, and heteroscedasticity of the variances and correlations. The mixed-effects model will be specified in a multilevel fashion so that different levels of variability (eg, individual characteristics and policy environment) can be taken into account. Specifically, state policies can be examined given the diversity of clinical locations and insurance expansion throughout the study timeframe. The pattern of changes in the outcome will be assessed for pre- and postperiods, respectively, based on the piecewise/segmented regression models. The slope of each segment indicates the trend of change in weight loss and diabetes outcome in that period. Therefore, the change in the trend/slope postpolicy implementation may reveal the actual impact of the new policy controlling for baseline level and trend. Such modeling strategies share the same spirit of interrupted time series analysis. Although the classical interrupted time series design often generates a single extended series of data, we have a large number of short series from each individual subject, namely, longitudinal data. Depending on the types of the outcomes, we will specify mixed-effects models based on logistic regression for a binary outcome, Poisson regression for a count outcome, and linear regression for a continuous outcome as detailed in equation a (Figure 4).

In the multilevel modeling, the first-level unit is the repeated measurement (at least annually, but potentially monthly or quarterly, dependent on variable availability) for the individual subject (pre- and postpolicy); the second-level unit is the individual subject; the third-level unit is the health system, provider, or clinic within the health system (cluster); and the fourth-level unit is the state. For example, let Y_{ijkt} denote the binary response of receiving obesity and/or nutritional counseling at year t as broader coverage change in 2013 for the k^{th} subject within the j^{th} cluster of the i^{th} state, t=–4, –3, ..., 0, 1, ..., 6, i=1, 2, 3; j=1, 2, ..., c_i, and k=1, 2, ..., n_{ij}, where c_i is the number of clusters within the i^{th} state and n_{ij} is the sample size within the j^{th} cluster of the i^{th} state. An individual subject may not be in the system for all the time points of measurement, so t will have a smaller range of values for that individual subject. The probability of receiving obesity and/or nutritional counseling, $\mu_{ijkt} = E(Y_{ijkt}) = Pr[Y_{ijk} = 1]$, can be described by equation b (Figure 4), a segmented logistic regression model where β_{mijk} (m=0, 1, 2) are subject-specific regression parameters, with β_{0ijk} being the log odds of receiving obesity and/or nutritional counseling at t=−4, and β_{1ijk} and β_{2ijk} being the slopes (annual change in log odds) for the pre- and postperiods, respectively.

In the framework of a mixed-effects model, each β_{mijk} is modeled by equation b (Figure 4) where x_{mijk} is the vector of regressors for the fixed effects, β_m is the corresponding vector of fixed-effects parameter coefficients, z_{ij} is a vector of cluster-level regressors for the random effects for the j^{th} cluster of the i^{th} state, γ_{1ij} is the cluster-level random-effect coefficients and is common to all m, and γ_{2mijk} is the subject-level random-effect coefficients associated with the parameter β_m for the k^{th} subject within the j^{th} cluster. The random effects are assumed to follow a multivariate normal distribution with mean zero. As the vector x_{mijk} may include subject-level, cluster-level, and state-level exposure variables, the fixed-effects parameter vectors β_1 and β_2 represent the effects of different exposure variables on the annual changes in the pre- and postperiods, respectively. Thus, we may perform statistical tests to examine whether there are differences in trends between the pre- and postperiods overall and for each state and whether the patterns of changes differ between the states.

Figure 4. Statistical analysis equations.

a. $$\text{logit}\ \mu_{ijkt} = \log\{\Pr[Y_{ijk} = 1]/\Pr[Y_{ijk} = 0]\} = \beta_{0ijk} + (t+4)\beta_{1ijk} = \beta_{0ijk} + 4\beta_{1ijk} + t\beta_{2ijk}$$

if $-4 \le t \le 0$, pre-period before policy changes
if $0 \le t \le 6$, post-period after policy changes

b. $$\beta_{mijk} = x_{mijk}^{T}\beta_m + z_{ij}^{T}\gamma_{1ij} + \gamma_{2mijk}$$

Similarly, for a count outcome Y_{ijkt} (eg, number of clinical visits), we define the expected value $\mu_{ijkt}=E(Y_{ijkt})$ and apply a Poisson regression model based on the natural log link function. The log expected number of clinical visits, $\log(\mu_{ijkt})$ can be modeled with the aforementioned segmented mixed-effects model. The use of an offset term in the models yields the estimates of the rate of clinical visits rather than the mean number of visits. The fixed-effect parameters, β_1 and β_2, represent the effects of exposure variables on the annual changes in log of incidence rates for the pre- and postperiods, respectively. For a continuous outcome Y_{ijkt}, we will model the mean, $\mu_{ijkt}=E(Y_{ijkt})$, with the mixed-effects model, and the parameters β_1 and β_2 indicate the effects of exposure variables on the annual changes in the outcomes for the pre- and postperiods, respectively. Besides mixed-effects models, we will also consider marginal models based on generalized estimating equation approach. Although mixed-effects models in general yield subject-specific effects except for the continuous outcomes, marginal models yield population-level effects. All final statistical models will be assessed with regard to the goodness-of-fit and the appropriateness of model assumptions.

For Aim 2, we will compare patient weight loss and diabetes-related outcomes among those who receive obesity IBT to those who do not, following implementation of preventive service coverage. We will also investigate obesity counseling as a continuous variable to examine impact of intensity (defined as the number of sessions) on outcomes, including weight loss. The outcome data collected after the broader coverage change will be used for the analyses in Aim 2. To compare the trend of change in each outcome between 2 groups, we will use the mixed-effects models as described above. The indicator of receiving obesity IBT, time, and their interaction will be the primary variables of interest in the model. In addition, patient and practice characteristics will also be included as covariates to control for their effects on the outcomes. To incorporate different starting dates of IBT and multiple IBT over different years, we will use the time-varying indicator of receiving IBT in the models. For subjects who receive IBT, we will also examine how the intensity of IBT (number of visits) is associated with changes in the outcomes. The number of screening and counseling will be used as a predictor in the mixed-effects models. Patient and practice characteristics can be adjusted in the regression model to reduce the selection bias of receiving IBT. The propensity score matching method has also been widely used to balance the characteristics of those who receive IBT with those who do not. We will consider demographics, insurance coverage, access to IBT prescription, medical comorbidities, and information on use of health care services to calculate the propensity scores. In addition, we will consider health behaviors, which are available for analysis from some institutions, and include validated standardized questionnaires assessing nutritional intake (specifically fruit and vegetable consumption), physical activity, and sleep. An initial step within this project is to inventory the availability of PROs across institutions, and therefore, limited details are available at this time. A subject with IBT will be matched with a subject without IBT based on age, gender, enrollment window, and propensity of receiving IBT. Then mixed-effects models can be used to compare the patterns of changes in the outcomes of interest between 2 groups. Statistical software SAS 9.4 and R environment will be used to implement the proposed analyses.

Subgroup Analyses

Owing to the heterogeneity of the population and a dynamic cohort in our study, we will investigate subgroup analyses to assess how the policy impact varies across different subgroups. Following the general modeling approaches as described above, we will examine the benefits of policy changes for different subgroups including (1) patients with insurance throughout the study period, (2) patients who obtained insurance after the policy changes, (3) patients without insurance throughout the study period, (4) patients newly enrolled in the system after policy changes, and (5) other subgroups of interest according to gender, age (eg, aged ≥65 years), race-ethnicity, and rural status. Meta-analysis has been a powerful approach to combining the effects of interest across different studies, different populations, and different subgroups [29,30]. We will adopt this method to evaluate the average impact of policy changes across subgroups. A forest plot will be generated to reveal how the addition of a subgroup to the meta-analysis may affect the average policy impact.

Propensity Scores Matching

In the modeling framework above, we adjust for subject-level and cluster-level differences by including the exposure variables at different levels as covariates in the models. We will also consider a secondary analysis with a propensity score–matching approach to adjust for these differences [31,32]. A wide array of patient measures in the EHR, including demographics, insurance coverage, medical comorbidities, health behaviors, and information on use of health care services will be used to calculate the propensity scores. A propensity score–based stratification analysis will be performed to evaluate the overall impact of health policy using the modeling framework similar to that described above.

Analyses of Diabetes Outcomes at Population Level

The primary analysis of our study focuses on the individual-level outcomes. The statistical models yield the estimate of average change at the individual level post policy implementation. Given the information in the EHR data, we can also aggregate the diabetes outcomes at the community level and clinic level. For example, the proportion of patients with controlled diabetes can be obtained for each clinic and used as the outcome variable in the statistical modeling. The proposed mixed-effects modeling framework is still applicable in this case. The statistical analyses can be performed in a similar fashion to that for the individual-level outcomes.

For example, our statistical analysis plan can be easily modified to compare the differences in weight loss and diabetes outcomes (including diabetes control, controlled blood pressure, use of a statin medication, receipt of an annual eye exam and annual urinary microalbumin test, and lower extremity amputations) between rural and urban areas. Although our main analysis is on individual-level outcomes, aggregated outcomes at the community or county level can also be extracted from the EHR data. For example, the proportions of patients with controlled diabetes in each county at each year can be obtained and used as the outcome variable after arcsine-square root transformation in the statistical modeling. We can evaluate the rural/urban effects on the pattern of changes in diabetes outcomes over years by including county-level characteristics such as rural versus urban in the mixed-effects models as fixed effects. The time origin in the analysis will be the beginning of the study period rather than the time when insurance policy changes occurred. The counties sharing similar characteristics (eg, access to the same health system) will be considered as a cluster, and the clustering effect will be accounted for in the mixed-effects model analysis by including cluster-level random effects. Instead of using segmented regression models to evaluate the trend in diabetes outcomes before and after the policy change, we will consider linear or nonlinear trends in the diabetes outcomes and allow rural and urban counties to have different patterns of changes in the models.

Given that the study investigates a natural experiment, there is no primary data collection planned. However, there remains a risk of missing data. It is anticipated that the EHR will have incomplete data on outcomes of interest, which will be handled statistically as described below. Furthermore, the availability of claims data will assist in improving rates of missingness. Finally, we expect most missing data will be noninformative, that is, because of patients moving away from the health care institution. We will use validated statistical methods to handle missing data. These include the likelihood-based mixed-effects models to handle missing outcome data and multiple imputation method for missing covariates. The assumptions about missing data will be assessed based on the documented missing reasons and statistically as well. As participants are not recruited to this study, there will be no dropout to account for in the study design. However, given the prospective study design, there remains a risk for missing data. A consort-type diagram will be created to document each step to fully account for and justify patients who might be excluded. The missing data pattern will be summarized for primary outcomes. Baseline characteristics will be compared between those with missing outcome data and those without. A sensitivity analysis based on different assumptions of missing data mechanisms will be performed to evaluate the robustness of findings to the missing data.

Statistical Power

Owing to the very large sample sizes that are anticipated for the research studies (more than 320,000 patients with diabetes and 2,000,000 patients at increased risk for diabetes), there is tremendous statistical power to detect very small effect sizes for individual-level exposure variables. Therefore, the clinical investigators on this project will need to examine each statistically significant result and determine whether it is also clinically significant. Furthermore, such large sample sizes ensure the robust estimation results from the proposed multilevel statistical modeling, which involves a large number of regression coefficient and covariance parameters. The major benefit of the large sample size for each research study is that it provides sufficient statistical power for investigating effects of interest within subgroups that might be constructed according to age, race-ethnicity, and cohort decompositions.

Results

Our PCORI-funded study is underway. To date, we have obtained our second data extraction from the PaTH CDRN and are performing data editing and cleaning. Next steps include analysis of early policy change (Multimedia Appendix 1).

Discussion

Overview of Proposed Findings

The overarching goal of this research is to understand the comparative effectiveness of obesity counseling as covered by CMS and other insurers in improving weight loss for adults either with or at increased risk of type 2 diabetes. As patients who are overweight are at highest risk for diabetes, improved weight management services could prevent diabetes and its negative health outcomes. Comparing weight and diabetes outcomes in 3 states using EHRs and claims data before and after this policy was implemented using the PaTH Network will allow important insight into policy effectiveness.

Limitations of Research Design

Limitations of the Data

Through the PaTH network, we have access to EHRs for patients who have been seen at Penn State Hershey Medical Center, University of Pittsburgh Medical Center, Johns Hopkins University, and Temple University Health System and, beginning in Fall 2015, the University of Utah and Geisinger Health System. Although this a uniquely large integrated research network, it only includes patients who seek care at one of these large health systems or affiliates and does not include those who preferentially seek care outside of large health systems or do not seek care at all. We address this limitation, in part, by supplementing our health record data with claims data where available. We will enrich the PaTH data with the UPMC Health Plan, Temple Health Plan, Johns Hopkins Health System, Geisinger Health Plan, and University of Utah

Healthcare claims data to ensure capture of outcomes data that occur outside of the PaTH health systems.

Data Integration

Our plans for data integration currently do not consider information extracted from images, videos, and free text, which can be important in some settings. However, our proposed design of the data infrastructure can be extended to incorporate such data in the future by leveraging state-of-the-art image analysis, video analysis, and natural language processing.

Residual Confounding

The possibilities of residual confounding cannot be ruled out because of unmeasured or unavailable factors. For example, no detailed data on individual behavioral risk factors (eg, diet and physical activity) are consistently available. Changes in individual behaviors will have large impacts on individual diabetes control. Similarly, data on built environment (eg, healthy food availability) are lacking. Finally, BMI and blood pressure are measured based on clinical practice not research protocol. They are subject to misclassification/measurement errors. Caution will, therefore, be exercised in interpreting our results.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Project milestones and timeline.

[PDF File (Adobe PDF File), 110KB - resprot_v8i4e12054_app1.pdf]

Multimedia Appendix 2

Peer-reviewed comments PCORI.

[PDF File (Adobe PDF File), 69KB - resprot_v8i4e12054_app2.pdf]

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Abbreviations

ADA: American Diabetes Association
BMI: body mass index
CDM: Common Data Model
CDRN: Clinical Data Research Network
CERC-DC: Comparative Effectiveness Research Core Data Center
CMS: Centers for Medicare and Medicaid Services
CPT: Common Procedural Treatment
EHR: electronic health record

HbA $_{1c}$: hemoglobin A_{1c}
IBT: intensive behavioral therapy
ICD: International Classification of Diseases
IRB: institutional review board
PCP: primary care physician
PCORI: Patient-Centered Outcomes Research Institute
PHI: protected health information
PNPRC: PaTH Network Protocol Review Committee
PRO: patient-reported outcome
SNOMED: Systematized Nomenclature of Medicine
UPMC: University of Pittsburgh Medical Center

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Protocol

Functional Magnetic Resonance Imaging Biomarkers Predicting Cognitive Progression in Parkinson Disease: Protocol for a Prospective Longitudinal Cohort Study

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Abstract

Background: Cardinal features of Parkinson disease (PD) are motor symptoms, but nonmotor features such as mild cognitive impairment (MCI) are common early in the disease process. MCI can progress and convert to dementia in advanced stages, creating significant disability and reduced quality of life. The primary pathological substrate for cognitive decline in PD is unclear, and there are no reliable biomarkers predicting the risk of conversion to dementia. A subgroup of PD patients with visual hallucinations may display more rapid conversion to dementia, suggesting that regional markers of visuoperceptual dysfunction may be sensitive to pathologic density in posterior cortical regions.

Objective: The purpose of this project is to characterize PD-MCI and evaluate the utility of genetic and neuroimaging biomarkers in predicting cognitive outcomes with a prospective longitudinal study. We will evaluate whether accelerated cognitive progression may be reflected in biomarkers of early posterior cortical changes reflective of α-synuclein deposition.

Methods: We will evaluate a cohort of early-stage PD patients with the following methods to predict cognitive progression: (1) serial neuropsychological evaluations including detailed visuoperceptual functioning across 4 years; (2) genetic analysis of *SNCA* (α-synuclein), *MAPT* (microtubule-associated tau), and *APOE* (apolipoprotein E); (3) an event-related functional magnetic resonance imaging paradigm of object recognition memory; and (4) anatomical and regional brain activation changes (resting-state functional magnetic resonance imaging) across 4 years.

Results: The project received funding from the National Institutes of Health in August 2017, and data collection began in February 2018. Enrollment is ongoing, and subjects will be evaluated annually for 4 years extended across a 5-year project including data analysis and image processing.

Conclusions: Cognitive, genetic, and structural and functional magnetic resonance imaging will characterize neural network changes predictive of cognitive progression in PD across 4 years. Identification of biomarkers with sensitivity for early prediction and estimation of risk for conversion to dementia in PD will pave the way for effective intervention with neuroprotective therapies during the critical stage when treatment can have the greatest impact.

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KEYWORDS

Parkinson disease; cognition; disease progression; dementia; mild cognitive impairment; biomarkers; functional neuroimaging

Introduction

Background

Parkinson disease (PD) is the second most common neurodegenerative disorder characterized by progressive movement deficits and is caused by degeneration of nigrostriatal dopamine neurons and deposition of α-synuclein in intraneuronal Lewy body (LB) inclusions [1]. Nonmotor features can characterize the earliest phase of the disease even before clinical motor impairment. Mild cognitive impairment (MCI) is a prominent nonmotor feature that is present early in the disease process and increases over time, eventually converting to dementia (Parkinson disease dementia [PDD]). Follow-up studies reveal that MCI is present in one-third of patients and progresses to PDD, with conversion greater than 80% after 15 to 20 years [2,3]. Prospective longitudinal studies demonstrate that PDD is common, with a 4-year prevalence 3 times higher than the general population [4,5]. However, dementia onset is variable, with a subset of patients demonstrating rapid conversion, resulting in significant disability and poor quality of life [4,6,7]. The neural and pathophysiologic mechanisms predicting rates of PD progression remain poorly understood and are key research priorities. Biomarkers signaling risk for PDD will facilitate intervention during early therapeutic windows, thus optimizing the chances of slowing progression.

Early cognitive deficits in PD have been characterized as executive and considered to be related to reductions in frontostriatal activity, suggesting a dopaminergic substrate [8]. However, characterization of MCI in early PD has revealed extensive deficits outside the executive domain and is not fully explained by dopamine depletion alone [9,10]. Therefore, identification of early reliable biomarkers that are predictive of risk for dementia conversion will require models of PD-MCI that focus on markers outside of the dopaminergic network. Widespread distribution of dopamine receptors in the neocortex is well recognized, with a rostrocaudal dopamine receptor gradient with the highest receptor densities in the prefrontal cortex and lowest densities in the occipital regions [11]. Therefore, biomarkers targeting posterior cortical changes may be more reliable for earlier prediction.

There is growing evidence of the presence of extranigral pathology that occurs before dopamine depletion. Multiple pathologies are linked to cognitive deficits in PD, including cholinergic, dopaminergic, and diffuse cortical LBs associated with α-synuclein, tau, and Alzheimer disease (AD)–like lesions of amyloid-β plaques [12,13]. PD shares a common neuropathological pattern to LBD and overlaps partially with AD, complicating early diagnosis based on cognitive profiles [14]. Although the spread of α-synuclein is the strongest correlate of PDD, up to 50% of patients also develop sufficient amyloid-β plaques and tau-containing neurofibrillary tangles for a secondary diagnosis of AD [15]. Thus, these pathologies may act synergistically to confer a worse prognosis.

Patients with parkinsonism with cognitive deficits in the first year are diagnosed with Lewy body disease (LBD), whereas those with cognitive deficits after motor deficits are diagnosed with PDD. Although the main features of PDD and LBD are similar (visual hallucinations, visuospatial deficits, attention and executive deficits, and variable memory deficits with parkinsonism), controversy still exists as to whether PDD and LBD are distinct entities. It is conceivable that they represent 2 points on a continuum, with the type and degree of concurrent pathology influencing the timing and rate of cognitive decline [16]. LB inclusions in neocortical and paralimbic regions in PD are predictive of the rate of cognitive decline and memory and visuoconstructional deficits [14]. This implies that the density of α-synuclein and concurrent amyloid-β could act as modulators in the relative timing of cognitive decline and may predict rates of cognitive progression [1]. This is supported by parietal and superior temporal cortical atrophy in early PD-MCI relative to late-onset cognitive decline in PD, even in the absence of cognitive differences [17]. This suggests that pathological burden in parietotemporal regions is greater in PD with early-onset cognitive decline [18]. To advance therapeutics targeting nonmotor features and determine whether PDD and LBD are distinct disorders, it is essential to determine whether the pathology responsible for early deficits also has a synergistic role in dementia conversion.

Current studies looking at different types of biomarkers suggest different possible contributors to PDD, but findings have been inconsistent across studies [19]. Understanding the relationships between genetic risk factors for distinct pathologies and their resultant clinical presentation in PD is crucial for the development of disease-modifying interventions. Evaluating early cognitive deficits in PD and markers of future cognitive progression will shed light on whether PD pathology progresses in a consistent, expected pattern. Prospective longitudinal studies are essential to identify the initial cognitive symptoms and temporal pattern of atrophy and neural progression predictive of outcomes [7,20] . Thus, based on the models of pathological staging and anticipated sequence resulting in cognitive decline, accelerated cognitive progression may be reflected in biomarkers of early posterior cortical changes reflective of α-synuclein [12].

Cognitive profiles provide an index of staging of neuroanatomic regions, reflecting density and distribution of pathologic burden. Symptoms of visual hallucinations are associated with posterior cortical involvement and predict 75% conversion to PDD in 2.5 years, with widespread atrophy providing critical clues for biomarker identification [21]. Although visual hallucinations are specific to cognitive decline in PDD, they are not sensitive, given the low incidence of reporting by patients. Thus, the detection of associated visuoperceptual deficits may improve prediction of posterior cortical pathology and future cognitive decline.

Objectives

The long-term objectives of this study are the investigation of the predictive validity of early cognitive profiles in PD and identification of genetic and magnetic resonance imaging (MRI) markers signaling more rapid conversion to dementia. In this study, we will target the posterior cortex as a reliable marker of pathologic burden based on the proposed caudal-rostral progression of α-synuclein and the rostrocaudal dopamine gradient, with lower occipital receptor density eliminating the

effects of dopamine replacement therapy (DRT). Our hypothesis, based on the models of pathologic staging, is that earlier involvement of posterior cortical regions and the dorsal and ventral visual pathways (with or without visual hallucinations) are reliable markers for cognitive progression. To date, there have been few longitudinal and MRI studies focused on biomarker identification signaling cognitive progression in PD. Neuroimaging techniques offer promise in detecting neuronal changes before performance decrements and identifying biomarkers of accelerated cognitive progression.

Methods

Overview

The primary objective is to investigate the prognostic value of PD-MCI subtypes and genetic variation in predicting the relative risk for progression to dementia utilizing a prospective longitudinal cohort followed for over 4 years. Tables 1 and 2 provide a detailed screening assessment and dependent study measures and timeline. The objectives will be addressed through the following methods: (1) neuropsychological evaluations and novel visuoperceptual tasks will be given annually for 4 years to nondemented PD patients (at baseline), and the predictive validity of visuoperceptual cognitive deficits relative to memory and executive deficits and ideal cutoffs (−1.5 vs −2 SD) for reliable prediction will be determined; (2) an exploratory genetic analysis of how variations in the *SNCA* (α-synuclein), *MAPT* (microtubule-associated tau), and *APOE* (apolipoprotein E) genes influence cognitive progression will be conducted; (3) the utility of task-activated functional magnetic resonance imaging (fMRI) as a probe for the risk for cognitive progression will examine altered posterior cortical networks before clinical manifestation; and (4) the anatomical and regional brain activation patterns predictive of cognitive progression will be determined.

Screening and recruitment will be conducted as outlined with year of testing denoted by 1-4. If we have attrition related to completing the MRI protocol or patients do not return for years 2-4, we will recruit additional patients in year 3 to ensure adequate numbers of patients and converters. The fifth year will be utilized for completion of data collection to account for attrition, image processing, and data analysis.

Patients

Nondemented idiopathic PD patients will be recruited and evaluated in the *on* medication state. The severity of PD will be graded by the Unified Parkinson Disease Rating Scale (UPDRS-III) motor section [22]. Subjects will be asked to provide consent in accordance with Institutional Review Board (IRB) policies and protected by Health Insurance Portability and Accountability Act regulations, and IRB approval has been obtained from the University of Maryland Baltimore (UMB), School of Medicine. We will recruit 120 PD patients who will be evaluated annually for 4 years on neuropsychological and MRI measures in a 5-year study. Patients will be recruited from the University of Maryland School of Medicine as well as through other advertisements to recruit patients from surrounding areas. Our goal is to complete 100 patients, so we will overrecruit because of anticipated attrition. Potential subjects will be screened, and information regarding the Unified Parkinson's Disease Rating Scale (UPDRS), mood, Activities of Daily Living (ADLs), and Montreal Cognitive Assessment (MoCA) will be acquired to determine the study eligibility [22,23]. The principal investigator is a clinical neuropsychologist who will review the study and the inclusion criteria and will confirm the diagnosis with the study neurologist who will examine all the patients.

Inclusion and Exclusion Criteria

General and specific inclusion and exclusion criteria for both PD patients and controls are reviewed below.

General criteria: (1) age 50 to 77 years to avoid early-onset PD and (2) no evidence of depression on the Beck Depression Inventory (BDI-II >18 is predictive in mild PD) [24].

PD criteria: (1) Diagnosis of idiopathic PD based on the presence of 2 cardinal features [25], (2) improvement with DRT, (3) minimal or mild disease severity based on the Hoehn and Yahr rating scale of <2.5 and motor UPDRS <30 *on* DRT medications [22], and (4) normal or MCI cognition based on MoCA screening (>21) at baseline [26].

Exclusion Criteria

(1) Other neurologic disorder or stroke; (2) dementia (MoCA <21 at baseline) or functional decline on instrumental ADLs related to cognitive deficits [27]; (3) major psychiatric disorder, including alcohol or substance abuse; (4) concurrent, unstable or serious medical condition; (5) major head trauma; (6) chronic use of psychoactive medications; (7) significant dyskinesia on neurological examination; (8) tremor greater than 2 for upper extremities and head tremor greater than 1 based on the MDS-UPDRS on neurological examination; and (9) claustrophobia, pacemaker, neurostimulator, or other implants or other factors that interfere with the ability to lay still in the MRI scanner for 1 hour.

Timeline for Schedule of Assessments

Study subjects will be enrolled and evaluated annually across 4 years (see Table 2 for a detailed timeline of enrollment and schedule of assessments). Neuropsychological, behavioral, and neurological assessments, including the MD-UPDRS motor section III, will be conducted annually. Genetic samples and cognitive activation paradigm will only be conducted at year 1 and utilized as predictors of 4-year outcomes, whereas the remaining MRI measurements will be conducted annually (Table 2).

Assessments

Neuropsychological Assessment

The battery was selected based on the identified PD cognitive deficits and task force recommendations. The battery will include estimates of premorbid verbal intellectual functioning (American New Adult Reading Test) [28], measures of both verbal and nonverbal memory and attention, and several executive tasks. Memory tests will use equivalent alternative forms across years 1 to 4 to control for practice effects [29].

Table 1. Screening, assessment, and dependent study measures.

Measures	Individual tests
Genetic markers	*SNCA* (α-Synuclein), rs356219
	MAPTH1/H2 haplotypes (microtubule-associated tau), rs1800547
	APOE 2/ 3/ 4 alleles (Apolipoprotein E), rs429358 and rs7412
Screening	Unified Parkinson Disease Rating Scale Motor Section III
Behavioral measures	Montreal Cognitive Assessment
	Beck Depression Inventory II
	Edinburgh Handedness Inventory
	Beck Anxiety Inventory
	The Parkinson Disease Sleep Scale
	The Parkinson Disease Questionnaire
	Neuropsychiatric Inventory of Psychopathology in Dementia
	Adelaide Activities Profile
Neuropsychological assessment	American New Adult Reading Test
	Digit Span and Letter Number Sequencing
	Phonemic and Semantic
	Hopkins Verbal Learning Test-Revised
	Benton Visuospatial Memory-Test Revised
	Boston Naming Test
	Judgment of Line Orientation
	Visual Object and Space Perception
	Visual Form Discrimination
	Stroop Color and Word Test
	Delis Kaplan Executive Function Scale Trails 1-5
	Delis Kaplan Executive Function Scale Tower Test
	Computerized Version of the Wisconsin Card Sorting Test
	Finger tapping
	Grooved pegboard
Neuroimaging	Cortical thickness; Voxel-based morphometry
	resting-state fMRI; Diffusion Tensor Imaging
	Task-activated fMRI imaging paradigm—object memory (encoding, immediate and delayed memory recall)

Table 2. Timeline of enrollment and schedule of assessments.

Data Collection Measures	Year 1	Year 2	Year 3	Year 4
Screening and recruitment	X[a]	X	__[b]	—
Unified Parkinson Disease Rating Scale -III (motor section)	X	X	X	X
Saliva samples for genetics	X	—	—	—
Neuropsychological and behavioral measures	X	X	X	X
fMRI Cognitive activation paradigm	X	—	—	—
Structural MR, rs-fMRI & DTI	X	X	X	X

[a]Denotes time points when data collection is active.

[b]Not applicable.

Attention

Visual attention will be evaluated with the Stroop Color-Word test [30], whereas auditory working memory will be evaluated by the Letter-Number Sequencing and auditory Digit Span backward and forward from the Wechsler Adult Intelligence Scale–Fourth Edition [31].

Executive Tasks

A computerized version of the Wisconsin Card Sorting Task [32] and the Delis Kaplan Executive Functions Scale (Trails and Tower of London) with demonstrated reliability and validity in measuring executive functions will be given [33].

Language

Language will be assessed by the Boston Naming Test [34] and phonemic and semantic fluency.

Memory Tasks

The Hopkins Verbal Learning Test [35,36] for verbal memory and the Brief Visuospatial Memory Test [37] will both be utilized in alternative forms across the years.

Sensorimotor Tasks

Motor tasks of speed, precision, and dexterity (finger tapping and grooved pegboard) will be evaluated bilaterally [38].

Other Measures

Other measures include evaluation of hallucinations (Neuropsychiatric Inventory [39] and thought disorder item UPDRS-TD [40]), mood and anxiety (BDI-II; Beck Anxiety Inventory) [41,42], quality of life (The Parkinson Disease Questionnaire-39]) [43], and ADLs with the Adelaide Activities Profile, which focuses on instrumental activities [27].

Visuoperceptual Tasks

The Judgment of Line Orientation (JLO) task and Benton Visual Form Discrimination tasks will measure visual orientation [44] and visuoperceptual discrimination [45]. An abbreviated version of the Visual Object and Space Perception battery will be given to evaluate silhouettes presented in unusual perspectives and progressive silhouettes as well as decision of objects presented in rotated manners [46]. On the basis of the tasks previously developed in our laboratory in early PD, subjects will be evaluated on *visuoperceptual judgments of equidistance* (judging line lengths and width intervals). Presentation software (Neurobehavioral Systems) [47] will present the perceptual stimuli (4-second presentation). The first task requires *length estimation* of 2 lines in either a vertical or a horizontal orientation and evaluation of whether they are the *same* or *different*. The second task, *width interval estimation*, compares 2 interval spaces between 3 horizontal lines to determine if they are the *same* or *different*. Subject responses will be entered as same, different, or a miss (failure to respond) by the experimenter. Each task contains 24 trials, randomized for each subject and varied by 3 line lengths (4, 8, and 12 cm) and 4 levels of difficulty (same, easy, difficult, and very difficult).

Genotyping

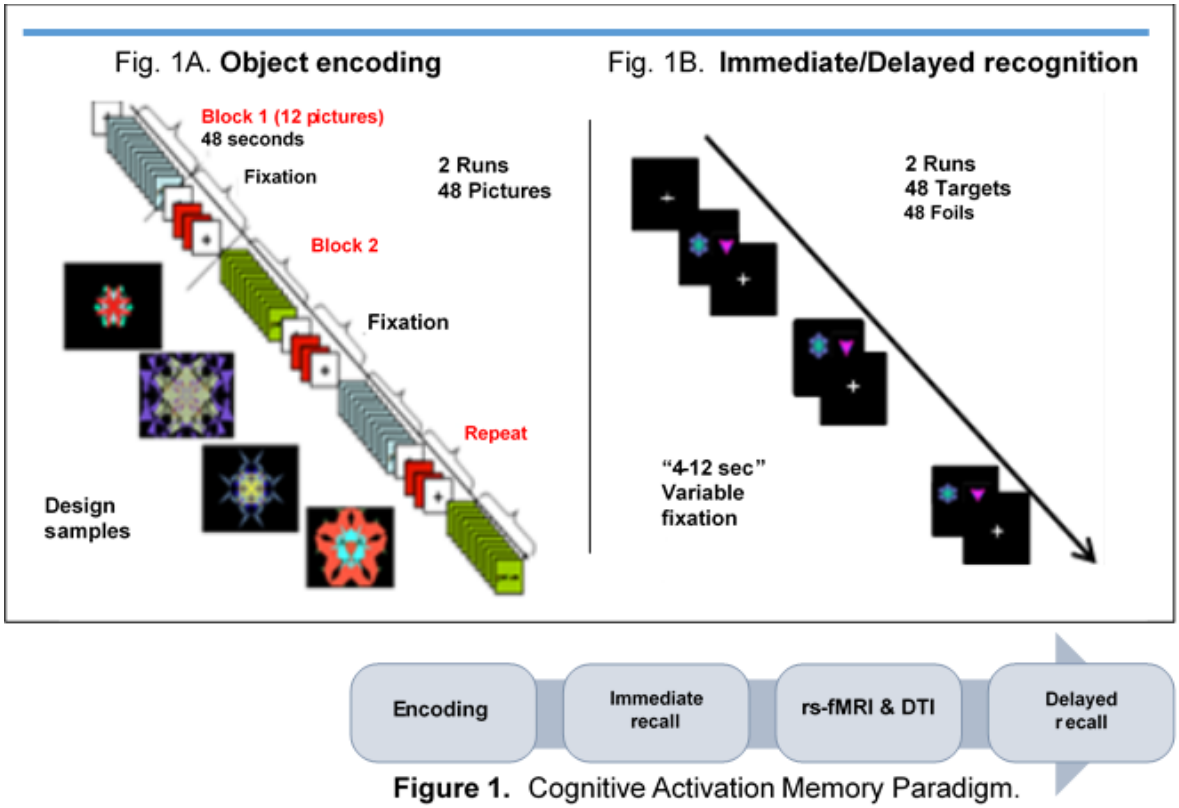
Genetic variations will be explored relative to cognitive and neuroimaging progression and 4-year outcomes to determine the association with cognitive progression. Genotyping for *SNCA* rs356219, *MAPT* H1/H2 haplotypes (rs1800547) , and *APOE 2/ 3/ 4* alleles (rs429358 and rs7412) will be conducted using DNA extracted from saliva and performed with TaqMan assays. TaqMan single nucleotide polymorphism assays will extract DNA from saliva samples, and they have been demonstrated to yield comparable results to blood samples but eliminate the need for an invasive procedure, reduce risk, and increase recruitment. To ensure optimal analysis and avoid false-positive amplifications, at least 2 no-template controls will be used per assay. Assays will be conducted by the UMB Center for Innovative Biomedical Resources genetics core facilities.

Imaging Protocol

Imaging is performed on a Siemens PRISMA 3T MRI scanner using a 64-channel receive head coil. After obtaining scout images in all 3 planes, a high-resolution volumetric sagittal T1-weighted-MPRAGE (TE=2.94 ms, TR=2300 ms, TI=900 ms, flip angle=9°, 1-mm isotropic resolution) is obtained, which serves as the anatomical reference from which regional and whole-brain volumes and cortical thickness are extracted. The total acquisition time for MPRAGE is 5 min and 30 s. Furthermore, 6 sets of fMRI data are then obtained in 2 phases. During the first phase, 2 encoding runs are performed, followed by 2 immediate recall acquisitions. After a delay of 18 min, the second phase consisting of 2 delayed-recall fMRI acquisitions is obtained (see Cognitive Activation Paradigm, Figure 1). Data for fMRI are obtained using a 2-dimensional multiband single-shot T2*-weighted, echo-planar imaging sequence (TE=30 ms, TR=2000 ms, Flip 90°, 2-mm isotropic resolution) with a multiband acceleration factor of 4 covering the entire brain in the axial plane [48-50]. Between the immediate-recall and delayed-recall sessions, both diffusion tensor data and rs-fMRI data are acquired. The diffusion tensor images are obtained using a multiband double-refocused spin-echo echo-planar imaging sequence (TE=78 ms, TR=3000 ms) using b-values of 0 and 2500 s/mm^2 and uniformly sampling the sphere in 136 directions with 5 b=0 acquisitions at an isotropic resolution of 2 mm for a total acquisition time of 7 min and 19 s. rs-fMRI data are obtained using a T2* gradient echo EPI sequence (TE=30 ms, TR=2000 ms; 300 volumes) also at an isotropic resolution of 2 mm for a total acquisition time of 10 min and 12 s. In addition, fast spin echo-based T2-weighted images (TE=100 ms, TR=5340 ms) and FLAIR images (TE=83 ms, TR=9000 ms; TI=2500 ms) are also obtained.

fMRI and rs-fMRI data will be preprocessed using both AFNI and SPM. Preprocessing includes slice timing correction, registration of all the volumes to the first volume of the time series, spatial blurring (6 mm FWHM), and band-pass filtering (0.01 Hz<f<0.1 Hz). Functional MRI data will be spatially normalized to a common Montreal Neurological Institute (MNI) template. The global signal from the mean BOLD time series from the whole brain mask and the 6 motion-correction parameters will be used as regressors in the model to remove the variance related to nonneuronal contributions and motion.

Figure 1. Cognitive activation memory paradigm. rs-fMRI: resting-state functional magnetic resonance imaging; DTI: Diffusion Tensor Imaging.



Cognitive Activation Paradigm

An fMRI event-related object memory task using fractal images will measure BOLD response in PD patients at baseline. Stimuli are based on the object and spatial memory study by Floel et al [51]. Stimuli will be presented on a screen and synchronized with the scanner via an optic relay triggered by the radiofrequency pulse, and responses will be acquired through Presentation software. The paradigm will consist of 6 BOLD sequences (2 for encoding, 2 for immediate recall, and 2 for delayed recall), but with an 18-min delay when structural and rs-fMRI data are acquired (Figure 1). During object encoding, subjects will view 48 images presented in a fixed block across 2 runs. Each run will include 24 designs presented across 2 trials in 4 blocks of 12 images. Stimulus presentation is 4 seconds for each image (48 secs for each block), followed by 2 baseline fixations separated by repeating 2 figures for 6 times (96 secs) between each of the blocks. Each run will last 8 min and 30 seconds for the encoding condition.

An event-related fMRI paradigm will evaluate immediate and delayed recognition of the 48 designs based on discrimination from 48 foils. Each of the recognition trials will consist of 2 runs with variable 4- to 12-second fixations between each stimulus presented for 4 seconds (runs last 7-8 min and 32 secs). Stimulus presentation order and interstimulus intervals will be randomized across 14 different experiments. Subjects will be instructed to look at the designs presented on the screen and recall whether the designs are old designs (targets) or new designs (foils). Responses and reaction times will be recorded by pressing the key press with their index finger for *yes* or pressing their middle finger for *no*. Data will be analyzed separately for *accurate*, *inaccurate*, and *missed responses*. Following encoding, the immediate recognition runs will be collected. An 18-min delay when structural and rs-fMRI are conducted will precede the delayed recognition recall condition.

Resting-State and Voxel-Based Morphometry

Cortical Thickness

MPRAGE images will be processed using the pipeline established in Free Surfer [52]. Cortical thickness from various regions of interest (ROIs) is then determined as the mean of difference between WM and pial surfaces. We will generate an average surface map to which each surface map will be aligned followed by generation of a group difference map.

Connectivity Analysis

Following the preprocessing steps as described earlier, we will register all the 300 volumes collected for rs-fMRI to the first volume of the time series. As differential head motion between groups can introduce artifacts, we will equate the PD and control groups with a *scrubbing* procedure to remove volumes compromised by motion [53]. The resting-state series will then be registered to the high-resolution structural images, spatially normalized to standard space using the MNI atlas, and resampled to a spatial resolution of 2.0 mm isotropic and then spatially blurred using a 5-mm Gaussian kernel. The segmented masks (GM, WM, and CSF) created as part of the measurement for cortical atrophy will account for time series variance from the nonneuronal contributions of CSF and WM. In addition, the 6 standard movement parameters from registration will be regressed out of the 4-dimensional data. Graph-theoretic analysis on selected ROIs that are relevant to PD cognition based on our

hypotheses will be performed and expanded to a more global approach using Graph Analysis Toolbox (GAT) [54]. The ROI method will consider regions such as *caudate, putamen, cingulate, orbitofrontal, dorsolateral prefrontal cortex (DLPFC), superior and inferior parietal, posterior and anterior visual cortex, superior and medial temporal*. Pairwise correlations between mean BOLD time series using ROIs will be utilized to create functional connectivity matrix followed by the Fisher transformation to z score association matrix. Various topological features of the networks will be captured at the global and regional level such as total connectivity, normalized clustering coefficient, normalized path length, density, global efficiency, and betweenness centrality [55]. Between-group comparisons will be made using a 2-sample *t* test after correcting for multiple comparisons with significance set at $P<.05$. To determine the relationship of the network topology with cognition, we will correlate all subtests of the neuropsychological and visuoperceptual assessments using the Pearson correlation coefficient comparing PD with normal cognition across 4 years and PD with cognitive progression.

Using a more global approach, we will perform cortical/subcortical parcellation to define 200 brain regions to identify and understand the influence of other networks on PD network topology and to assess whether taking such interactions into account influences predictions in PD outcomes. The extracted time courses from each of these regions will be correlated against one another to produce a 200×200 adjacency (correlation) matrix, followed by the Fischer transformation to z score association matrix. Similar metrics will be extracted as in the case of the limited ROIs described above.

Activation maps from fMRI will be analyzed using statistical parametric methods, and contrasts will be conducted using multiple regression with the General Linear Model, allowing for multiple predictors to be built into the model [56]. Regressors representing the experimental conditions of interest will be modeled with a hemodynamic response function and entered into the multiple regression analysis using both fixed- and random-effects models. Whole-brain statistical analyses will be conducted, and statistical parametric maps will be generated to examine brain regions that differ in activation between the groups and conditions (encoding and immediate and delayed recall). These analyses will be performed in each group separately using a repeated-measures analysis of variance model and then between groups (PD and PD-MCI). We will inspect the entire brain for areas of activation, and areas will be considered significant if they exceed a threshold of $q<.001$ (False Discovery Rate). We will evaluate the relationship between brain activation and cognition inside and outside the scanner.

Statistical Analysis and Power

A sample of 120 PD patients is planned for this study. On the basis of the experience of longitudinal studies in PD, the attrition (mortality and loss to follow-up) is anticipated at 16% for 4 years. Thus, initial recruitment of 120 patients will yield about 100 subjects after 4 years. On the basis of published data, we estimate 70% PD-NC and 30% PD-MCI patients in our sample, and conversion rates of 60% from NC to MCI and 80% from MCI to PDD after 4 years. One of our primary goals is to evaluate progression patterns to determine time-specific differences between groups (NC vs MCI at baseline and PDD vs MCI, MCI vs NC, and PDD vs NC at year 4). Our study will have 80% power to detect medium-to-large average differences across time between the different groups under various within-subject correlations. In terms of predictive models for 4-year outcomes, our study will have 90% power to detect at least 0.86 area under the receiver operating characteristics curve (AUROC) for PDD conversion and 95% power to detect at least 0.74 AUROC for MCI at year 4.

To study differential cognitive progression patterns, generalized estimating equations will be used for describing the longitudinal trajectories of neuropsychological and visuoperceptual performances between PD-NC and MCI groups comparing baseline performance with different time points. The model will provide estimates of PD-MCI versus PD-NC differences at specific time points and longitudinally. Covariates such as age, UPDRS, and visual illusions or hallucinations will be added to the model to enable determination of adjusted differences.

We will investigate the prognostic value of baseline cognition in predicting relative risk for progression to PDD through a multiple logistic regression model. The best combination of baseline measures and covariates included in the prediction model will be selected by the elastic net procedure. Summary statistics of the AUROC will be used to evaluate the predictive power. Sensitivity, specificity, positive predictive value, and negative predictive value will be calculated from the optimal threshold determined by the Youden index. The prediction models will be cross-validated by training and testing methodology.

Results

The project received funding from the National Institutes of Health in August 2017, and data collection began in February 2018. Enrollment is ongoing, and subjects will be evaluated annually for 4 years extended across a 5-year project including data analysis and image processing.

Discussion

Overview

Cardinal features of idiopathic PD include motor symptoms attributed to dopaminergic depletion of the dorsal striatum. Nonmotor features of the disease such as cognitive impairment are common early in the disease process and can dominate in advanced stages, creating significant disability and poor quality of life. Follow-up studies reveal that MCI is present in one-third of the patients and can progress at variable rates to PDD. After 15 to 20 years, more than 80% of patients with MCI are diagnosed with PDD [2]. However, the neural and pathophysiologic mechanisms underlying variable cognitive deficits and their progression in PD remain poorly understood. Cognitive profiles in nondemented early-stage PD can be widespread, extending beyond expected frontostriatal circuitry. Furthermore, DRT can have a paradoxical effect on attention and memory, with evidence for overdosing of nondepleted

ventral striatal circuits early in the disease process, suggesting that these deficits may be unreliable predictors of cognitive progression [9,10]. PD-MCI is heterogeneous in clinical presentation (executive, memory, and visuospatial), reflecting the presence of extranigral pathology in addition to dopamine. The co-occurrence of LB inclusions (α-synuclein) and Alzheimer pathology (amyloid-β and tau) is essential for the development of PDD, but the neurobiological basis of PD-MCI is unknown. Density of amyloid-β is predictive of neocortical atrophy, but how the predominate pathology in PDD (α-synuclein) influences clinical features or signals conversion to dementia is unclear.

Our central hypothesis, based on models of pathologic staging, is that earlier involvement of posterior cortical regions and the dorsal and ventral visual pathways (with or without the presence of visual hallucinations) are reliable markers for future cognitive progression. Our strategy toward this overarching goal is to characterize cognitive, genetic, and neural network progression in PD over a 4-year period. This allows evaluation of variable timing of onset and accelerated rates of cognitive progression, reflecting a deviation from expected stages of progression. Prospective longitudinal studies are essential to identify the initial cognitive symptoms and temporal pattern of atrophy and neural progression predictive of outcomes. These studies have been lacking, with overreliance on cross-sectional motor and pathological dementia studies in PD [7,20].

Our project is built on the most recent advances in scientific understanding of cognitive, genetic, and neural markers of PD progression. We will translate this information to clinical applications through the development and validation of novel cognitive and neuroimaging markers that signal onset of PDD. Although the visuoperceptual and posterior cortical changes may not predict conversion in all patients, our model allows simultaneous measurement of other cognitive domains and associated brain regions, thus allowing verification of alternative hypotheses and combinations of cognitive domains.

Cognitive Progression in Parkinson Disease

The Movement Disorder Task Force guidelines for the diagnosis of PD-MCI are focused on identifying the earliest stage of cognitive impairment by providing PD-specific criteria [7,20]. The heterogeneity in PD-MCI is recognized, with nonamnestic subtype as the most common, but few studies have evaluated PD-MCI subtype and conversion to PDD. In the few studies conducted, many different subtypes have been implicated [20]. In a 5-year longitudinal study, posterior cortical cognitive deficits were associated with PDD [57]. We aim to establish whether early cognitive and genetic profiles and neural network changes before clinical manifestation can be used for the estimation of pathological burden to assess risk for rapid cognitive progression.

Genotyping Cognitive Risk in Parkinson Disease

There is contradictory evidence regarding α-synuclein levels in PD and how expression levels might be modified by genetic variability [58]. As blood α-synuclein levels may not be sensitive early in PD, measures of genetic variation serving a regulatory role might be useful for early prediction [59]. Variation in the SNCA gene has demonstrated influences on blood and brain and likely influences the expression of α-synuclein in PD expressed by genotype rs356219 [58,59]. Although APOE status does not appear to be associated with PD [60] and findings have been inconsistent regarding PDD, 2 recent studies reported that the APOE *4* allele predicted cognitive deficits in PD [61]. The MAPT H1 haplotype is a well-known risk factor for PD, but there have been contradictory findings as to whether it is a risk for rapid cognitive progression in PD [61]. Genetic variation impacts the age of onset and disease risk, with *SNCA* and *MAPT* genes contributing to progression and cognitive impairment [62]. There is also racial genetic variation influencing the risk of PD and presentation, although genetic variation impacting cognition has not been well investigated.

Task-Activated Functional Magnetic Resonance Imaging

This study will evaluate the utility of task-activated fMRI as a probe for the risk of cognitive progression by examining altered posterior cortical networks before clinical manifestation. It remains unclear whether PD-MCI profiles confer a higher risk of conversion to PDD. Frontal executive and posterior cortical cognitive functions have been considered as risks for conversion, whereas the amnestic memory has been a focus in AD prediction. Combining cognitive and neural biomarkers may improve the prediction of conversion to PDD [63]. Task-activated fMRI offers promise for detecting activations during cognitive tasks to identify the salient aspects of subclinical impairment that are predictive of cognitive outcomes. There have been few fMRI biomarker investigations in PD, although 1 study identified overactivation in DLPFC and posterior parietal regions on a subclinical visuospatial task [64]. However, the predictive nature of these findings is unclear. We have developed a novel fMRI paradigm that targets posterior cortical regions through visuospatial processing and also activates memory regions, allowing for the possibility of more than 1 cognitive profile predicting conversion. BOLD patterns during encoding and immediate and delayed recall of task-activated nonverbal memory will evaluate dorsolateral prefrontal cortex (executive), medial temporal (memory), and occipito-parieto-temporal (visuospatial) activations as predictors for 4-year outcomes. We predict that greater percentage signal change in occipito-parieto-temporal regions during a visuospatial performance at baseline will predict cognitive progression in multiple cognitive domains.

Anatomical and Regional Brain Activation Patterns Predictive of Cognitive Progression

Significant atrophy has been associated with transition from MCI to AD [65,66]. However, there is limited work on cortical thinning in early PD, and no longitudinal studies have evaluated cortical thickness measures as biomarkers signaling rapid cognitive progression in PD [17,67]. Critically important to prediction is evaluating differences in patterns of cortical atrophy based on the timing of onset of cognitive progression. This could reveal an anatomical basis for the timing of cognitive decline, thus elucidating the pathological burden in PD [17].

There is an increased interest in studying resting-state brain networks to try and understand interactions between disparate brain regions. Rs-fMRI measures the strength of functional interactions between brain regions based on temporal correlations of the spontaneous fluctuations in the resting-state BOLD signal, such that synchronous temporal changes in signal are functionally connected [68]. Rs-fMRI has been used to test the efficiency and strength of large-scale neuronal networks in the absence of a task. Although rs-fMRI has revealed the natural history of amnestic MCI to AD, very little is known about its efficacy as a biomarker in PD [69,70]. Characterizing differences in PD will elucidate temporal changes in functional networks related to relative changes in frontal, medial-temporal, and posterior cortical regions with cognitive progression and provide neural insights into the timing of pathophysiological changes in PD.

Cortical thickness, voxel-based morphometry, and rs-fMRI will characterize the evolution of regional brain degeneration annually for 4 years in PD patients. We predict a higher rate of cortical thinning and decreased functional connectivity in occipito-parieto-temporal regions in PD patients with cognitive progression.

Conclusions

This project will incorporate specific areas of innovation, including the use of predictive models; inclusion of novel fMRI biomarkers; segregation of motor, executive, and visuoperceptual task demands; and conceptualization of PD progression based on nonmotor features. Making predictions is a critical task in translational medicine and is of great importance for diagnosis, prognosis, and prediction of treatment response [71,72]. Our predictive model will provide a unique contribution by using cognitive, genetic, and neuroimaging markers to characterize cognition in PD. Previous neuroimaging investigations have focused on PET and SPECT, and there have been few task-activation paradigms developed for PD. The proposed project is innovative in establishing a combined cognitive and fMRI approach for early identification of risk for cognitive progression and to establish the phenotypes of PD connectome using graph theoretic analysis. The proposed project will contribute to a new conceptualization of neurodegeneration in PD. This new framework will include variable rates of onset and progression of both motor and nonmotor features, with recognition that pathology can deviate from expected stages and have accelerated progression.

Summary

There are significant challenges in PD biomarker development with potential to advance therapeutics, in particular, related to nondopaminergic responsive features of PD. Study findings will address these challenges and provide insight into pathophysiological mechanisms by characterizing heterogeneity in cognitive, genetic, and neural temporal progression. This will contribute to an altered conceptualization of PD and LBD neurodegeneration based on the timing of onset and progression of cognitive deficits relative to structural and functional changes. Currently, there is no reliable biomarker predictive of risk for rapid cognitive decline, and there have been few longitudinal studies of temporal progression. Identifying reliable biomarkers will aid in the early and accurate prediction of risk for PDD and provide objective monitoring and response to treatments in the earliest stage when therapies have their greatest impact. Identification of patients at risk for early cognitive progression will have a high impact on patient management strategies and will facilitate intervention at the earliest stage when treatments can have their greatest impact on progression. Study results will provide a foundation for the development of disease-modifying agents and preventative clinical trials.

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Authors' Contributions

BHP led on writing the manuscript. RG, LJ, and HC were involved in developing the study protocol. All authors participated in the critical review of the methods and read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AD: Alzheimer disease
ADLs: Activities of Daily Living
AUROC: area under the receiver operating characteristics curve
BDI: Beck Depression Inventory
DLPFC: dorsolateral prefrontal cortex
DRT: dopamine replacement therapy
fMRI: functional magnetic resonance imaging
IRB: Institutional Review Board

LB: Lewy body
LBD: Lewy body disease
MCI: mild cognitive impairment
MNI: Montreal Neurological Institute
MoCA: Montreal Cognitive Assessment
MRI: magnetic resonance imaging
PD: Parkinson disease
PDD: Parkinson disease dementia
ROIs: regions of interest
rs-fMRI: resting-state functional magnetic resonance imaging
DTI: Diffusion tensor imaging
UPDRS: Unified Parkinson Disease Rating Scale

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Protocol

Supporting the Process of Help-Seeking by Caregivers of Functionally Dependent Older Persons Through Electronic Health: Protocol for a Multicenter Co-Design

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Abstract

Background: It is often only when the initial signs of exhaustion appear that caregivers first may engage in help-seeking behavior, but it is difficult for them to know which is the most appropriate formal service in their situation. Electronic health (eHealth) can support caregivers in keeping the older person they are caring for at home, but few eHealth tools designed for supporting the process of help-seeking by caregivers of functionally impaired older persons have been developed using a co-design approach.

Objective: This paper aims to describe the protocol of a project that tries to assist caregivers to target their needs and those of the older person they support early in their help-seeking process, and guide them effectively to the formal service most appropriate for their situation. This project aims to answer the following questions: (1) What type of tool can better support caregivers to identify their needs and those of the older person they are caring for and then refer them to an appropriate formal service? and (2) What information should be found in such a tool?

Methods: This study presents a description of the process of an ongoing multicenter research project based on a co-design approach, which includes 3 phases (1) identification of caregivers' needs in terms of tools to support their help-seeking behavior, (2) development of a tool, and (3) evaluation of its usability.

Results: The project began in January 2016 with the ethics application for the 3 phases of the project. For phase 1, recruitment began in December 2016 and ended in September 2017. Phase 2 began in the spring of 2017 and ended in June 2018. All the co-design sessions have been completed. Phase 3 of the project will begin in September 2018.

Conclusions: Although there are some challenges associated with this type of methodology, the methodology still remains relevant, as it involves future users in the development of a tool, which increases the chances that the tool will meet the users' needs.

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KEYWORDS

caregivers; aged; help-seeking behavior, community-based participatory research; eHealth; telemedicine

Introduction

Background

Aging of the population leads to a reorganization of health and social services (HSS) for older persons because of the greater pressure on the HSS network. Keeping older persons in their homes as long as possible is economically and socially desirable [1]. Moreover, this wish is shared by the older persons themselves [2]. Nonetheless, this depends, in part, on caregivers [3]. A caregiver, in this study, refers to anyone who provides care and services to a functionally impaired older person on a voluntary and weekly basis [3]. Although it is gratifying for a number of caregivers, contributing to looking after older persons at home is a task that can prove demanding on a day-to-day basis. Caregivers feel poorly equipped to assume this role, which is described by some as a moral responsibility [4]. Moreover, success in home care for older persons depends on the capacity to respond to the needs of those suffering a loss of independence [5,6]. There are many risks for the older person when the support is inadequate or when the burden is too great [7]. Reinhard et al [7] report such potential risks as (1) abuse, (2) medication errors, (3) negligence, and (4) conflicts with the caregiver.

Electronic health (eHealth) can support caregivers in keeping the older person they are caring for at home [8]. Indeed, a number of arguments support the idea of turning to eHealth to help caregivers of functionally impaired older persons in their role. These include acceptability [9], the current use of the internet [10], fewer problems related to moves and respite [8], reduced costs [11], its availability at all times and in all locations [12], the possibilities of using a variety of pedagogical modalities [13], and the efficacy of this type of intervention [14].

Telemedicine, tele-assistance, assistive technologies, communication-linked technologies, tracking systems, Web-based services, and mobile apps [15] are among the various types of eHealth tools for caregivers. Few of these tools were developed with a co-design approach. In addition, very few eHealth tools developed for caregivers have specifically focused on the process of seeking help. It is often only when the initial signs of exhaustion appear that caregivers first undertake the process of help-seeking behavior, but it is difficult for them to know which is the most appropriate formal service in their situation, without assistance from HSS professionals [7].

With the objective of developing an eHealth tool, which supports the process of caregivers' help-seeking behavior, a review of the literature was conducted to identify different theoretical models that could support this process.

Theoretical Frame

We found a number of works bearing on modeling of the process of help-seeking [16-25]. Nevertheless, there is no consensus on the greater relevance of any 1 model [25]. *Levkoff's help-seeking behavior model for dementia* seems to correspond to the process of help-seeking behavior for the caregiver until the latter contacts a care provider [22]. Indeed, this model is specific to the help-seeking behavior for dementia and includes 4 components: the illness and the experience of symptoms, evaluation of symptoms, the decision to look for formal services, and contact with care providers. Recognizing the symptoms (either by the one being helped or by the caregiver) begins the process of help-seeking behavior. Subsequently, the caregiver must interpret the symptoms (using cognitive and sensory capacities), evaluating the degree of severity and the potential duration. The decision to seek help and to contact a care provider depends on a number of factors. To better understand the limitations of these last 2 steps, we identified in a previous study [26] 5 categories of factors influencing the search for assistance: informational factors, factors linked to the service, experiential factors, personal factors, and relational factors. Each stage of *Levkoff's help-seeking behavior model for dementia* and the comprehension of factors limiting the recourse to formal services offer a potential transition where interventions could facilitate the process of assistance.

Objectives

Consistent with this perspective, the purpose of this paper is to describe the protocol of a project that aims to assist caregivers to target early in their help-seeking process their needs and those of the older person they support and guide them effectively to the formal service most appropriate to their situation. The 3 objectives of the project are (1) identifying the needs of the caregivers in terms of tools to accompany their process of help-seeking behavior, (2) developing a tool for caregivers that corresponds to the needs they have expressed, and (3) evaluating the usability of the tool.

Methods

Research Design

To attain these objectives, this study is based on a participatory design, more specifically, a co-design approach. Co-design is defined as the creation of useful knowledge and actions, in this case, an eHealth tool, which involves groups experiencing the issue, even in the research process; they assume simultaneously the role of creators, decision makers, and users [27]. Thus, caregivers, acting as designers, can intervene directly in their future eHealth tool and draw upon their knowledge to develop

technologies that respect their needs and their ways of doing things [28]. This project has 3 phases (Figure 1). The objective of phase 1 is to identify the needs of caregivers of functionally impaired older persons. On the basis of the results from this phase, the objective of phase 2 will be to co-design an eHealth tool to support the help-seeking process of caregivers. Finally, phase 3 will be a usability study aimed to verify the results obtained with the co-design process.

The Research Sites

The study takes place in 11 regions of Québec (Côte-Nord, Mauricie, Centre-du-Québec, Capitale-Nationale, Chaudière-Appalaches, Montérégie, Bas St-Laurent, Gaspésie, Outaouais, Montréal, and Laval). The meeting places vary, depending on the availability of locations (eg, municipal or community premises or those connected to the HSS network).

Participants and Selection Criteria

The number of participants and the selection criteria for each group of participants are as follows.

1. Caregivers: The objective is to recruit a total of 50 caregivers. In the context of this project, any person who provides unremunerated assistance on a sustained (weekly) basis to a functionally impaired older person will be considered a caregiver.
2. Community workers: The goal is to have 30 members of community associations involved in this project. These must offer services or interact directly with caregivers of functionally impaired older persons.
3. Health and social service professionals (HSSP): The objective is to involve 30 professionals from the public sector of HSS. Like the community workers, these must offer services or interact directly with caregivers of functionally impaired older persons. They may be nurses, nursing assistants, client care attendants, home care workers, occupational therapists, physiotherapists, doctors, social workers, psychologists, or others.

Recruitment

To have access to a diversity of perspectives, it is hoped that the participants will present a variety of characteristics, in terms of their profession (social worker, occupational therapist, physiotherapist, doctor, nurse, etc), their organization (administrative agency, association, organization, and other), and their sociodemographic attributes. A purposive sampling strategy will be used via advertising in local community centers, family medicine groups (FMGs), and community organizations. For the HSSP, direct contact will be made with the management of older persons services. The latter will target potential participants as a function of selection criteria, and the HSSP will establish contact with the research team. A network sampling approach will also be used as recruitment through advertising alone will be insufficient to reach all the types of participants targeted. Thus, community organizations (through a direct approach) and HSSP willing to recruit caregivers to participate in the study will be solicited. When caregivers express interest in participating in the study, HSSP and community workers will be asked to transmit their coordinates so that research agents could establish contact with them.

The Research Team

All stages (recruitment, data collection, and analysis) will be done by 1 or more members of the research team. The research team is made up of the study director; a researcher in gerontology (DG); 2 doctoral students (KL and MT), one of who has experience in user experience and the other in participatory studies; and finally, a research professional with expertise in qualitative research (MC).

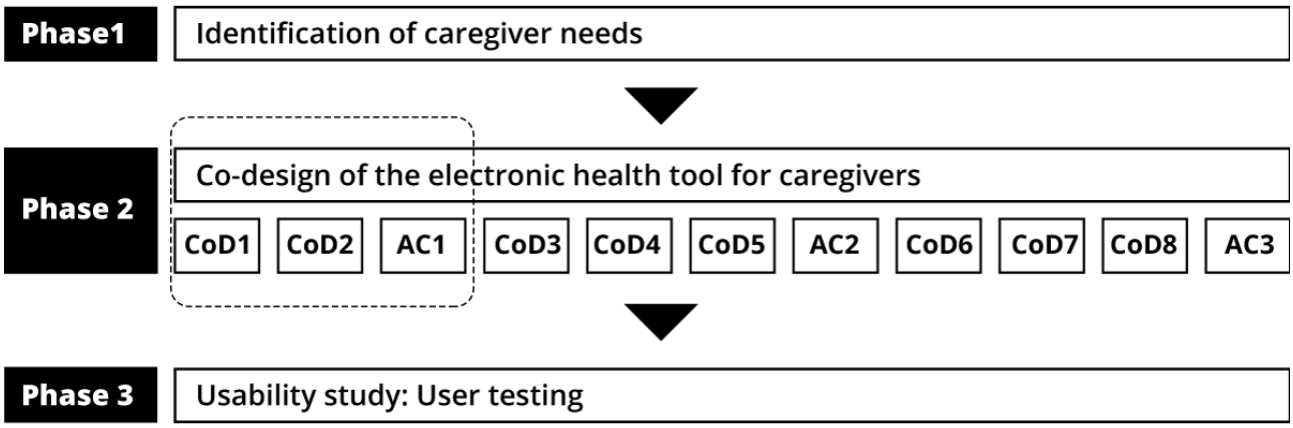
Phase 1 (Objective 1): Identify the Needs of Caregivers in Terms of Tools to Support Their Process of Help-Seeking Behavior

Online Questionnaire

Data Collection

A total of 2 distinct forms of data collection will be used to document caregivers' needs for support in their process of seeking help. The first is targeted at community workers and those from the Québec HSS network. They will be consulted via an online questionnaire inspired by Levkoff's help-seeking behavior model for dementia [22] (see Multimedia Appendix 1).

Figure 1. Phases of project. AC: advisory committee session; CoD: co-design session.



Analysis

Considering that the online questionnaire is essentially composed of open-ended questions, we will use the method of analytical questioning [29]. The NVivo software (QSR International) [30] will be used to facilitate this analysis.

Participants

The participation of 55 HSSP or community workers (approximately 5 participants per targeted region) or a number sufficient to reach the data saturation level is envisaged. The goal is, above all, to reach data saturation.

Individual Interviews

Data Collection

The second form of data collection consists of semidirected individual interviews with caregivers. The interview plan covers sociodemographic data (including a profile of the use of digital tools such as the internet, electronic tablets, and mobile phone); open-ended questions also based on Levkoff's help-seeking behavior model for dementia [22]; and finally, a questionnaire related to the level of literacy, the All Aspects of Health Literacy Scale (AAHLS) [31] (see Multimedia Appendix 2). This measure is important to consider in the development of an eHealth instrument designed for a group, which is homogeneous in its role (in other words, all people who care for an older person) but heterogeneous in its characteristics (with widely varying ages and levels of education). The AAHLS has been validated in English for individuals aged between 18 and 65 years in face-to-face encounters but may be adapted to telephone interviews as it is a self-evaluation measure rather than a direct evaluation of capacities. With this measure, it is not a case of categorizing the levels of literacy but rather of developing a descriptive analysis of participants' capacities [31]. The instrument was translated into French (a free translation) and tested beforehand.

Analysis

As for the online questionnaire, we will rely on analysis through analytical questioning [29]. The NVivo software [30] will be used to facilitate this analysis.

Participants

We expect the participation of 27 caregivers (approximately 2 to 3 participants per targeted region) or a sufficient number to reach the data saturation point.

Phase 2 (Objective 2): Develop a Tool for Caregivers That Meets the Needs They Have Expressed

Co-Design Workshops

In general, co-design includes the creation of a group comprising 8 to 12 people, who jointly develop an eHealth instrument over 3 to 5 co-design meetings, lasting between 90 min and a day [32-37]. Nonetheless, in the context of this project, it is, on the one hand, unrealistic to develop a tool supporting the process of help-seeking behavior in merely 5 working sessions. On the other hand, it is also unrealistic to involve caregivers in all the sessions of such a process, given their onerous responsibilities and lack of available time. In addition, it is important to include the perspective of a number of regions of Québec to take account of the differences in available resources. We, therefore, opted for a different methodology, that is, each co-design session will be composed of a different group. It consists of 8 co-design sessions (with participants of the 11 administrative regions targeted by the project), which will take place over a period of 13 months. The co-design sessions will last 3 hours and will be facilitated or moderated by the research team. Each co-design session is scheduled to continue the work of the previous session until a prototype is made. We aim to have approximately 1 month between sessions to allow the research team to analyze the data and prepare for the next session based on the results of the previous session and at the same time, respect the end of funding. These working sessions will be interspersed with meetings with an advisory committee (which also includes caregivers, community workers, and HSSP) whose mandate is to guide the progression of the prototype and ensure continuity, so that the material stemming from the working sessions is truly integrated into the prototype (Figure 1).

Co-design involves the use of tools and techniques, which combine narratives, creativity, and imagination [38]. A variety of methods will be used (group discussions, world café, individual work, collective sessions, and mock-ups) to ensure we reach all participants based on their individual characteristics and to guarantee that power is shared within the group. This process is intended to be iterative, varying from one session to the next, to cover all the issues effectively. The collaboration of a user experience expert will be necessary to direct the planning of objectives for each session. The results of phase 1 of the project will be presented to the co-designers to fully integrate knowledge about caregivers' needs for support in their process of seeking help.

Data Collection

The data will be obtained from (1) notes taken by the team, (2) artifacts produced by each group, and (3) notes taken after the working sessions via a meeting with the research team to share their impressions. The co-design sessions and those of the advisory committee will be filmed to further develop certain aspects of other methods of data collection if necessary.

Analysis

An analysis by analytical questioning [29] will also be performed using NVivo software [30] to meet the objectives of each session. The final form of the tool (website, mobile app, etc) is unknown as it is the co-designers who will decide on its ultimate version.

Participants

We aim to recruit 6 to 10 participants in each co-design (caregivers, community workers, and HSSP) with a majority of caregivers to ensure a strong voice from this subgroup.

Phase 3 (Objective 3): Evaluating the Tool's Usability and User Satisfaction

The third phase is planned to gauge the instrument's usability. This is a matter of observing potential future users accomplish tasks using the tool, with the aim of identifying any potential problems. Furthermore, 2 distinct methods will be used for the study of usability [39] in the context of an individual encounter

with the participant in a location of their choice, for a maximum of 1 hour. The 2 methods employed are the think-aloud approach, to measure usability, and the questionnaire, to measure user satisfaction.

Think-Aloud Method

First, in a process of digital tool development, the think-aloud method is frequently used to reveal usability problems that the user might encounter with the tool [39]. In general, this method aims to capture a systematic process of thinking aloud and analyze this process to gain a deeper appreciation of any problems, which could arise during the use of the digital tool [40]. As this think-aloud method can prove difficult for participants, a trial run will take place with a task similar to that which will be actually evaluated [40]. These will both take place after the tool is developed (phase 2).

Data Collection

The sessions will be filmed in a context, which includes the individual and the tool, as well as another screen, which allows the user to see directly what is happening with the tool. This will allow for the transcription of all the verbal data and permit us to associate them with the digital tool.

Analysis

The transcriptions will be coded to identify step by step how the person performs the task, as well as the problems encountered. The codes will be generated through an inductive approach [40].

Participants

The selection of a representative sample of potential users is crucial with this type of method, which includes those with a variety of skills. Although it is generally admitted that calling upon 5 participants is sufficient for a usability study, seeking the participation of 10 individuals with diverse perspectives increases the validity of the results by 25% [41]. Consequently, a purposive sample with 5 caregivers and 5 community workers or HSSP is our objective.

Questionnaire

Data Collection

As for user satisfaction (the second method), the most common method used is the questionnaire [39]. The standardized questionnaires used most often are those for user interaction satisfaction, the modified technology acceptance model questionnaire, and the International Business Machines Corporation (IBM) usability questionnaire [39]. The modified technology acceptance model questionnaire was conceived in a telemonitoring context and is less relevant to this study [42]. The questionnaire for user interaction satisfaction in its shorter version includes 20 questions with responses on a scale from 1 to 10. The purchase of a license is required. As for the IBM usability questionnaire [43], it contains 19 questions with responses on a scale from 1 to 7. This questionnaire is designed to be administered after the performance of the task, that is, immediately after the think-aloud method. It is the latter questionnaire, which was selected for this study.

Analysis

A descriptive analysis will be performed (means, percentage).

Participants

The participants will be the same who have done the think-aloud exercise. The questionnaire will be administered during the same session.

Ethical Considerations

This project was approved by the Comité d'éthique de la recherche des Centres de santé et de services sociaux de la Vieille-Capitale (the Research Ethics Committee of the Health and Social Service Centres of the Old Capital). As this is a multicenter project, it also needed and received the approval of each research ethics committee of HSS network centers for the regions targeted through a formal agreement. There is no compensation offered for phase 1 of the project, as this stage does not involve any traveling. A monetary compensation of Can $20 for each participant is, however, planned for phases 2 and 3. There are no physical or moral risks to the study participants. However, it is possible that this could be inconvenient due to a required reorganization of the usual routine or supervision. Throughout the research, the raw data will be rendered anonymous before being analyzed. Only 2 research professionals will have access to the list containing the names and codes, which will be stored separately from the research material, data, and information and consent forms. All the research material, including the information and consent forms and the recordings, will be kept in a locked filing cabinet in a locked room. The digital data will be stored in encrypted files, access to which will be protected by the use of a password to which only the principal researcher and research assistants will have access. Finally, all the material and data will be kept for 5 years and then destroyed.

Peer review of the protocol required by the ethics committee is presented in Multimedia Appendix 3.

Results

The project began in January 2016 with the ethics application for the 3 phases of the project. Ethical approval was received in November 2016. Thus, participants could not be recruited for 11 months. For phase 1, recruitment began in December 2016 and ended in September 2017. By August 2017, 38 community workers and HSSP had completed the online survey. In addition, 15 caregivers have been interviewed. A paper is being written to present the results of phase 1.

Phase 2 began in the spring of 2017 and ended in June 2018. All the co-design sessions have been completed. A prototype has been developed and is being improved following feedback from participants in the recent co-design sessions. Moreover, 3 papers are being written to present the results of phase 2.

Phase 3 of the project will take place from September 2018 to December 2018.

Discussion

Reminder of the Purpose of the Study

Keeping older persons at home largely depends on the help provided by caregivers. However, they need support to identify the needs of the older person they are assisting, their own needs, and the formal services available to meet them [26]. The goal of this multicenter project is to develop an eHealth instrument, which will facilitate this process of looking for help. Nonetheless, this project, following the process chosen by the research team, entails certain challenges.

Challenges Met Until Now

One of the first challenges encountered was obtaining ethical approval. On the one hand, the multicenter nature of the project required obtaining a letter of support from each of the 11 organizations of the HSS network selected by the project. The presentation of the project and the different intermediaries and particularities for each organization were such that 11 months were necessary to complete the ethical process.

Another challenge was that of the recruitment of caregivers, this is, of course, a challenge common to other projects involving those kinds of persons [8]. Although more than 30 FMGs were contacted to request the participation of caregivers, this did not result in the recruitment of any participants. In addition to the fact that we do not have the confirmation that the FMGs actually posted the study project, we hypothesize that the caregivers do not recognize themselves as a caregiver or legitimate to bear this identity [26] and, therefore, do not feel concerned by the project unless the approach is straightforward. To date, the optimal method of recruitment has been through contact with community workers and HSSP. Nevertheless, on the one hand, this reduces the potential number of caregivers, and on the other hand, it leads to a bias in the selection process, due to the fact that these caregivers already have access to a formal service. Therefore, this is a limitation of the project, which needs to be taken into account during the analysis of the results.

Anticipated Challenges

Moreover, the methodology selected to develop an eHealth tool, which genuinely responds to the needs of caregivers, is based on a co-design approach. To our knowledge, few studies have employed this methodology to develop an eHealth tool for caregivers. Co-design includes future users, in this case, caregivers, in the development of the tool, as co-designers. Therefore, this implies a sharing of power with people untrained in either research or design. This is a challenge not faced by other studies led only by research teams. The sharing of discourse and decision-making power is clearly a major challenge not only for researchers but also for future users [44]. As mentioned by Meiland [45,46], 1 of the risks of this method is that the users cannot express their own needs or ideas and instead may simply rally around the dominant figures in the group. To lessen this risk, 2 doctoral students will examine this aspect of co-design. The thesis of 1 of the doctoral students associated with this project bears on potentially unspoken elements in co-design sessions, and she will validate the data with individual interviews following the co-design sessions, if some elements of content were not raised. These potentially unspoken issues will be discussed in the working sessions with the advisory committee, to be able to take them into account, while obviously continuing to respect confidentiality. The second student's thesis will bear, among other matters, on the hoped-for genuinely democratic process, which co-design approach can entail. Moreover, the role of the advisory committee is to ensure that the content emerging from the co-design sessions is effectively incorporated into the development of the tool and that it is not simply the preferences and expertise of researchers that prevail.

Another challenge of this project will be to ensure consistency among the different co-design sessions. Usually, the participants are the same from one session to another, which ensures fluidity between sessions and stimulates the acquisition of design skills. This will not be the case in this study. For this reason, previous group decisions should be presented at each new session to ensure participants' understanding and consistency of decision making. In addition, the role of the advisory committee is to ensure consistency. Moreover, the choice of analyzing the data between each session is designed to also maintain this common thread.

Finally, 1 of the common challenges for all co-design projects is the design of a tool by those who do not necessarily possess any expertise in design or even basic computer skills. Among other things, 1 of the pitfalls encountered in this sense is the difficulty of envisaging new technologies or discussing abstract concepts, such as potential functionality, for example [35]. Among the solutions used to counter these problems is the use of prototypes (light and medium fidelity) to help participants visualize what is discussed [44].

eHealth can support caregivers of older persons in their process of seeking help. This study aims to develop this type of tool through a co-design methodology. Although there are some challenges associated with this type of methodology, it still remains relevant, because it really involves future users in the development of a tool that, in our opinion, increases the chances that it will meet their needs.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Online questionnaire for health and social services or community workers.

[PDF File (Adobe PDF File), 51KB - resprot_v8i4e11634_app1.pdf]

Multimedia Appendix 2

The interview plan of semidirected individual interviews with caregivers.

[PDF File (Adobe PDF File), 122KB - resprot_v8i4e11634_app2.pdf]

Multimedia Appendix 3

Scientific evaluation of the protocol.

[PDF File (Adobe PDF File), 123KB - resprot_v8i4e11634_app3.pdf]

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Abbreviations

AAHLS: All Aspects of Health Literacy Scale
eHealth: electronic health
FMG: family medicine group
HSS: health and social services
HSSP: health and social service professionals
IBM: International Business Machines Corporation

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Protocol

Family in Rehabilitation, Empowering Carers for Improved Malnutrition Outcomes: Protocol for the FREER Pilot Study

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Abstract

Background: Interventions to improve the nutritional status of older adults and the integration of formal and family care systems are critical research areas to improve the independence and health of aging communities and are particularly relevant in the rehabilitation setting.

Objective: The primary outcome aimed to determine if the FREER (Family in Rehabilitation: EmpowERing Carers for improved malnutrition outcomes) intervention in malnourished older adults during and postrehabilitation improve nutritional status, physical function, quality of life, service satisfaction, and hospital and aged care admission rates up to 3 months postdischarge, compared with usual care. Secondary outcomes evaluated include family carer burden, carer services satisfaction, and patient and carer experiences. This pilot study will also assess feasibility and intervention fidelity to inform a larger randomized controlled trial.

Methods: This protocol is for a mixed-methods two-arm historically-controlled prospective pilot study intervention. The historical control group has 30 participants, and the pilot intervention group aims to recruit 30 patient-carer pairs. The FREER intervention delivers nutrition counseling during rehabilitation, 3 months of postdischarge telehealth follow-up, and provides supportive resources using a novel model of patient-centered and carer-centered nutrition care. The primary outcome is nutritional status measured by the Scored Patient-Generated Subjective Global Assessment Score. Qualitative outcomes such as experiences and perceptions of value will be measured using semistructured interviews followed by thematic analysis. The process evaluation addresses intervention fidelity and feasibility.

Results: Recruitment commenced on July 4, 2018, and is ongoing with eight patient-carer pairs recruited at the time of manuscript submission.

Conclusions: This research will inform a larger randomized controlled trial, with potential for translation to health service policies and new models of dietetic care to support the optimization of nutritional status across a continuum of nutrition care from rehabilitation to home.

Trial Registration: Australian New Zealand Clinical Trials Registry Number (ACTRN) 12618000338268; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=374608&isReview=true (Archived by WebCite at http://www.webcitation.org/74gtZplU2).

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KEYWORDS

carers; protein-energy malnutrition; telehealth; intervention; pilot study; older adults; subacute; rehabilitation; aged

Introduction

Background

In older Australians, protein-energy malnutrition (PEM) is highly prevalent and a strong independent contributor to poor health, but is preventable and treatable [1-4]. PEM is defined as the unintentional and preventable loss of lean tissues such as muscle, blood and immune cells, and viscera, with or without fat loss, due to prolonged inadequate dietary intake or uptake of protein and energy [1]. Although PEM may occur at any age, it is most prevalent in older adults due to the higher prevalence of PEM risk factors such as multimorbidity and polypharmacy, and the physiological and social changes that occur during the aging process [5]. A sufficient increase in protein and energy intake and uptake to meet individualized requirements will cease the loss of lean tissues and reverse PEM, except in severe cachectic states [1]. However, encouraging malnourished older adults to consume appropriate types and quantities of foods encounters many diverse barriers due to its deeply complex physiological, socio-economic, and environmental risk factors, as well as unique presentation in each individual [5,6]. Individualized and long-term nutrition support is required to overcome these barriers and enable the older adult to improve their nutritional status [3,7]. Thus, the model of care adopted by many hospitals, which involves short-term treatment by health professionals during a health care admission only, is usually insufficient to effectively treat PEM [5,8].

Interventions to improve the nutritional status of older adults and the integration of formal and family care systems are critical research areas of the United Nations (items 2.6.10 and 2.10.7) [9], and implementing these approaches in rehabilitation facilities is of primary importance in Australia. Australian rehabilitation units have the highest prevalence of PEM internationally (45%-65% versus 30%-45% in the United States, Europe, and Asia when using the same diagnostic tool, N=17 studies, N=4591 participants) [10]. Although the goal of rehabilitation is to increase independence, observational research identified that older patients admitted to rehabilitation with PEM and receiving usual care were being discharged to the community with PEM, where they remained malnourished for at least 12 weeks in their own homes [10]. A recent meta-analysis found the prevalence of PEM in older Australians living in their own homes is 6% (95% CI, 4.4%-8.2%), which represents 228,000 malnourished older adults in 2017 [11]. Further downstream health consequences are severe, where PEM significantly predicts decreased physical function, institutionalization, and rehospitalization, poor quality of life, and death [3,10,12].

Family carers are an untapped resource and feasible group of people eager to support malnourished patients in the long-term [13]. There is a direct causal link between poor nutrition knowledge of family carers and increased PEM risk in older adults [14]. Conversely, studies have found that empowering family carers of malnourished older adults living at home (via training, education, and follow-up) can improve the nutritional status, quality of life, and physical function of the older adult, without increasing carer burden [15,16]. A qualitative study found that family carers believe it is the responsibility of rehabilitation staff to ensure the family carers are engaged as key members of the nutrition care team and that their preexisting caring relationship with the older adult is recognized and respected [13]. The qualitative study further identified the preferred method of engagement was via telephone, which is supported by a recent systematic review and meta-analysis, which found that telehealth was a feasible and effective method to provide PEM treatment post-hospital discharge [17]. The FREER (Family in Rehabilitation: EmpowERing Carers for improved malnutrition outcomes) pilot study will be the first to translate this evidence as a patient- and carer-centered model of care for the rehabilitation and post-rehabilitation older adult setting.

Therefore, this study aims to (1) determine if the FREER intervention in malnourished older adults during and postrehabilitation improves nutritional status, physical function, quality of life, service satisfaction, and hospital and aged care admission rates up to 3-months post discharge, compared with usual care, (2) evaluate secondary outcomes including carer burden, carer service satisfaction, and patient and carer experiences, and (3) assess the feasibility and intervention fidelity to inform a larger randomized controlled trial (RCT).

Methods

Study Design

This is the protocol for a pragmatic mixed-methods two-arm historically-controlled prospective pilot intervention study. This protocol has been reported according to the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) 2013 Checklist [18] as well as the Template for Intervention Description and Replication (TIDieR) Checklist [19]. The

FREER pilot study has been prospectively registered with the Australian New Zealand Clinical Trials Registry Number (ACTRN12618000338268).

Participants and Setting

The recruitment site will be a single government-funded rehabilitation unit (34 beds, average length of stay of 22 days) in rural New South Wales, Australia (conveniently sampled), which is co-located with an acute care hospital. Patients are usually transferred from acute care to the rehabilitation units if they are not independent enough to return to the community after acute illness. However, admissions from the community are also accepted and are usually for the management of chronic conditions such as Parkinson disease or chronic obstructive pulmonary disease. The rehabilitation unit does not admit patients with preexisting dementia or severe cognitive impairment and provides services to general rehabilitation patients (ie, does not have age or diagnosis-specific admission criteria). Both eligible patients and family carers will be recruited according to the eligibility criteria (Textbox 1). Reflecting the pragmatic nature of the study, palliative patients and patients with unexpected discharge to residential aged care are included in the study. According to the Patient Generated Subjective Global Assessment (PG-SGA), patients rated as B (suspected of malnutrition or moderately malnourished) and C (severely malnourished) will both be considered as having PEM. Patients rated as A (well-nourished) will be excluded.

Potentially eligible patients identified by the rehabilitation clinical team using existing malnutrition screening upon admission will be placed on a high protein, high energy diet code, and referred to the study accredited practicing dietitian (MW, herein referred to as the "study dietitian" throughout) for full eligibility screening. Additionally, the study dietitian will attend team ward meetings and discuss patient lists with the rehabilitation clinical team. Ineligible or nonconsenting patients will receive usual care and will not be affiliated with the study. Consecutive rolling recruitment will continue over a maximum of 12 months. Informed by historical control group data [10], it is expected there will be approximately 90 eligible and consenting patients admitted to the rehabilitation unit per year (approximately 280 admissions per year, 40% of patients eligible, and 80% consent rate). Therefore, during the recruitment period, the minimum sample size of 30 patient-carer pairs will be met.

Historical Control Group and Usual Care

Participants in a prospective observational study conducted 2013-2014 will act as a historical control group [10]. The historical control participants were recruited from 2 government-funded rural rehabilitation units in New South Wales (n=14 and n=16 participants respectively), one of which is the study site for the FREER pilot study, with participants having the same eligibility criteria as FREER. They had a mean age of 80 years and 57% were female [10]. The historical control group received usual care, which included being placed on a standard high protein-high energy diet [20] during admission and receiving standard nutrition support from the existing rehabilitation dietitian, but only if referred by the usual clinical pathways. The usual care provided to the historical control group has not changed at the time of the FREER pilot study and therefore is the same care provided to patients' ineligible for FREER. Although the service was available, no participants in the historical control group received outpatient follow-up by a community dietitian [10]. Family carers of patients in the control group were not engaged specifically but may have been involved in some discussions with the rehabilitation dietitian during their care recipient's admission. The outcomes in the historical control group have been published elsewhere [10,12].

Textbox 1. Inclusion and exclusion criteria.

Inclusion

- Adults (≥65 years) admitted to rehabilitation with protein-energy malnutrition diagnosed by the Patient Generated Subjective Global Assessment
- Having a family carer (≥18 years). Family carers will be considered persons (including family or friends) who assist with activities of daily living up until the point of hospital admission, with no financial reimbursement for caring duties beyond a carers pension, with contact with the patient of ≥4 times per week, either in person or by telephone
- Family carer is English speaking and able to act as translator for the patient if the patient is non-English speaking
- Family carers do not have any health-related eligibility criteria applied; however, need to have sufficient independence to assist the patients with activities of daily living

Exclusion

- Patient and/or carer are unable to give consent
- Patient is receiving enteral or parenteral feeding
- Discharge is planned in <6 days from date of eligibility screening
- Patients living in residential aged care prior to rehabilitation admission are excluded. However, patients previously community-dwelling but discharged to residential aged care will be included using an intention-to-treat approach
- The patient and/or carer do not live in the local area. For example, admitted during holiday, or plan to move away from the local area (1.5 hours drive from the unit) within 3 months postdischarge

Sample Size

As a pilot intervention study, the sample size was chosen to reflect resources and funding availability, as well as aiming to match control and intervention participants in a 1:1 ratio. Therefore, the current pilot intervention will aim to match the historical control group sample size (n=30), for a final sample of n=60 patients. The historical control group did not collect data on family carers, as they were not engaged as part of usual care, and therefore not available for recruitment. Therefore, the sample size for family carers will be n=30.

Blinding and Randomization

Randomization is not possible due to the study design. The use of a historical control group for the pilot study was chosen to limit intervention contamination within the small rehabilitation unit as resources did not allow for 2 prospective cluster sites to be recruited. Blinding of participants and personnel to the intervention is not possible due to the nature of the intervention (nutrition counseling), study design of the historical control group (researchers not blinded in the historical control group), and lack of resources to fund blinded outcome assessments for the pilot intervention study.

The FREER Intervention

By integrating formal and family care for malnourished rehabilitation patients, the FREER intervention aims to establish family carers as partners in the nutrition care team, thereby empowering and enabling them to manage and improve the efficacy of their preexisting nutrition-related care in the long term. In order to truly empower the family carer, the level of engagement between the dietitian, family carer, and patient in the FREER intervention model of care is derived from the Patterson, Kirk, and Wallace model, in which all team members have equal involvement and influence [21].

We have applied the four-step systematic approach for using the theoretical domains framework [22] to develop and establish the preliminary feasibility of the FREER intervention strategies. This was done through literature reviews [15-17], a qualitative study of family carer support needs and preferences [13], and stakeholder engagement (n=20 health care staff, unpublished). This pilot study will now establish preliminary efficacy and feasibility of the FREER intervention. All FREER intervention components will be delivered by the study dietitian and will use 3 individualized and needs-based strategies described in Multimedia Appendix I [23,24].

Psychological Model of Behavior Change

Patient and family carer engagement strategies will apply the theory of planned behavior and reasoned action to increase an individual's ability to make recommended changes [25]. Therefore, all engagements with the study dietitian will include education and shared goal setting, problem-solving, and contingency planning [25]. This model of behavior change was selected by the research team as it was considered the most appropriate to create partnerships with the patient and family carer, to lead to empowerment rather than dependency.

Quantitative Outcome Measures

The selected quantitative outcome measures have been validated and previously piloted in the target population [10,12], and are outlined in Table 1. Nutritional status as defined by the PG-SGA numerical score [26] is the primary outcome (increasing score indicates increasing severity of PEM with typical scores 0-30). The PG-SGA was chosen in preference to the Mini Nutritional Assessment [27] and other nutrition assessment tools as both its score and categorization have the strongest criterion validity in this population and it has shown sensitivity to change in 1 week [1]. Secondary outcomes for the patient include (1) additional measures of nutritional status (PG-SGA rating of A, B or C), (2) energy and protein intake (kJ and grams per day), (3) mid-arm circumference (MAC), (4) physical function by Modified Barthel Index (MBI) [28], (5) Functional Independence Measure (FIM) [29], (6) body weight (kg), (7) health-related quality of life using a generic preference-based instrument (AQoL-6D) [30], (8) rehabilitation length of stay, (9) patient nutrition service satisfaction as per purpose developed Nutrition Service Satisfaction Survey modified from the Patient Satisfaction Survey with Inpatient Clinical Nutrition Services (Multimedia Appendix 2) [31], (10) 3 month rehospitalization (yes or no; and length of stay), (11) aged care admission (yes or no; and level of care). Secondary outcomes of the family carer are carer burden (Zarit Burden Interview Score [32]) and carer nutrition service satisfaction (Carer Nutrition Service Satisfaction Survey modified from the Patient Satisfaction Survey with Inpatient Clinical Nutrition Services and shown in Multimedia Appendix II) [31]. All assessment tools and physical measures for the patient will be completed by the study dietitian during patient interview, excepting the service satisfaction questionnaire which will be completed by the patient. All assessment tools for the family carer will be self-completed unless via telephone interview, or the carer has limitations with reading or writing.

The primary and secondary outcomes will be measured at baseline (recruitment T1), rehabilitation discharge (T2), and 12-weeks postdischarge (T3), as described in Table 1. Outcomes will be assessed at the rehabilitation site (T1 and T2) and a home visit or medical records as relevant (T3). If the participant is not able to be assessed at discharge at the rehabilitation site, T2 outcomes will be informed via telephone interview and medical records wherever possible; however, the physical measures including a component of the PG-SGA and the MAC would not be performed in this instance.

Table 1. FREER pilot study primary and secondary outcomes, assessment methods, and timepoints.

Outcome	Baseline (T1)	Discharge (T2)	Postdischarge (T3)	Measure and source of data
Nutritional status	X	X[a]	X	• PG-SGA[b] score and category • Patient and carer interview
Weight (kg)	X	X	X	• Calibrated study scales or medical records • Patient interview
Energy intake (kJ)	X	X	X	• 24hr dietary recall • Patient and carer interview
Protein intake (g)	X	X	X	• 24hr dietary recall • Patient and carer interview
Mid-arm circumference	X	X	X	• Tape measure • Patient interview
Physical function	X	X	X	• Modified Barthel Index • Patient and carer interview supported by allied health care team • Medical records
Physical function	X			• Functional Independence Measure • Medical records
Health-related quality of life	X	X[a]	X	• AqoL-6D[c] • Patient interview
Patient nutrition satisfaction			X	• Patient Satisfaction Survey • Self or carer-completed
Rehabilitation length of stay		X		• Medical records
Rehospitalization and length of stay			X	• Medical records
Residential aged care admission			X	• Medical records • Patient or carer report
Carer burden		X	X	• Zarit Burden Interview • Self-completed
Carer nutrition satisfaction			X	• Carer Satisfaction Survey • Self-completed
Patient and carer experiences and perceptions of value[d]			X[e]	• Qualitative interview conducted via telephone

[a]If T1 and T2 occur 6 days or less apart this measure will not be repeated as it will have assumed not to have significantly changed within that short time period as per feasibility data [10].

[b]PG-SGA: Patient Generated Subjective Global Assessment.

[c]AQoL-6D: Assessment of Quality of Life-6D.

[d]A subgroup of participants will be invited to participate by consecutive sampling with a target sample size of n=10 carers and n=10 patients.

[e]The interviews will be conducted up to 2 weeks following T3 by an independent researcher.

Qualitative Outcome Measures

To understand the carer and patient experience and perception of the value of the FREER intervention, the first 10 participant pairs (both patient and carer, total n=20) who consent to be interviewed will participate in 30 to 60 minute semistructured interviews. Participants will be invited to participate in the interviews up to 2 weeks post T3 (Table 1) via telephone. The first interview with the patient and carer, who will be interviewed together if possible, will be an open discussion focused on topics identified in the literature and will be used to develop the semistructured interview schedule for the remaining interviews. The interviews will be recorded and analyzed qualitatively, using thematic analysis of verbatim interview transcripts based on the principals of grounded theory. For

independence, the interviews will not be performed by nor in the presence of the study dietitian who implemented the FREER pilot intervention, and the interviews will be conducted and reported according to the Qualitative Research Review Guidelines (RATS) [33].

Process Evaluation

A quantitative process evaluation will be simultaneously implemented. The intervention fidelity, intervention adaptions, and attrition rate will be recorded through researcher logs and voice-recorded telehealth consultations. Resources used to implement the process evaluation are outlined in Multimedia Appendix II.

Adverse Events

As the patients are recognized to have acute or chronic morbidity requiring an inpatient admission, as well as being diagnosed with PEM at baseline, medical events and continued PEM are likely to be frequent as reflecting this medical and nutritional status. The FREER nutrition intervention reflects the current usual and best dietetic practice where only the method of engagement with patients and family carers is modified. Although nutritional treatment for PEM is considered low-risk adverse events may occur.

Adverse events possibly or directly related to FREER intervention methods will be recorded. These may be related to (1) nutrition-related biochemistry, (2) bowel habits, (3) allergic reactions to recommended foods and beverages, or (4) hydration status but will only be considered adverse events if status worsens from baseline. These intervention-related adverse events will be considered serious if they lead to the transfer from rehabilitation to acute care, additional intervention by the rehabilitation physician, or mortality.

Ethical Considerations and Withdrawals

This study was approved by the North Coast New South Wales Human Research Ethics Committee (Approval HREC/18/NCC/47) and Governance (528N), as well as the Bond University Human Research Ethics Committee (528N-HREC/18/NCC/47). Written informed consent will be required for patients and family carers prior to their participation. Withdrawal of the patient or the carer from the study will cease the FREER intervention being delivered to both members of the caring pairs. However, the nonwithdrawing patient will continue to be asked to participate in outcome assessments if the carer withdraws from the study.

Statistical Analysis

Intention-to-treat analysis will be used to evaluate quantitative outcome measures. However, those discharged home and those discharged to aged care will be reported separately. If the intervention group sample size is substantially smaller than the historical control group, cases will be matched to create a 1:1 ratio of control versus intervention. Outcomes and participant characteristics will be summarized via descriptive statistics. Changes in the control group over time have been previously analyzed and published [10]; however, the intervention group will be analyzed for change over time in continuous variables using linear mixed models, and chi-square tests for changes over time in categorical variables.

To determine the difference in primary and secondary outcomes between the intervention and control group over time, both continuous and categorical outcome variables will be analyzed via a marginal model using generalized estimating equations, with study group allocation and time in months as main predictors, and adjusting for baseline outcome measures.

Results

Recruitment for the FREER pilot study began July 4, 2018, and is ongoing. At the time of manuscript submission, 14 participant pairs have been identified as eligible, with nine pairs (n=18 participants in total) consenting (preliminary recruitment rate is 9/14, 64%). The reasons for nonparticipation were family carer not interested (3/5, 60%) and patient not interested (2/5, 40%). Three family carers have withdrawn from the study at T2 (discharge). The stated reasons for withdrawal were (1) family carer being overwhelmed with caring duties (1/9, 11%), (2) family carer being overwhelmed with caring duties in the context of worsening carer health (1/9, 11%), and (3) changes to the family caring structure (1/9, 11%). Three of 9 (33%) patients were withdrawn following T2 because of (1) death due to the complication of a preexisting condition (2/3; 67%), and (2) geographical relocation out of the study area (1/3; 33%). The preliminary carer attrition rate is 33% (3/9) and the patient attrition rate is 33% (3/9).

Discussion

Although compared with usual care, supportive nutrition interventions to increase dietary protein and energy intake in malnourished patients across all settings decrease all-cause mortality (risk ratio .78, 95% CI: 0.66-0.92, N=12 trials, N=6683 participants), the evidence is biased by poor quality study designs with limited translation of effective models of care to the clinical setting [2]. The pragmatic design of the FREER intervention will support translation to practice. Although the current pilot study has limitations related to study design, including the use of a historical control group causing selection bias and a lack of blinding, it will provide sufficient preliminary feasibility and efficacy data to inform the development of a future adequately powered, and well-designed RCT. In addition to the need for high-quality RCTs which evaluate nutrition interventions for malnourished older adults, research engaging family carers as part of the medical and nutritional care team is in demand [34,35]. By using a relevant framework [22] this research is designed to inform health service policies and will provide the foundations of future interventions translated into other health care settings and rehabilitation units.

Conflicts of Interest

None declared.

Multimedia Appendix 1

The FREER intervention strategies.

[PDF File (Adobe PDF File), 36KB - resprot_v8i4e12647_app1.pdf]

Multimedia Appendix 2

FREER intervention and research materials.

[PDF File (Adobe PDF File), 349KB - resprot_v8i4e12647_app2.pdf]

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Abbreviations

AQoL-6D: Assessment of Quality of Life-6D
FREER: Family in Rehabilitation: EmpowERing Carers for improved nutrition outcomes
MAC: mid-arm circumference
PEM: protein-energy malnutrition
PG-SGA: Patient Generated Subjective Global Assessment
RCT: randomized controlled trial

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Protocol

The Future of Health Care: Protocol for Measuring the Potential of Task Automation Grounded in the National Health Service Primary Care System

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Abstract

Background: Recent advances in technology have reopened an old debate on which sectors will be most affected by automation. This debate is ill served by the current lack of detailed data on the exact capabilities of new machines and how they are influencing work. Although recent debates about the future of jobs have focused on whether they are at risk of automation, our research focuses on a more fine-grained and transparent method to model task automation and specifically focus on the domain of primary health care.

Objective: This protocol describes a new wave of intelligent automation, focusing on the specific pressures faced by primary care within the National Health Service (NHS) in England. These pressures include staff shortages, increased service demand, and reduced budgets. A critical part of the problem we propose to address is a formal framework for measuring automation, which is lacking in the literature. The health care domain offers a further challenge in measuring automation because of a general lack of detailed, health care–specific occupation and task observational data to provide good insights on this misunderstood topic.

Methods: This project utilizes a multimethod research design comprising two phases: a qualitative observational phase and a quantitative data analysis phase; each phase addresses one of the two project aims. Our first aim is to address the lack of task data by collecting high-quality, detailed task-specific data from UK primary health care practices. This phase employs ethnography, observation, interviews, document collection, and focus groups. The second aim is to propose a formal machine learning approach for probabilistic inference of task- and occupation-level automation to gain valuable insights. Sensitivity analysis is then used to present the occupational attributes that increase/decrease automatability most, which is vital for establishing effective training and staffing policy.

Results: Our detailed fieldwork includes observing and documenting 16 unique occupations and performing over 130 tasks across six primary care centers. Preliminary results on the current state of automation and the potential for further automation in primary care are discussed. Our initial findings are that tasks are often shared amongst staff and can include convoluted workflows that often vary between practices. The single most used technology in primary health care is the desktop computer. In addition, we have conducted a large-scale survey of over 156 machine learning and robotics experts to assess what tasks are susceptible to automation, given the state-of-the-art technology available today. Further results and detailed analysis will be published toward the end of the project in early 2019.

Conclusions: We believe our analysis will identify many tasks currently performed manually within primary care that can be automated using currently available technology. Given the proper implementation of such automating technologies, we expect considerable staff resources to be saved, alleviating some pressures on the NHS primary care staff.

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KEYWORDS

qualitative research; supervised machine learning; automation; interdisciplinary research; task performance and analysis

Introduction

Automation technologies are rapidly changing employment practices across many sectors of the UK economy. The progress of advancements during the digital age has seen new technologies replacing and augmenting human labor in a diverse range of tasks, reshaping the experience of millions of customers and employees. In this protocol, "Automation" is defined as applications of robotics, artificial intelligence, machine learning, machine vision, and similar emerging and mature digital technologies that will allow human work to be substituted by computer capital. It is within this scope that our work aims to understand the state-of-the-art automation in the primary health care sector. A recent example of applying automation technologies to augment or replace human labor is Amazon, a company that recently launched a grocery store—Amazon Go—that uses computer vision to eliminate the role of the cashier, which relates to over 3.5 million people in the United States [1,2]. In addition, Amazon and others also harness intelligent material-moving robots to work alongside the 2.5 million freight and stock hand laborers in warehouses and commercial buildings [3]. Looking ahead, continued progress in state-of-the-art automation technologies will cause further disruption to workers in knowledge- and information-based occupations, who were previously thought to be less susceptible to automation. However, despite widespread concern regarding new technology replacing jobs or how technology will change the structure of jobs, we lack detailed real-world evidence about what can and cannot be automated at the task level; tasks, not entire occupations, are automated. This lack of understanding can be confusing and dangerous for policymakers who want to set effective policies to mitigate the consequences and foster potential benefits.

Dominant frameworks for measuring automation have previously focused on different "types" of occupations and the skills that are required to perform them [4-6]. These studies conclude that occupations with so-called "routine" tasks are the most susceptible to automation, and specifically, manual occupations are easier to automate than cognitive or knowledge-based occupations. Researchers at the University of Oxford analyzed the US Department of Labor Occupational database (O*NET) and found that 47% of US employment is highly susceptible to automation over the next few decades [4]. They propose a probabilistic machine learning approach using numerical occupation features that represent "bottlenecks" to automation and analyzed over 700 occupations, producing an estimate of the *probability of automation* for each. Multiple follow-up studies applied these probabilities to other countries' employment data, assuming an occupation's risk of automation is comparable across countries. Deloitte reported [7] that 35% of current UK employment is at high risk of becoming automated over the same time period. Furthermore, a paper from the Bruegel Think Tank [8] estimated the share of jobs at high risk across Europe to range between 45% to >60%, with southern European workforces (eg, Portugal and Romania) facing the highest probability of potential automation.

From these studies, health care–oriented roles are often estimated to be at low risk of automation. This is, in part, because many health care tasks require a high level of skills that align with the bottlenecks to automation identified [4], such as assisting and caring for others, manual dexterity, social perception, originality, negotiation, and persuasion. A secondary reason for these low-risk estimates is a general lack of empirical data describing work practices, work flows, and the skills required to perform many health care roles, in what is a largely interrupt-driven environment containing many exceptions and social negotiation.

Automated technologies are often speculated to target or displace vulnerable, low-skilled workers. Health care is one of the few economic sectors where automation is seen as an opportunity to address pressures [9,10]. Specifically, the UK National Health Service (NHS) primary care system in England currently faces numerous building pressures such as staff shortages, increased workloads, increased demand, reduced budget, skill shortages, and decreased patient consultation time [10-12]. Generally, automation may address some of these pressures. However, there is a potential threat that through increased automation of tasks, the roles performed by health care staff will need to be reconfigured as described previously [13], which may ultimately affect patients' relationship with their general practitioner and the level of care provided.

A key aspect of our approach is to start with tasks, rather than occupations, to understand what *technically* can be automated and how an occupation's work might be impacted as a result. By collecting granular task-level data, we capture a more accurate effect of automation, since it is tasks, rather than entire occupations, that are automated by new technologies. This approach also provides the most valuable real-world policy insights, with recommendations over entire workflows, potentially saving considerable resources.

The future health sector will undoubtedly involve automation of routine tasks such as scheduling or laboratory test-review tasks; it is also likely to involve technologies that are uniquely developed and still in their infancy. The current applications of automation in health care are a rich and well covered topic with decades of history. The literature includes examples such as electronic medical records, personal health records, remote test ordering and repeat prescriptions, check-in and booking systems, patient access to appointment systems, telehealth and telemedicine systems, physician order entry, clinical decision–support systems, much of the pharmacist's work [14],

automation of data collection from patients in the waiting room [15], and a reduction in provider-to-provider communication [16]. Additionally, numerous different software systems have an element of automation; for example, computerized physician order entry (CPOE) is a decade-old technology that has helped automate workflows such as requesting lab work, checking for allergies, and electronic prescribing [17]. A sophisticated CPOE system can automate some, if not most, of a clinician's work with increasing efficiency. However, it is not completely automated, and a human clinician is still required to keep notes, converse with colleagues, work directly with the patient, reference materials, and likely work in other systems besides CPOE. This example of CPOE systems and similar support systems exemplifies the core of our study: There are automated and partially automated systems to be found throughout primary care. Nonetheless, there is a lack of understanding of the effects of automation to provide further policy and workflow recommendations. Furthermore, the implementation of automation technologies on the assumption that they will *always* provide typical benefits associated with technology may be a false promise, as many information system–implementation projects in health care run over budget, fail to deliver expected results, and demand compromises; these projects also require significant amounts of organizational support and maintenance [18].

Clinical decision–support systems (CDSSs) are similar information systems to computerize physician order-entry systems. A CDSS is an information system designed to, as the name suggests, support clinicians through the process of making decisions on a diagnosis or recommending a treatment or change in therapy. The type of system can range in complexity, depending on what is automated from the clinician's decision-making tasks. A simple CDSS will only check the input from the clinician to confirm that the input is valid and within the range of the specified field, producing an error or notification if the data are invalid. Automated CDSSs are developed for specific clinical specializations and involve the use of data models, standardized medical knowledge ontologies, and other medical and clinical knowledge along with data inputs from electronic medical records to support diagnoses based on the system's guidelines. Complex CDSSs use a series of computational, data mining, and statistical methods to support complex reasoning on classifications of disease, predictions of a disease, or patient concern [19]. Although CDSSs benefit the clinical decision-making process and most studies show that these systems provide benefit, they are easily susceptible to automation bias—the phenomenon where clinicians overly rely on decision systems to the detriment of their own reasoning [20]. Thus, it is important to be mindful of the potential detriments of automation. Understanding the full range of tasks that can be automated and how automation of certain tasks influences the overall work of the clinician is an important step to preventing automation bias.

Prior work also exists in the use of mobile robotics in health care. Areas such as robot-assisted logistics, telepresence and companion robots, education and communication robots, motivational persuasive robots, ageing society robots, and home-assistance robots, all introduce automation health care [21].

Robotic systems are in their infancy, and although many novel approaches are under development for the health care domain, our study does not focus on recommending what specific *type* of technology will or can automate a task. Instead, we seek to understand to what extent health care tasks *technically* can be automated using currently available technology and to interpret and disseminate the effects of this automation in the health care domain.

We have organized the protocol for this study along two aims: (1) to observe and collate a comprehensive understanding of what occupations and tasks occur in primary health care practices and (2) to use expert knowledge of the current state-of-the-art automation technologies as a guide to estimate what tasks and work practices are automatable.

Methods

Design

Our approach constitutes a multimethod research design [22]. Aim 1 uses multiple techniques for gathering qualitative data based on the observed tasks performed by all occupations in primary care. Aim 2 employs a survey and quantitative machine learning framework to analyze the empirical structured qualitative data gathered for aim 1.

A critical part of the problem we intend to address is a formal framework for measuring task-level automation, which is lacking in the literature. This is compounded in the health care domain by a general lack of detailed, health care–specific occupation and task data for good policy insights. Therefore, our first aim focuses on addressing this lack of data by collecting qualitative, high-quality, detailed task-specific data from multiple UK primary health care practices. The second aim then proposes a formal, quantitative framework for probabilistic inference of *task*- and *occupation*-level automatability.

Figure 1 presents a graphical view of the two aims, and specifically, how they interact in the dataset-formulation stage. The project can be summarized by the following key stages:

- Fieldwork: Detailed qualitative observational work over a period of 12 months while visiting primary care practices in England.
- Task specification: Qualitative analysis to categorize observed work into a formal concept of a *task* within primary care. As a basic unit of work, a task contains a detailed description of work performed and many indicator variables.
- Primary care survey: Conduct an online survey of primary care staff, aimed at understanding and validating task specification and the tasks that most impact daily workloads.
- Dataset formulation: A process of recording each observed task performed by each occupation in a practice and formulating a matrix of observed occupation-task pairs.
- Expert survey: Conduct a large online survey on automation, including top academics and industry experts in machine learning, robotics, and artificial intelligence, to rate how

automatable specific tasks are today (not restricted to the health care domain).
- Augmenting the dataset: Our primary care occupation-task dataset, meticulously derived in aim 1, is augmented with numeric attributes available from a publicly available occupational survey produced for the US Department of Labor called the O*NET database.
- Machine learning predictions: The numeric O*NET attributes describing the skills, knowledge, and abilities each task requires are used as input in a machine learning model, trained on the tasks where expert estimates are available (from the survey), in order to predict the automatability of health care tasks.
- Insights: Analysis performed on the automatability of tasks in primary care, the occupations that involve them, aligned with detailed qualitative analysis to form policy recommendations to aid current working practices.

Each of these stages is further detailed in the following sections for aim 1 and aim 2.

Aim 1

Process

We first address the general lack of detailed data on the topic of automation in the NHS health system. Our aim is to observe work practices and collect data for a comprehensive list of tasks performed by each occupation in NHS primary care. This collection of detailed and rich data is guided by interviews, document collection, photographs, detailed field notes, and occupation shadowing. These observational data are qualitatively analyzed and organized into a formal dataset that supports the second aim of the project: Analyzing the data using machine learning techniques to infer automatability. The dataset created in aim 1 is validated using focus groups, where tasks performed by an occupation are presented and discussed in person.

The qualitative work detailed in aim 1 of this protocol complies with the requirements of the Department of Health Research Governance Framework for Health and Social Care 2005 in the United Kingdom and is approved by both a research ethics committee and the NHS Health Research Authority. No patient data are collected as part of this research.

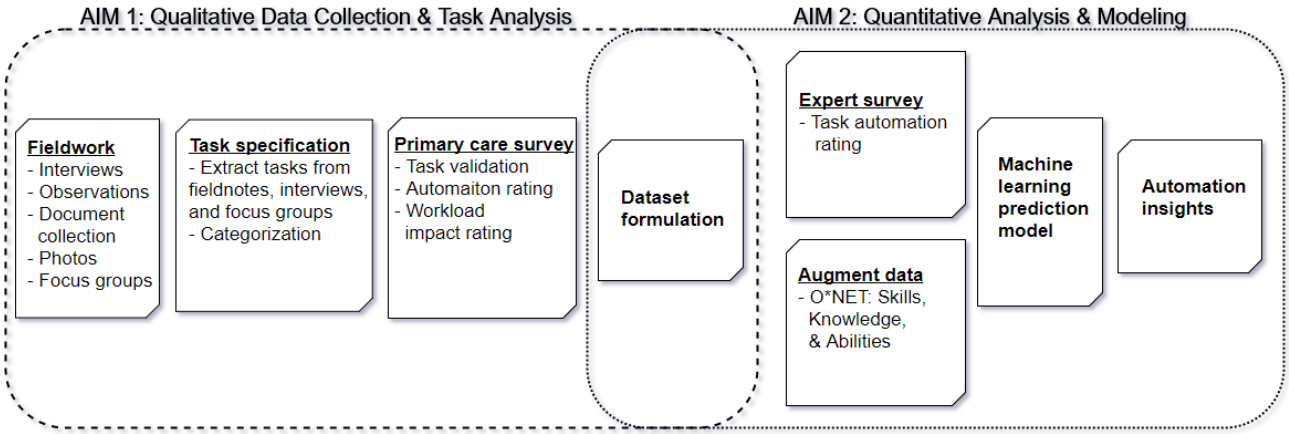
Fieldwork

To understand the work practices of all primary care staff, from partner general practitioners to receptionists, we employ an ethnographic method to observe situated practices, ask questions, gather documents, write detailed field notes, and catalogue each occupation with as much clarity as possible. Time spent on site at each health center ranges from 3 days to over a week. Prior to starting fieldwork, the field researcher works with practice staff to build a schedule, where time can be made available with each occupational type. Since this project is interested in the *tasks* each *occupation* performs, we do not need to observe every member of the staff, but only a representative subset if there are multiple employees of each occupation type. When developing this schedule, we will also make time for the field researcher to attend general practitioner meetings, chronic disease clinics, and other special events that showcase other occupational tasks of primary care. To date, six practices have been recruited, with task data collected on every occupation type in each practice.

The field research focuses on four streams of data collection:

1. Observation of day-to-day work and tasks performed by staff members. This includes asking detailed questions and behavioral queries to understand specific skills required to accomplish tasks, the description of specific computer use and software configuration, or the specific order in which filing must be performed (ie, any details about identified routine tasks).
2. Collection of documents such as training manuals, job-description documents, policy and protocol manuals, and other organizational documents that describe work tasks and how the practice is to be run. This can extend to photographs of documents or information scattered throughout the practice to understand how work and tasks are documented and distributed.
3. Photographs of work spaces and manual physical tasks in the general practice.
4. Audio-recorded discussions of work processes or tasks taking place and any specific required skills necessary to perform day-to-day tasks.

Figure 1. Study design. O*NET: US Department of Labor Occupational database.



Focus Groups

At the end of the field researcher's observations and initial data collection, a focus group is conducted with all primary care staff at the facility, given staff availability. The focus group, while providing additional data, serves as a validation technique for the collected data. During the focus group, the field researcher presents their representation and descriptions of tasks to each occupation in turn to achieve an accurate representation. Additional information can be added to the collected data at this stage through conversations with the individual workers to best portray each occupation's work.

In addition to task validation, the focus group allows for discussion of health care professionals' perceived benefits, opportunities, and challenges to automation of work in primary care. The field researcher also presents several different scenarios that involve the automation of different types of work in the health center. These scenarios are intended to generate discussion between participants in the focus group about potential changes in work due to automation.

Task Validation and Workload Measurement Survey

The second validation technique utilized in this study is the distribution of a survey to support the accuracy of task descriptions for each occupation and to provide a rating of how automating a task would impact individual's workload. The survey aims to augment the tasks gathered throughout the fieldwork, focus groups, and interviews described above. Survey respondents are shown the set of tasks that are performed in their occupation. For a subset of tasks, the survey asks the question, "If it were possible to fully automate the above task, i.e. entirely performed by a computer or a collection of technologies, how would it influence your daily workload?" The response options include "I do not perform this task," "There would be no change in my workload," "There would be little change in my day to day workload, and would not save much time," "Automating this task would provide me time to work on other tasks in my workload," and "Automating this task would eliminate a core aspect of the work identified in my job description." The survey data collected are used to augment the detailed observation task dataset created throughout the aim.

Aim 2

Process

In the second part of the project, we develop a formal, quantitative method for inferring the automatability of all health care tasks observed during aim 1. First, we augment the collected health care occupation-task dataset with existing high-dimensional data about skills, knowledge, and abilities required to perform each task (120 numeric attributes). Second, a large and comprehensive survey of machine learning, robotics, and artificial intelligence experts is conducted to elicit expert estimates regarding the current state of automation of real-world tasks, not specifically restricted to the health care domain. Third, these estimates are used to train a probabilistic machine learning model to identify patterns connecting task automatability to the occupation and task characteristic attributes. The three steps—augmentation of task dataset, automation of expert survey, and development of the machine learning model—are discussed in detail below.

Augmenting Task Dataset

The detailed observational and qualitative health care–specific data captured in aim 1 is transformed into a matrix of occupational roles and tasks performed, with each row representing a unique occupation-task pair plus indicator variables. We then augment these identified occupation-task pairs with numeric attributes from a publicly available occupational survey produced for the US Department of Labor: O*NET 2016 database. O*NET provides key features of an occupation as a standardized and measurable set of variables as well as open-ended descriptions of specific tasks each occupation performs; its strengths and weaknesses are reviewed in detail in a previous study [23]. The database contains information on more than 1000 US occupations using a modified form of the Standard Occupation Classification system, comprising over 2000 detailed work activities and nearly 20,000 individual occupation-specific tasks arranged in a hierarchical structure. A simplified hierarchy of the O*NET taxonomy is presented in Figure 2.

Figure 2. Simplified overview of O*NET database architecture, representing occupations (o_1, o_2), tasks (t_1...t_7), work activities (w_1, w_2, w_3), and major occupation groups and activity groupings. O*NET: US Department of Labor Occupational database.

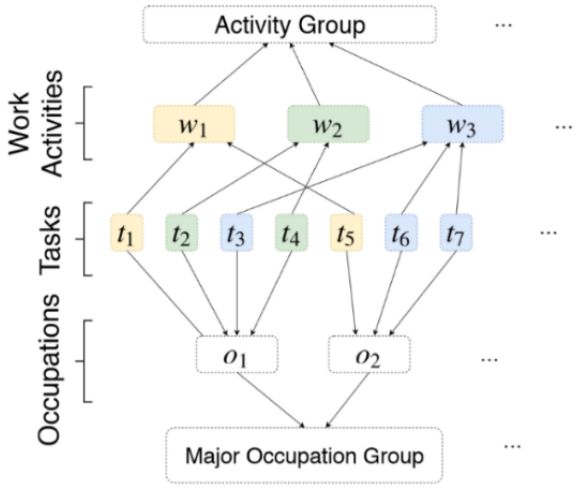
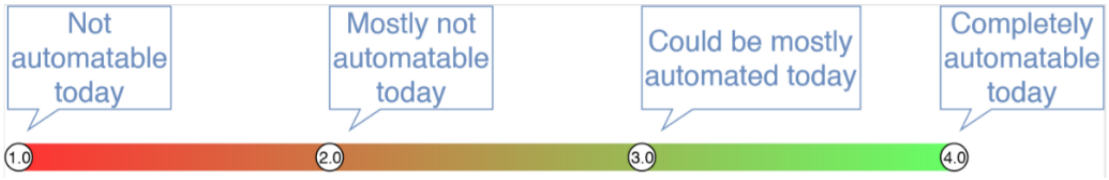


Figure 3. Our continuous scale of automatability.



The O*NET occupational variables include 35 skill attributes such as "coordination," "critical thinking," and "time management"; 33 knowledge attributes such as "mathematics," "clerical," and "sales and marketing"; and 52 abilities such as "depth perception" and "speech recognition."

The variables described as "bottlenecks to automation" in previous literature [4] are a subset of the 120 O*NET variables used in our study. Further, in a recent report by McKinsey Global, 18 of the O*NET variables were used to represent work activities [23]. We will not manually select a subset of the variables in this work. The numerical attributes are designed to provide an accurate representation of an exemplar employee within each O*NET occupation, where each occupation is *also* represented by the collection of tasks they are required to perform. We assume that an occupation's skills, knowledge, and abilities inform those needed to perform the occupation's list of tasks. Next, we aggregate the occupation variables into work-activity variables by taking a weighted average of an activity's tasks, normalizing it over the combined weight of the task's relative importance to its occupation and work activity.

We manually match the observed health care tasks to their corresponding "work activities" within the O*NET hierarchy, allowing for a one-to-many weighted mapping. This allows the observed health care tasks to be augmented with high-quality O*NET variables related to the level of skills, knowledge, and abilities required to perform such tasks. The result of these manipulations is that each observed health care occupation task is represented by a vector of 120 numeric attributes, which are vertically stacked to become a training data matrix for our proposed machine learning model.

Automation Expert Survey

The second step is elicitation of expert knowledge of state-of-the-art automation technologies. In order to obtain estimates on how automatable our health care–specific tasks are, we survey machine learning, robotic, and artificial intelligence experts at the forefront of research and commercially available technology. The survey is designed such that each participant is presented with five O*NET occupations (chosen to be representative of the feature space, with an emphasis on high employment, and hence, familiar occupations). Survey participants rate how automatable the five "most important" tasks are (task importance is relative to occupation, as defined in O*NET). The survey asks the question, "Do you believe that technology exists today that could automate these tasks?" Participants rate each task with one of the following options: 0, Unsure; 1, Not automatable today; 2, Mostly not automatable today (human does most of it); 3, Could be mostly automated today (human still needed); and 4, Completely automatable today.

Our demographic is specifically technology experts, as opposed to health care experts, because we believe that annotating basic tasks requires little-to-no subject matter knowledge. If respondents feel any doubt in their ability to assess the automatability of a task, they can select the "Unsure" option.

We combine each task's multiple expert labels using Independent Bayesian Classifier Combination (IBCC), a principled Bayesian approach to combine multiple classifications [24]. IBCC creates a posterior probability over labels that reflect individual labeler's tendencies to agree with other labelers over the ultimately chosen label values. We then average the IBCC task scores into their task's work activities (corresponding to the tasks' parent in the O*NET hierarchy; Figure 2). A score of 4 represents a fully automatable work activity, and a score of 1 represents an activity that cannot be automated using currently available technology (Figure 3).

We believe a survey of experts, combined using IBCC, provides a robust ground truth estimate to what extent activities are automatable using currently available technology. One important note is that the survey results provide a measure of what *can* be automated using technology, with no prediction of future technological advancements (ie, not what necessarily *will* be automated, given technology uptake or societal pressures).

Development of the Machine Learning Model

Finally, we plan to use a machine learning framework to learn functional mapping between the skills/knowledge/ability feature vectors (the 120 O*NET attributes) of a work activity and the ground truth automation scores elicited from our expert survey combined using IBCC. Gaussian processes [25] are a modeling tool that have a natural advantage in this scenario and offer advantages to policymakers, such as providing formal estimates of uncertainty within the model. The algorithm uses the trends and patterns it has learned from labeled data to provide a smoothly varying, probabilistic assessment of automatability as a function of the input variables. For the Gaussian process, this function is nonlinear, meaning that it flexibly adapts to the patterns inherent in the training data. Gaussian processes have been successfully applied to occupation-based data [4,26], personalized electronic health monitoring [27], and patient-risk monitoring [28].

We will train the Gaussian process model on 314 work activities present in O*NET, for which expert labels are available from the survey. We will specifically use the ordinal likelihood function [29] to reflect the nature of having discrete labels but with an ordinal interpretation ("not at all" to "completely" automatable). In brief, we will optimize the Radial Basis Function kernel hyperparameters by minimizing the negative marginal log likelihood [21]. Once trained, the model will allow us to estimate the automatability of "unlabeled" work activities (ie, activities where expert labels were prohibitively difficult

to obtain). This is performed using open-source software GPFLow [30]. The Gaussian process model is evaluated based on its ability to predict the automatability of work activities "held out" from the training process. We compare models based on their "tolerance accuracy" score, which is the percent of predictions within 0.5 of the ground truth IBCC survey score. This is a sensible score for our task and allows more flexibility in our multiclass ordinal setting than strict accuracy or average error. We find that the ordinal Gaussian process performs better than other methods such as random fields, neural networks (with ordinal loss), or ordinal regression.

Results

We have recruited six general practice medical centers as of October 2018. We have started looking at each occupation and their work practices in primary care. We anticipate that the results will be available in early 2019. The initial findings will be disseminated in a report for the project funder, The Health Foundation. Some preliminary findings from the project are presented below.

We have identified 16 unique occupational roles in primary care. These 16 occupations conduct all the work that occurs in primary care and have currently catalogued over 130 unique tasks. In general, each occupation performs 10-20 tasks regularly. For practice staff (nonclinical occupations), there are three to eight tasks that require collaboration of another person to complete. For example, signing off prescriptions or letters, reviewing documents, gathering signatures from multiple people, or entering a portion of data into an electronic system.

Apart from face-to-face meetings and phone calls, we observed that nearly every other task relies on a desktop computer in some way. This heavy use of desktop computers is an important indicator for future automation, since it is likely that software-based automation will be a large driver of further automation such as robotic process automation. For example, most staff in primary care spend the majority of their time interacting with the electronic medical record; however, we have observed that different occupations use the software in different ways.

Going forward, we expect to determine how a task could be restructured, what technologies the task might require, how much time an occupation spends in performing tasks, and how multiple staff collaborate on tasks, all of which highlight important factors used to address the second aim of our research.

Inductive qualitative content analysis has been performed as part of aim 1. The results of this analysis have produced categories that we will continue to build on and plan to use in future analysis. These categories will help us identify work that can be automated or presents a technological challenge to automation. Specifically, we are interested in potential correlations between the identified categories of primary care work and their association with the probability of task automation. This correlation will help us identify categories of work or entire workflows that are closely correlated with high or low probabilities of task automation in order to propose future automated workflow design within the health care domain.

Discussion

In this protocol, we address two issues: one is an inherent lack of detailed data on task-level work practices of occupations in primary care and the second is the development of a formal representation for estimating task automatability and its impact on health care occupations.

Through this work, we advance earlier research from the University of Oxford [4] on automation and its effects on employment. Specifically, we address the understanding that occupations are unlikely to be automated in their entirety, but their composite tasks may be automated, by taking a task-level approach to modeling automation [13,31,32] and identifying where efficient workflows could arise. We believe this work will inform policy decisions and best practices in primary care on the design and configuration of occupational workloads and tasks in primary care. Specifically, we hope to provide some guidance about where in the general practice surgery work can be automated, what kind of work is most amiable to automation, and what type of skills that cannot be easily automated are important for the health care sector to invest in their future workforce.

There is a common belief that typical health care–related occupations are associated with a low risk of automation. Through our detailed task-level data collection and expert elicitation, we gain clear insight into which tasks are *technically* automatable. In turn, our machine learning model learns which tasks require a human to manually perform them and specific attributes that drive higher or lower automatability estimates using sensitivity analysis.

From our initial fieldwork, we have found that many forms of automation already exist in health care. We observed that these forms of *automation* increase the productivity of human employees; however, they often do not remove tasks entirely. In fact, some of these forms of automation have created *more* work for staff. Although automation has allowed humans to process tasks more efficiently, more administrative work needs to be processed as well. We anticipate that our analysis will inform the design and reconfiguration of work processes in primary health care and lead to recommendations of new automated processes.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

O*NET: US Department of Labor Occupational database
NHS: National Health Service
CPOE: computerized physician order entry
CDSS: clinical decision support system
IBCC: independent Bayesian classifier combination

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Protocol

Hospital in Motion, a Multidimensional Implementation Project to Improve Patients' Physical Behavior During Hospitalization: Protocol for a Mixed-Methods Study

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Abstract

Background: Despite the evidence of the adverse consequences of immobility during hospitalization, patients spend most of the time in bed. Although physical activity is a modifiable factor that can prevent in-hospital functional decline, bed rest is deeply rooted in the hospital culture. To attack this, a multidimensional approach is needed. Therefore, Hospital in Motion, a multidimensional implementation project, was designed to improve physical behavior during hospitalization.

Objective: The primary objective of this study is to investigate the effectiveness of Hospital in Motion on inpatient physical behavior. Secondary objectives are to investigate the effectiveness on length of hospital stay and immobility-related complications of patients during hospitalization and to monitor the implementation process.

Methods: For this study, Hospital in Motion will be implemented within 4 wards (cardiology, cardiothoracic surgery, medical oncology, and hematology) in a Dutch University Medical Center. Per ward, multidisciplinary teams will be composed who follow a step-by-step multidimensional implementation approach including the development and implementation of tailored action plans with multiple interventions to stimulate physical activity in daily care. A prepost observational study design will be used to evaluate the difference in physical behavior before and 1 year after the start of the project, including 40 patients per time point per ward (160 patients in total). The primary outcome measure is the percentage of time spent lying, measured with the behavioral mapping method. In addition, a process evaluation will be performed per ward using caregivers' and patient surveys and semistructured interviews with patients and caregivers.

Results: This study is ongoing. The first participant was enrolled in October 2017 for the premeasurement. The postmeasurements are planned for the end of 2018. The first results are expected to be submitted for publication in autumn 2019.

Conclusions: This study will provide information about the effectiveness of the Hospital in Motion project on physical behavior and about the procedures of the followed implementation process aimed to incorporate physical activity in usual care. These insights will be useful for others interested in changing physical behavior during hospitalization.

Trial Registration: Netherlands Trial Register NTR7109; https://www.trialregister.nl/trial/6914 (Archived by WebCite at http://www.webcitation.org/76dyhdjdd)

International Registered Report Identifier (IRRID): DERR1-10.2196/11341

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KEYWORDS

hospitalization; implementation science; activities of daily living; interdisciplinary care; mobility; physical activity

Introduction

Background

More than 2 million patients are admitted to Dutch hospitals yearly, with a mean admission time of 7 days [1]. Although hospital admissions are necessary to diagnose or treat patients for health issues, hospital admissions also have downsides. Diverse studies show that hospitalized patients spend most of the time lying in bed, whereas in the last 20 years, a growing body of evidence is established showing the adverse consequences of bed rest [2,3]. Restricted physical activity and immobilization can increase hospital-related complications [3,4], and many studies have proven that inactivity is associated with reduced muscle mass and strength [5]. In addition, bed rest results in an increased risk of diverse medical complications [6-8]. Moreover, lower levels of physical activity are associated with a functional decline and new disability in activities of daily living (ADL) after discharge [3,4,9-12]. This functional decline is labeled as a hospitalization-associated disability (HAD), and HADs have profound implications for patients as it leads to long-term care in nursing homes, readmissions, and even death [11]. In research reports, HADs are described as both preventable and iatrogenic and as a direct result from the actions of a health care provider or institution. HADs can, therefore, be considered as collateral damage of the treatment in a hospital in which health care professionals and policy makers have a responsibility in resolving this problem [13]; especially, as early mobilization and higher levels of physical activity during hospitalization have proven to decrease the risk of complications and length of stay (LOS) [14].

Nevertheless, patients are reflexively put into pajamas, transferred into bed [15], and spend less than 6% of the day being active [2-4,9]. Lack of knowledge and time is often mentioned by caregivers as a barrier to promote physical activity [16,17]. This lack of time results in nurses prioritizing their medical tasks above assisting with patient mobilization and stimulating physical activity in patients with the ability to perform their own ADL tasks [16,17]. Studies targeting sedentary behavior during hospitalization have shown that physical activity is a modifiable factor that can prevent in-hospital functional decline [14,18-20]. These studies mostly focused on single interventions, whereas sedentary behavior is deeply rooted in the hospital culture. A multidimensional project focusing on environment, caregivers, and patients using multiple interventions may possibly be even more effective [21]. Even so, literature suggests that a comprehensive and flexible framework may help create sustainable interventions, leading to significant changes in clinical practice [22]. However, projects or studies to improve physical behavior focusing on the whole system, integrating physical activity in all levels of daily hospital care, are not common. Moreover, these studies focused mainly on elderly, whereas low mobility is of all ages [19,22]. Therefore, Hospital in Motion, a multidimensional project to improve patients' physical behavior during hospitalization, has been developed.

Objectives

The primary objective of this study is to investigate the effectiveness of Hospital in Motion on physical behavior within 4 wards (cardiology, cardiothoracic surgery, medical oncology, and hematology).

Secondary objectives are to investigate the effectiveness on length of hospital stay and immobility-related complications of patients during hospitalization and to monitor the implementation process.

Methods

Context

In November 2015, the project Hospital in Motion was started at the University Medical Center Utrecht (UMC Utrecht). Hospital in Motion is a complex multidimensional project primarily designed to improve physical behavior during hospital stay, defined as a decrease in patients' sedentary behavior (lying) and increase in physical activity (ie, standing, walking, and exercising). This project follows 2 approaches. The first approach focusses on creating a hospital-wide awareness of the high amount of sedentary behavior during the hospital stay and the known associated adverse effects, and the necessity to incorporate physical activity in usual care. The second approach includes the development and implementation of tailored action plans for each clinical ward. In 2016 and 2017, a pilot study was performed on the geriatric department. Preliminary results and gained experiences during this pilot form the basis of this study protocol.

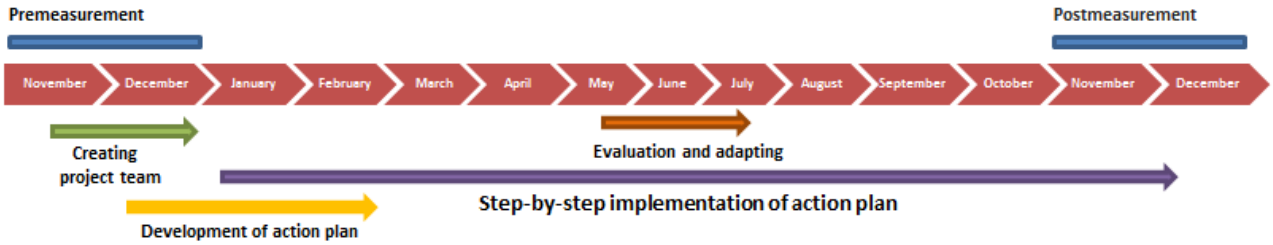
Setting

This study will be conducted within 4 wards (cardiology, cardiothoracic surgery, medical oncology, and hematology) of the UMC Utrecht, the Netherlands. Per ward, a tailored action plan will be implemented. The study protocol was assessed and approved by the medical ethics committee of the UMC Utrecht (study protocol number 16-250). Verbally informed consent was obtained from all patients.

Study Design

An observational study with a prepost design will be used to evaluate the effectiveness of Hospital in Motion on physical behavior. In addition, the implementation process will be evaluated by using a qualitative approach. Data will be collected before and after implementation. The duration of the implementation project is planned for 10 months, starting in January 2018 (Figure 1).

Figure 1. Timeline of the implementation project Hospital in Motion.



Implementation Approach and Interventions

Hospital in Motion will be implemented following the step-by-step model of Grol and Wensing (Figure 2) [23]. Steps 1 to 3 include the development of proposal for change, analysis of actual performance, and problem analysis. Step 4 includes the selection of strategies and measures to change practice, which will be identified by a multidisciplinary project team per ward. During step 5, an action plan consisting of multiple interventions will be developed, tested, and executed at each ward. This plan will consist of 6 general topics:

1. Education: Education is an important cornerstone for increasing awareness on the importance of physical activity [17,24], for example, education for the staff members about the dangers of bed rest and posters and leaflets for patients about the importance of staying active during hospital stay.
2. Physical activity as part of usual care: For successful implementation, physical activity needs to be incorporated in usual care and all caregivers with direct patient contact need to be involved [17,25], for example, integrating questions on the physical activity level in the anamneses of nurses and physicians, standardized reporting of daily mobility levels in the patient records, and discussing the patients mobility during multidisciplinary meetings.
3. Involving third parties: Involving the social environment (ie, family, friends, or volunteers) to improve inpatient physical behavior, for example, family and visit leaflets with information about the importance of physical activity during hospitalization and tips to improve patients' physical activity [26,27].
4. Stimulating environment: Currently, hospital wards are not stimulating environments for performing physical activity [28]. Changes in the environment are conditional for stimulating physical activity, for example, by adjustments of the accommodation inpatient areas, introducing shared lunching, and visualizing walking routes.
5. Mobilization milestones: Daily mobilization goals are successful in increasing walking distance, ADL activities, and number of mobilization moments out of bed [14]. The use of a mobility scale or activity trackers are examples of interventions, which could be used to set personal mobility goals.
6. Technology support: Implementing technological applications such as cycle ergometers with interactive screens, activity trackers, or mobile apps to support, stimulate, and measure physical activity [29].

Outcome Evaluation

In total, 160 patients will be included during a period of 2 months (40 patients per ward). Each patient admitted in the specific ward is eligible to participate in this study. Exclusion criteria for participating in this study were delirium and other cognitive impairments, whereby patients who were not able to provide informed consent were excluded. Patients receiving terminal care were also excluded.

Primary Outcome

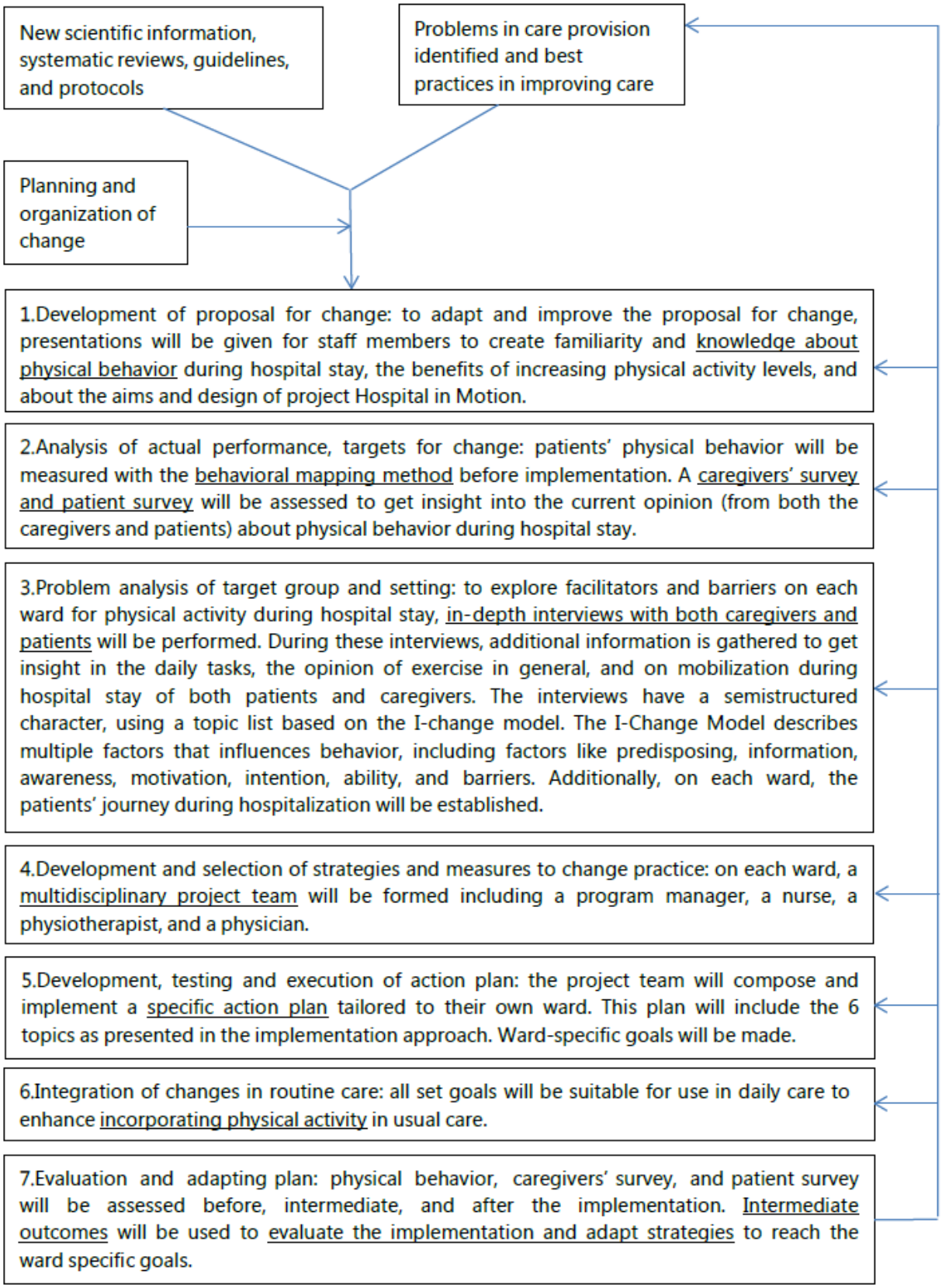
Physical behavior will be measured with the behavioral mapping method [30] and will be assessed before and after the implementation period (Figure 1). Patients will be observed on a random weekday of their stay in a fixed order every 10 min for 1 min. During this minute, the patients' location, body position, daily activity, and direct contact will be registered [30]. A maximum of 8 patients per ward per day can be observed, and observations take place from 9 am until 4 pm.

Physical behavior is defined as the percentage of the total observed time that a patient spent in a specific body position. A distinction will be made between lying, sitting (bedside or chair), and moving (standing, transferring, walking, and cycling). The primary outcome in this study is the percentage of time spent lying.

Secondary Outcomes

Secondary outcomes are the percentages of time spent sitting and moving, LOS, and the incidence of immobility-related complications (ie, pneumonia, aspiration, chest infection, pulmonary embolism, deep-vein thrombosis, urinary tract infection, and pressure sores) [31]. LOS and immobility-related complications will be retrospectively retrieved out of the electronic patient file.

Figure 2. Implementation model based on the study by Grol and Wensing.



Patient Characteristics

Demographic characteristics that will be documented are gender, age, admission reason, specialism, the use of mobilization tools (ie, rollator, walker, crutches, or stick), urine catheter (yes/no), infusion (yes/no), and main perceived limitations during physical activity (eg, pain and exhaustion). In addition, the health perception and physical functioning of patients will be assessed.

The subjective believed health questionnaire is used to obtain the health perception, defined as "individual's experience of physical and mental functioning while living his life the way he wants to, within the actual constraints and limitations of individual existence" [32]. The questionnaire consists of 8 questions; question 1 and 2 focus on subjective health, scored on a ladder-type scale from 0 to 10. Question 3 to 8 focus on perceived control and acceptance, scored between 1 (completely disagree) and 7 (totally agree) [33].

The Activity Measure for Post-Acute Care (AM-PAC) is a validated measurement instrument based on the activity limitation domain of the International Classification of Functioning, Disability and Health. In this study, the AM-PAC "6-Clicks" measures of basic mobility and daily activity in acute care will be used. These short forms have shown to be valid for assessing patients' activity limitations in acute care settings [34,35]. Handgrip strength can indicate the overall strength of an individual and can provide insight into the level of physical function [36,37]. Handgrip strength will be measured with the Jamar hydraulic hand dynamometer, which is an isometric, hydraulic, and easily accessible tool with excellent test-retest reliability (r>0.80) and interrater reliability (r=0.98) [36,37]. The 30-seconds chair stand test is a reliable and valid measurement method for lower extremity strength assessment and a good indicator for a person's level of physical function [38].

Sample Size Calculation

In this study, per ward 40 patients will be included per time point. This number is based on earlier studies evaluating physical behavior with the behavioral mapping method [39]. Patients will be included on 4 wards, leading to a total study population of 160 patients. To check if this number is adequate for powered effectiveness analyses, a sample size calculation was performed. For the sample size calculation, unpublished observation data from the UMC Utrecht in 2016 were used, in which 80 patients across the hospital were observed according to the behavioral mapping method. These data demonstrated that patients spent 56.01% of the time lying, with an SD of 32.53. On the basis of an earlier study evaluating the implementation of a multidimensional intervention to improve patients' physical behavior, a decrease of 15% in the time spent in bed is expected to be feasible [18]. According to the sample size calculation, including a power of 80% and a P value of .05, a sample size of 74 patients would be needed. This confirms that the proposed sample size of 160 patients is more than adequate to evaluate the effectiveness of Hospital in Motion.

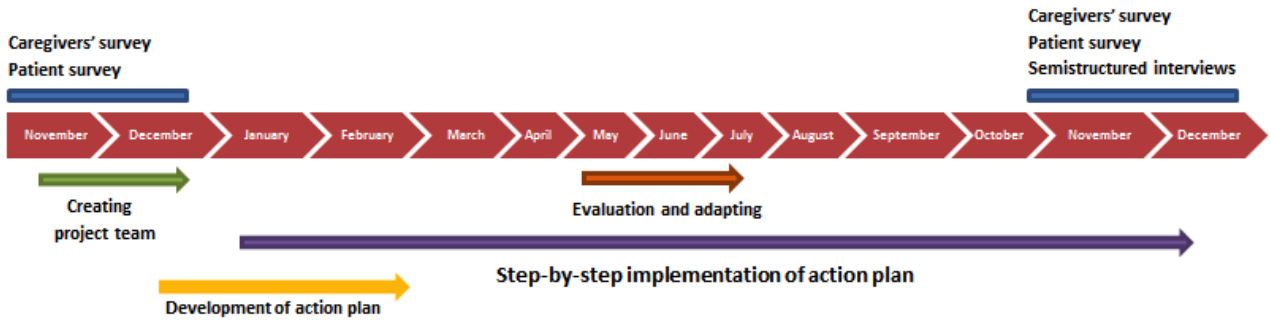
Process Evaluation

Process evaluations are advised to monitor implementation processes of complex interventions and to evaluate factors of influence on the implementation. In this study, the framework of the medical research council guideline 2008 is followed to guide the process evaluation [40]. The 3 key functions of this framework include implementation, mechanisms of impact, and context. Implementation contains the goals and interventions that have been delivered by the project, including the adaptations, dose and reach, and how this delivery is achieved. The mechanisms of impact include the response (of caregivers and patients) to the interventions, the mediators, and all unexpected pathways and consequences. Context includes all other factors that may affect the implementation, interventions, and outcomes, such as barriers (eg, openness to changes, motivation, workload, and money) and facilitators [40]. For the process evaluation of the Hospital in Motion study on the different wards, a caregivers' survey, a patient survey, and semistructured interviews with patients and caregivers are developed, which contain items of the 3 key functions of a process evaluation. The caregivers' survey and the patient survey will be conducted before and after the implementation period. The semistructured interviews will be conducted at the end of the implementation period (Figure 3).

For the caregivers' survey, questions are formulated focusing on the willingness to change and motivation of the caregivers to help improve patients' physical behavior. In addition, questions are included to investigate the current state of the 6 topics of the action plan. The scoring of the questions is based on the visual analog scale; a score between 0% and 100% agreement can be given per question. The survey will be sent to all caregivers of the included wards before and after the implementation period.

For the patient survey, the level of encouragement patients perceived from care providers and the environment to be physically active in the past 2 days will be investigated using 6 statements with a 5-point scale. This patient survey will be performed before and after the implementation period. After the implementation, the survey will be supplemented with questions to investigate the success of the implementation of the action plans per ward.

Figure 3. Timeline of process evaluation.



Semistructured interviews with patients and caregivers: After the implementation, semistructured interviews with both patients and caregivers will be undertaken. The interviews will be guided with a topic list based on the 3 key functions of process evaluation as described before [40].

Statistical Analysis

All statistical analyses will be conducted using IBM SPSS statistics software 25. All outcome variables will be tested on normality with the Kolmogorov-Smirnov test. Patients' characteristics will be described using descriptive statistics and tested with the Chi-square test, Mann Whitney test, or independent samples t test. Physical behavior is defined as the percentages of the total observed time that a patient spent lying, sitting, and moving. For both the primary outcome (the percentage of time spent lying) and the secondary outcomes (percentage of time sitting and moving), the changes in percentages after implementation will be analyzed. In addition, between-group analyses will be performed per ward. The differences between pre- and postmeasurements will be analyzed with an analysis of covariance, whereby the covariate(s) include baseline variables that may differ between pre- and postmeasurements. If data are not normally distributed, log transformation will be executed before testing.

The process evaluation will be based on the caregivers' survey, patient survey, and semistructured interviews. Categorical data will be analyzed using Chi-square test and continuous data by using the Mann Whitney test or independent sample t test. To correct for multiple testing, a post hoc multiple comparison test will be performed. The semistructured interviews will be audio recorded and transcribed. Data analysis will follow 3 steps: coding, categorizing, and selecting themes, which will be performed in NVivo 11.

Results

This study is ongoing. The first participant was enrolled in October 2017 for the premeasurement. The postmeasurements are planned for the end of 2018. The first results are expected to be submitted for publication in autumn 2019.

Discussion

Despite the evidence about the negative consequences of low levels of physical activity, patients still spend most of the day in bed, leading to unnecessary functional decline and new disabilities in ADL [2,3]. Previous studies demonstrated that increased amounts of physical activity during hospitalization may prevent this functional decline [41]. Furthermore, 3 recent studies reported the results of the implementation of a single intervention to improve physical mobility during hospital stays [14,20,42]. The first study implemented a mobility scale and demonstrated an improved level of physical functioning on a general medicine unit [14]. The second study implemented an enforced mobilization protocol in patients following gastrointestinal cancer surgery and found a reduced number of postoperative pulmonary complications [20]. The third study is a large-scale study in which the implementation of specific mobilization goals (mobilization within 24 hours, mobilization 3 times a day, and progressive and scaled mobility) showed a 10% increase in the frequency of mobilization out of bed [42]. However, to integrate physical activity in usual care, multidimensional approaches with multiple interventions focusing on the whole system are suggested to be more successful [16]. The Eat Walk Engage program of Mudge et al is a good example of a multidimensional approach using multiple interventions, which demonstrated a reduced LOS after the implementation [19]. However, it still remains unclear if physical activity is a modifiable factor during hospital stay.

The Hospital in Motion study has the strength that it contains multiple interventions tailored per ward, developed by a multidisciplinary project team. In addition, it is one of the first known large projects using a multidimensional approach, focusing on the physical environment, caregivers, and patients, instead of only 1 element, to improve physical behavior during hospitalization. Another strength of the Hospital in Motion study is the primary outcome of physical activity. As previous studies mostly included medical outcomes (eg, LOS, remissions, and mortality), levels of physical functioning or frequency of mobilization and the actual amount and change of physical activity have not been evaluated [14,19,20,42]. To get more information about patients' physical behavior, it is important to assess and evaluate the physical activity levels of patients during hospitalization. For this purpose, the behavioral mapping method is used. This method provides insight into the actual activity level of patients during an average hospital day and also assesses environmental factors such as the people in direct contact with the patient and the patients' daily activity. This enables detailed evaluation of inpatient physical behavior and differences per ward.

Diverse factors could influence the success of the implementation of Hospital in Motion. The action plan is a multidimensional package of interventions aimed to improve physical behavior. It contains multiple interventions aimed to incorporate physical activity in usual care procedures, targeting the whole care system. This strength is a challenge at the same time. Many factors may affect the implementation process, such as the functioning of the project team, caregivers' motivation and willingness to change, available time, and perceived workload. The appropriate study design has been discussed extensively within the research team because of the possible influence of confounding factors. As this study primarily aims to integrate physical activity in daily hospital care, more classic research designs (ie, randomized controlled trials) are less suitable. By following a step-by-step implementation process and by performing a process evaluation, the authors will provide useful insights into the changes in usual care and the successful and unsuccessful elements of the implementation process.

Authors' Contributions

PB and LMMvD declare to be equally contributing authors, as both of them provided equal contributions in drafting the protocol. PB, LMMvD, KV, and CV designed the framework and methodology. PB and LMMvD developed the research protocol and drafted the manuscript. KV and CV critically revised the manuscript and approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

ADL: activities of daily living
AM-PAC: Activity Measure for Post-Acute Care
HAD: hospitalization-associated disability
LOS: length of stay
UMC Utrecht: University Medical Center Utrecht

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Protocol

Exposure to Potentially Harmful E-Cigarette Emissions via Vape Tricks: Protocol for a Mixed-Methods Study

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Abstract

Background: The number of adolescents and adults using e-cigarettes, referred to as *vaping*, has dramatically increased. E-cigarettes can be used to perform *vape tricks* by inhaling and exhaling the e-cigarette aerosol in patterns to create visual effects or large clouds. To create these effects, the puffing patterns associated with vape tricks may be different than standard ad-lib e-cigarette usage. The prevalence of vape tricks and the harm associated with exposure to e-cigarette emissions when performing vape tricks is currently unknown.

Objective: Our objectives are to characterize duration, heart rate, respiratory rate, tidal volume, minute volume, and physical activity metrics associated with the performance of vape tricks and to characterize the emission of e-cigarettes when performing vape tricks in a manner suitable to inform novel exposure modeling.

Methods: The study will recruit e-cigarette users with a history of performing vape tricks. Data collection will occur in two different sessions. In the first session, participants will be asked to puff on their e-cigarette as they normally would for 20 minutes. The second session will be a vape tricks session, where users will be asked to perform a series of up to five different vape tricks with their e-cigarette. Data will be collected through screener surveys, in-person interviews, video recordings, a personal exposure monitor, and a biometric garment.

Results: Data analysis is pending and scheduled to take place in the fall of 2019.

Conclusions: This study will be used to assess the feasibility of using a biometric garment to complement environmental and observational data. The approach may provide greater insight into the health risks of performing vape tricks compared to typical e-cigarette use.

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KEYWORDS

electronic nicotine delivery systems; vaping; human exposure modeling; digital health; wearable electronic devices

Introduction

Adolescent and adult use of e-cigarettes, referred to as *vaping*, has increased dramatically since e-cigarettes were introduced to the US market in 2007 [1,2]. In 2016, 15% of US adults reported having tried e-cigarettes and 3% used them some days or every day at the time of the study [3]. Among US youth that same year, 6% of 8th graders, 11% of 10th graders, and 13% of 12th graders reported vaping in the past 30 days [4].

E-cigarette use poses a variety of possible health harms. Most, though not all, e-cigarettes contain nicotine, a substance that impairs adolescent and fetal brain development and can be toxic through ingestion of, or dermal exposure to, high concentrations [5]. Adolescent e-cigarette use may lead to future initiation of cigarette smoking [6]. Although e-cigarettes generally produce fewer harmful constituents than combustible tobacco, their aerosol can contain formaldehyde, acrolein, diacetyl, and other harmful chemicals [7,8]; advanced vaping devices, which heat the liquid inside the device to a higher temperature, produce greater quantities of these chemicals [9]. In some in vitro and in vivo studies, exposure to e-cigarette liquids and aerosols has been linked to reduced cell viability, proinflammatory responses, and impaired immune response [10,11]. Long-term and short-term health effects in users are unclear [12-14]. One potential benefit is that e-cigarette use could help smokers quit, but the evidence about whether e-cigarettes can serve as successful smoking cessation products is extremely inconsistent [15,16].

Youth and adults report using e-cigarettes for a variety of reasons, including curiosity, appealing flavors, friends' use, and the desire to use a product that is less harmful than cigarettes [17,18]. Youth and young adults also report using e-cigarettes to perform *vape tricks*, where they inhale and exhale e-cigarette aerosol in patterns to create visual effects or attempt to create the largest cloud of aerosol [19,20]. In a recent, nonrepresentative survey of adolescents recruited through social media, 78% reported having tried performing vape tricks and the majority had watched them being performed in person (84%) or online (74%) [21]. Most tricks are performed using advanced devices that reach high temperatures, producing greater levels of harmful chemicals [9]. Performing vape tricks may also involve different puffing patterns than ad-lib use. If vape tricks require deeper or longer inhalations, this pattern could potentially result in increased exposure to harmful emissions.

The population-wide prevalence of vape trick behavior is not yet known, nor is the exact level of harm associated with vape tricks. In an attempt to begin addressing this gap, this paper describes the protocol of a feasibility study where the primary aim is to collect and compare the heart rate, breathing rate, and activity metrics associated with performing vape tricks alongside the metrics of standard ad-lib e-cigarette usage. A secondary outcome consists of using initial study results to program a smoking machine that will be used during subsequent study phases.

Methods

Approval

This study protocol underwent review and received approval by RTI International's Office of Research Protection Institutional Review Board. Additional modifications or changes to the proposed protocol will be submitted as a separate amendment. Breeches or adverse events will be documented by the research team and reported to the Institutional Review Board.

Participant Eligibility Criteria

The target population for this study is current e-cigarette users between 18 and 29 years of age with a product usage history of e-cigarettes to perform vape tricks at least once during the past 3 months, experience performing at least two different tricks, performing at least one trick five to nine times, and prior use of nicotine-free liquids when performing tricks. Participants will be not excluded based on race, sex, or cigarette smoking status. To accomplish the feasibility assessment, RTI will limit the number of recruitments to a target sample of 30 participants. The study team believes 30 participants is an appropriate number of participants to test data collection procedures and obtain a sufficient amount of data for analysis. Individuals will be excluded if they are younger than 18 or older than 29 years of age; pregnant; or suffer from claustrophobia, heart disease, an acute or chronic lung disease, or other chronic systemic illness. The RTI research staff are aware that the proposed methods for recruitment could potentially bias the sample; however, since the proposed study is a feasibility assessment, we are primarily concerned with recruiting the necessary number of participants and not with equal distribution of variables across participants.

Participant Recruitment

E-cigarette users will be recruited via email and flyers posted at local vape shops, hookah bars, and other venues that young adult e-cigarette users may visit. The RTI research staff will visit the prospective venues and receive permission from the venue to hand out the recruitment flyers and ask venue staff to provide input on how best to reach the target population. Employees at AVAIL Vapor shops in Raleigh and Durham, North Carolina, will also conduct in-person recruitment by distributing flyers and study information sheets when interacting with customers at their stores. The recruitment materials will instruct potential participants to go to a website, which will direct them to the online screening survey to assess eligibility.

Recruitment will also occur online through social media ads and postings on websites such as Reddit, Facebook, and Instagram. For the social media recruitment, ads will not specify the study population or study goals in order to conform with ad platform requirements. Clicking on these social media ads will link participants to the screener survey where they will be presented with information about the study before being asked any screening questions.

Screened individuals deemed as eligible will be contacted by study staff via email, phone, or both to confirm eligibility and to schedule an appointment to visit the RTI lab. Prior to their appointment, participants will be informed that they will need to bring their own e-cigarettes and nicotine-free, hash oil-free liquids. Eligible individuals who are scheduled for a lab visit will also be contacted 24-48 hours before their visit via email to confirm the time and date. At the lab visit, staff will offer participants additional flyers if they are willing to share with others who might be interested in taking the screening survey and participating in the study.

Informed Consent

Upon arrival at the RTI research facility, the RTI research staff will conduct the informed consent procedures. Written informed

consent will be obtained from individuals who have completed the screening questionnaire and meet the screening criteria prior to enrollment in the study. As part of the consent process, participants will be informed that their participation is entirely voluntary and that they can stop at any time. If they stop before the end of the appointment, they will be compensated for activities completed (see Study Design section for information about compensation). Any questions asked by the participant will be answered before completing the informed consent process. The consent form will be signed and dated by the study participant and the RTI staff member conducting the consent procedures.

Since the participants' sessions will be filmed, they will be asked to sign a standard RTI video release form. In addition, participants will be required to sign an attestation form stating that they meet the inclusion and exclusion criteria for the study, and women will be required to sign on the attestation form stating that they are not pregnant. As part of this study, a Hexoskin shirt will be worn; the Hexoskin is a shirt with biometric sensors worn directly against the skin. As such, participants will be asked if they currently have any open wounds on their chest or back where the Hexoskin shirt will be worn. If open wounds are present, the participant will not be allowed to enroll in the study.

Study Design

After enrollment, participants will be fitted with the Hexoskin device, and each participant will then be assigned to complete either an ad-lib session or a vape tricks session. Each session will take place in RTI's controlled exposure chamber, will last 20 minutes apiece, and will be videotaped. During the ad-lib session, participants will be instructed to puff on their e-cigarette as they normally would for the duration of the session. Participants will be offered the use of a television or tablet during the 20-minute ad-lib session.

During the vape tricks session, participants will be asked to stand in the chamber and perform a series of two to five vape tricks using their own device while being videotaped. Participants will be asked to perform tricks that they had an established history of performing prior to their participation in the study. Participants will be asked to repeat each trick four times, up to 20 tricks total, with a required minimum resting period of 30 seconds between trick attempts (ie, approximately one trick per minute). In the case of false starts or errors as they perform tricks, participants will not be allowed to attempt more than 30 tricks during a single 20-minute session. Participants will be allowed to rest for longer than 30 seconds or stop their participation in the study at any time. These time limits are based on the averages from prior studies of user puffing behavior. All participants will be compensated US $100, even if they stop before the end of the appointment.

Proposed Variables by Data Source

Screener Survey and In-Person Interview

The online screening survey will assess age; cigarette smoking; health status, specifically whether the participant has any of 15 health issues that would result in exclusion; and how frequently they vape different e-cigarette device types (ie, nonrefillable, refillable without special features, and refillable with special features like temperature control). The screener will also assess individuals' history of performing vape tricks, including whether they have done tricks in the past 3 months; which tricks they have performed (eg, *jellyfish*, *ghost inhale*, or other); the number of times they have tried those tricks; and what type of e-liquid they have used when doing tricks (eg, flavored or unflavored and with or without nicotine).

Before participants begin their first vaping session in the exposure chamber, study staff will conduct brief interviews. The interviews will cover the following topics: how participants would describe vape tricks to someone unaware of the behavior, participants' first experiences with vape tricks, what tricks they know how to do, what tricks they will perform during the session, and whether they have ever competed in a vape tricks or *cloud chasing* competition (ie, trying to make the biggest cloud). Finally, the interviewer will ask the participant to describe the e-cigarette device they brought with them, including where they got the device, whether they built it, what features it has, and what kind of e-liquid they usually use with it.

Video Data Collection

Participants will be videotaped during the in-person interview, ad-lib vaping session, and vape tricks session. Qualitative coding will be conducted on ad-lib vaping and vape tricks videos to determine puff duration for both ad-lib and vape trick sessions. For the ad-lib vaping session, an analyst will record the time of the beginning of each puff. For the vape tricks session, the analyst will record the beginning of each trick puff, the time the inhale ends, and the time the trick ends. The beginning of the puff will be measured from the moment the e-cigarette is put up to the participant's mouth. If the participant positions the e-cigarette in such a way that it is difficult to see the beginning of the puff, the analyst will also consider inhalation noise in their determination. The end of the inhale will be measured visually by looking at when a participant stops breathing in and by listening for the time at which noise from vaping ends.

Hexoskin

The Hexoskin device will record the heart rate, respiratory rate, tidal volume, minute volume, and any participant movement (eg, steps, acceleration, and position). Data collected by the Hexoskin device and recorded video data will be used to determine the inhalations recorded by the Hexoskin device that result from puffs taken on the user's e-cigarette. These metrics will be summarized when comparing the data generated during the ad-lib session and the vape trick session across participants.

Micro-Personal Exposure Monitor

The Micro-Personal Exposure Monitor (MicroPEM; RTI International) is a small wearable sensor that collects up to 500 µg of particulate matter (PM) on a 25 mm polytetrafluoroethylene filter for gravimetric and speciation analyses. The device itself weighs less than 240 g and has a proprietary noise dampener in the flow control system, which effectively reduces the noise level to less than 3 dB above background at 1 m. The laser-based light scattering nephelometer collects real-time PM concentration data at up to

3-second resolution over a range of 3-15,000 μg/m^3. The three-axis accelerometer monitors the frequency and intensity of movement for protocol compliance determination. The nephelometer and accelerometer data can be combined to calculate the potential inhaled dose. Quality control metrics continuously monitored are temperature, relative humidity, pressure drop across the filter, battery voltage, and sample flow rate.

Exposure Chamber

The RTI controlled exposure chamber, where all vape tricks and ad-lib sessions will be conducted, allows for control of temperature, humidity, and ventilation; the chamber size is 4.6 m x 3.4 m. Temperature and humidity in the chamber will be maintained at 23°C and 40% relative humidity, respectively. Ventilation will be controlled through an adjustable high-efficiency particulate air (HEPA)-filtered air plenum and conforms to American Society of Heating, Refrigerating, and Air-Conditioning Engineers (ASHRAE) specifications. The controlled ventilation rate will be set at a sufficient value to ensure that the air inside the chamber has been exchanged between subjects (ie, approximately 25 exchanges per hour). Electric power within the chamber will be supplied by nine 120 volts alternating current (VAC) 60 Hz outlets housed on dedicated circuits. We will place a model 3321 aerodynamic particle sizer (APS) spectrometer (TSI Inc) in the chamber with the participants. Participants will not interact with the APS and the APS will not alter the ambient air in the chamber. The APS is a high-performance, general-purpose particle spectrometer that measures both size and airborne concentration of the particles. The airflow through the APS passes through a high-efficiency filter to remove any particles before being exhausted into the room. We will place the APS on a table located 1 m from the participant using their e-cigarette device. The APS power cord will be connected to an electrical outlet behind the table and in the opposite direction from the participant. The APS pump will create an audible, noticeable hum that does not pose a risk.

Study Outcomes

The primary outcome is to conduct a feasibility assessment comparing the heart rate, breathing rate, and activity metrics associated with those performing vape tricks to those associated with more typical ad-lib use of e-cigarettes. This will be accomplished through concurrent data collection using video- and sensor-based technology. In addition, a secondary outcome is the use of study results to program a smoking machine that will draw emission samples from e-cigarettes during a subsequent study phase that does not involve human subjects.

Data Management

Data collected via electronic survey for screening purposes will include each participant's email address and/or phone number, as well as their contact name to schedule the lab visit and deliver reminders. Access to the screening survey itself will be housed in RTI's Enhanced Security Network, which is where Voxco is housed, constructed to the Federal Information Processing Standard (FIPS) to ensure security. At the conclusion of data collection, participant email addresses will be removed from study documents and destroyed. Contact information will be removed from all data files and destroyed to deidentify the dataset from the Enhanced Security Network files 12 months after data collection.

Each participant will be assigned a numeric study ID that will be used to designate all monitoring data collected through the Hexoskin device, the MicroPEM sensor, the exposure chamber, as well as the video and audio data. The data collected will be referenced only by these numbers in any laboratory documents, electronic database, and documented or published material. All collected data will be securely stored on RTI servers. Deidentified Hexoskin device data will also be stored on the online Hexoskin dashboard. Separately, any images from videos of participants for publication or reporting will be deidentified by cropping, blurring, or obscuring faces or other identifying information with black redaction boxes. Raw video and images will be destroyed at the conclusion of data analysis; only deidentified images or sample video will be stored for use in publications and reports.

Data Analysis

Video Data Collection

An analyst will review the video from each participant to determine when their exhale ends by recording the time at which the vapor stream stops coming out of the participant's mouth.

Hexoskin

The VivoSense (Vivonoetics) data analysis and software program will be used for complex respiratory analysis of the Hexoskin device data to generate quantitative profiles of both the ad-lib and vape trick sessions suitable for exposure modeling. Qualitative data from coded video will be used to isolate sensor data associated with ad-lib and vape trick sessions. Output from both modes of data collection will be matched and compared against one another to assess concordance.

Micro-Personal Exposure Monitor

MicroPEM PM2.5 (ie, diameter of less than 2.5 μm) and relative humidity data will be collected at a rate of one measurement every 10 seconds. Temperature will be logged every 30 seconds. This data will be plotted in a graph to show variability in PM2.5 as a function of temperature and relative humidity.

Exposure Chamber

Data from the APS will be analyzed to describe any changes in the aerosol concentration and particle size distribution following vape trick use of e-cigarettes.

Results

Data analysis is pending and scheduled to take place in the fall of 2019.

Discussion

Overview

Although the national prevalence of performing vape tricks is not known at this time, some studies suggest that this may be a popular activity among e-cigarette users, especially among

youth [19-21]. This study will be the first to examine puff topography and activity metrics associated with vape tricks and the first to characterize exposure to potentially harmful emissions resulting from that behavior. This study benefits from a mixed-methods approach that combines biometric sensor data and aerosol emissions data to best characterize how vape tricks differ from ad-lib vaping.

Limitations

This study has several limitations. Because the protocol requires an in-person study visit, data collection will be geographically limited to the area around Research Triangle Park, North Carolina, potentially limiting generalizability. In addition, the recruitment sample runs the risk of potential bias since participants must be 18-29 years of age and have a history of performing vape tricks in the past 3 months; their breathing patterns, heart rates, and other metrics may not be equivalent to those who are younger or older or who are less experienced with vape tricks. For both the vape tricks and ad-lib vaping sessions, participants' performance in the lab setting may not be identical to their performance in real-world settings. Further, use of the Hexoskin biometric shirt to conduct a topography study or to quantify respiratory exposure has not been previously validated.

Conclusions

This research protocol describes the steps that will be utilized to characterize vape trick behaviors and subsequent aerosol emissions as part of a mixed-methods laboratory study. The results of this study should provide some initial data to help determine whether performing vape tricks poses a greater risk to health than ad-lib vaping. Ultimately, if a sufficient body of evidence suggests that vape tricks are more harmful than ad-lib vaping, tobacco control researchers and regulators might consider developing interventions to prevent this behavior. Future research using the methodology described here could be used to provide more accurate assessments of vaping behaviors obtained in a naturalistic setting, which could better account for sporadic but impactful variations in vaping behavior.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

APS: aerodynamic particle sizer
ASHRAE: American Society of Heating, Refrigerating, and Air-Conditioning Engineers
FIPS: Federal Information Processing Standard
HEPA: high-efficiency particulate air
MicroPEM: Micro-Personal Exposure Monitor
PM: particulate matter
VAC: volts alternating current

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Protocol

Evaluation of Clinical Outcomes and Simultaneous Digital Tracking of Daily Physical Activity, Heart Rate, and Inhalation Behavior in Patients With Pulmonary Arterial Hypertension Treated With Inhaled Iloprost: Protocol for the Observational VENTASTEP Study

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Abstract

Background: Pulmonary arterial hypertension (PAH)—a progressive, ultimately fatal disease—patients often experience dyspnea, which can limit their daily physical activities. Iloprost is an inhaled therapy for PAH that has shown efficacy in clinical trials. However, clinical trials in PAH have provided only limited data on daily physical activity. Digital monitoring of daily physical activity in PAH is therefore attracting growing interest. To fully understand a patient's response to treatment, monitoring of treatment adherence is also required. The Breelib nebulizer for administration of iloprost saves inhalation data, thus allowing digital monitoring of adherence.

Objective: This study aims to perform parallel digital tracking of daily physical activity parameters, heart rate, and iloprost inhalation data in patients with PAH, before and after starting inhaled iloprost treatment. The primary objective is to investigate correlations between changes in digital measures of daily physical activity and traditional clinical measures. Secondary objectives are to assess iloprost inhalation behavior, the association between daily physical activity measures and time since last inhalation, changes in sleep quality and heart rate, the association of heart rate with daily physical activity measures and iloprost inhalation, and adverse events.

Methods: VENTASTEP is a digital, prospective, observational, multicenter, single-arm cohort study of adults with PAH in Germany, starting inhaled iloprost treatment via the Breelib nebulizer, in addition to existing PAH therapy. The study comprises a baseline period without iloprost treatment (≤2 weeks) and an observation period with iloprost treatment (3 months±2 weeks). The Apple Watch Series 2 and iPhone 6s are used with a dedicated study app to continuously measure digital daily physical activity parameters and heart rate during the baseline and observation periods; the watch is also used with a 6-min walk distance (6MWD) app to measure digital 6MWD at baseline and the end-of-observation visit. Inhalation frequency, completeness, and duration are monitored digitally via the nebulizer and the BreeConnect app. Sleep quality is assessed using the Pittsburgh Sleep Quality Index at baseline and the end-of-observation visit. Changes in traditional outcome measures (6MWD, Borg dyspnea scale, EuroQol 5-dimensions questionnaire, functional class, and brain natriuretic peptide [BNP] or N-terminal proBNP) between baseline and the end-of-observation visit will be correlated with changes in digital daily physical activity parameters and digital 6MWD as the primary analysis.

Results: The first participant was enrolled in February 2018 (estimated study completion by July 2019; planned sample size: 80 patients).

Conclusions: The VENTASTEP study will inform future research on the utility of digital parameters as outcome assessment tools for disease monitoring in PAH. The study will also provide insight into clinical outcomes, daily physical activity, and quality of life in patients adding inhaled iloprost, to existing PAH therapy.

Trial Registration: ClinicalTrials.gov NCT03293407; https://clinicaltrials.gov/ct2/show/NCT03293407 (Archived by WebCite at http://www.webcitation.org/6ywPGcn4I)

International Registered Report Identifier (IRRID): DERR1-10.2196/12144

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KEYWORDS

digital monitoring; heart rate; daily physical activity; inhalation; behavior; pulmonary arterial hypertension; iloprost; Breelib; health-related quality of life; sleep

Introduction

Background

Pulmonary arterial hypertension (PAH) is a progressive disease in which increased pulmonary vascular resistance leads to right heart failure and death. The most common symptom of PAH is persistent dyspnea on exertion, which can limit the ability of patients to perform ordinary daily physical activities [1].

Iloprost is an inhaled prostacyclin-based therapy for PAH that reduces pulmonary vascular resistance through vasodilatory and antiproliferative effects [2-4]. Inhaled iloprost was shown to have a rapid onset of action and improved 6-min walk distance (6MWD), pulmonary vascular resistance, symptoms, and health-related quality of life (HRQoL) at 12 weeks compared with placebo in patients with PAH or chronic thromboembolic pulmonary hypertension in a phase 3 randomized controlled trial [2]. Iloprost also showed beneficial effects when added to the endothelin receptor antagonist (ERA) bosentan [3] and when added to dual combination therapy with ERAs and phosphodiesterase-5 inhibitors [5] in patients with PAH. According to current treatment recommendations, iloprost may be added to dual combination therapy to ensure timely treatment escalation for patients with intermediate risk who respond inadequately to initial therapy [6].

Clinical trials of inhaled iloprost and other pharmacotherapies in PAH have thus far provided only limited data on parameters such as daily physical activity that directly measure the impact of the disease on daily life [7]. Daily physical activity can now be measured continuously with wearable technology that is available to consumers and widely used, providing unprecedented opportunities for biomedical research [8]. Digital monitoring of daily physical activity is therefore attracting growing interest as a potential outcome measure in PAH [9-11], with observational studies showing reduced daily physical activity in patients with PAH compared with controls without PAH [11-13] and significant associations between digital daily physical activity parameters and maximal inspiratory and expiratory pressures [14], right ventricular and pulmonary vascular status [15], peripheral muscle oxygenation [15], 6MWD [9-12], HRQoL [9,10,15,16], and transplantation-free survival [16]. These observational data suggest that digital monitoring of daily physical activity has the potential to become an important tool in the evaluation of disease course and treatment response in PAH. Currently, the 6MWD is used to guide treatment decisions in PAH [17,18] but is assessed only intermittently (eg, every 12 weeks), leaving long intervals in which physicians have no information on the activity status of their patients. Continuous measurement of daily physical activity (eg, as part of a patient support program) could allow earlier detection of deterioration and more rapid adjustment of PAH treatment.

The emerging potential of digital approaches for monitoring and improving treatment adherence and linking adherence to physiological measures was recently highlighted in patients with respiratory diseases [19]. Daily physical activity in patients with PAH has not yet been assessed with simultaneous digital monitoring of adherence to PAH treatment. The recently approved Breelib nebulizer (Vectura Group plc) for administration of iloprost saves inhalation data, thus allowing digital monitoring of adherence [20,21].

Objectives

This study aims to perform parallel digital tracking of daily physical activity parameters, heart rate, and iloprost inhalation data in patients with PAH, before and after starting treatment with inhaled iloprost. The primary objective is to investigate the correlation between changes in digital daily physical activity measures and changes in traditional clinical measures of disease course and treatment response. Secondary objectives are to assess iloprost inhalation behavior, the association between daily physical activity measures and time since last inhalation, changes from baseline in sleep quality and heart rate (at rest and during 6MWD test), the association of heart rate with daily physical activity measures and iloprost inhalation, and adverse events. Other objectives are to assess activity status (active, inactive, and watch not worn), assess the feasibility of digital measurement of 6MWD by comparing digital and traditional 6MWD measurements, identify digital measures linked to outcomes of special interest such as 6MWD, and evaluate changes from baseline in clinical outcome measures, daily physical activity, and HRQoL that occur when inhaled iloprost is added to existing PAH therapy.

Methods

Study Design

VENTASTEP is a digital, prospective, observational, multicenter, single-arm cohort study of adult patients with PAH in Germany, starting treatment with inhaled iloprost via the Breelib nebulizer in a real-world setting.

Heart rate and daily physical activity parameters are monitored digitally using a wearable and a smartphone (the Apple Watch Series 2, 42 mm, Apple Inc and iPhone 6s, Apple Inc; supplied by Vodafone GmbH; see Discussion section for rationale) with a dedicated study app and a 6MWD app (both created by xbird GmbH). Inhalation data (including the average number of daily inhalations, the average daily proportion of complete and incomplete inhalations, and average daily inhalation duration per session) are monitored digitally via the nebulizer and the BreeConnect app (Bayer AG). Traditional clinical outcome measures (eg, physical examination, 6MWD, and laboratory values) are assessed by the investigators, and sleep quality and HRQoL are assessed as patient-reported outcomes.

Patients can only be enrolled in the study if the decision to treat with iloprost has been made by the treating physician in advance and independently of study inclusion. Patients routinely treated within specialized PAH centers and meeting the criteria for enrollment are asked to participate in the study by their physician. Enrolled patients are informed by their investigator about the study objectives and the digital methods applied.

Furthermore, study participants are trained in the correct handling of the wearable and smartphone. Training in the use of the nebulizer is conducted in accordance with routine procedures on behalf of the Ventavis patient support program VENTAPLUS (implemented by Contra Care GmbH, Nürnberg, Germany).

Final data analysis will be performed by the contract research organization (CRO) Institut Dr. Schauerte, Munich, Germany.

Ethical Considerations

The study protocol has been approved by the ethics committee of the Justus Liebig University Giessen (approval no. AZ 153/17). Before documentation of any data, informed consent is obtained from the patient in writing.

Patients

Patients with PAH (pulmonary hypertension group 1 according to the current clinical classification [18]) at intermediate risk and in World Health Organization functional class (WHO FC) III are eligible for inclusion in the study, if they have shown an inadequate response to initial therapy with one or more PAH drugs or clinical deterioration after an initial treatment response, and a therapy escalation with inhaled iloprost (administered via the Breelib nebulizer) has been agreed by the patient and physician independently of the study. Other inclusion criteria are patients aged 18 years or above at the initiation of inhaled iloprost, no previous treatment with inhaled iloprost, willingness to wear the Apple Watch Series 2 for the duration of the study, and signed informed consent. Patients are excluded if they are allergic to nickel and methacrylates (which are present in the Apple Watch Series 2) or if they are participating in an investigational program with interventions outside of routine clinical practice.

Study Devices

Apple Watch Series 2

The Apple Watch Series 2 is a wrist-worn, commercially available wearable with a 3-axis gyroscope, a 3-axis accelerometer, Bluetooth 4.0, and optical (photoplethysmography) heart rate sensors. A built-in global positioning system (GPS) sensor enables more accurate distance and pace measuring. GPS data are not captured continuously in this study; only significant GPS location changes (≥500 m) are recorded.

iPhone 6s

The iPhone 6s is a commercially available smartphone. Its functionality has been reduced to the following minimum requirements for this study: measurement of movement (using the built-in 3-axis gyroscope and 3-axis accelerometer), measurement of atmospheric pressure (using the built-in barometer), and gathering of data from the nebulizer and the wearable. For data that are gathered by both the wearable and the smartphone (eg, accelerometer data), the Apple iOS automatically selects the more reliable data source for each second of usage.

Breelib Nebulizer

The Breelib device is a handheld, battery-powered, vibrating mesh nebulizer for administration of inhaled iloprost that automatically saves inhalation data such as frequency, completeness, and duration of inhalations. The data are transferred to a smartphone using Bluetooth and are stored in the BreeConnect app. A summary of the data can be sent to the treating physician and/or nurse at regular intervals.

Apps

The study app (developed by xbird) and BreeConnect app (developed by Bayer) are preinstalled on the smartphones used in this study; the 6MWD app (developed by xbird) is preinstalled on the wearables. Once installed on a specific smartphone, the study app automatically creates a numeric unique identifier, which is used as a pseudonym for all data related to that device.

The study app automatically captures daily physical activity and heart rate data from the built-in sensors of the wearable and the smartphone for the duration of the study period. Some of the sensor data are preprocessed by the operating system (Apple Health Kit, Core Location, and Core Motion) before being captured by the study app. All data passively collected by the study app are listed in Table 1.

The 6MWD app saves the number of steps taken, heart rate, and distance walked during the 6MWD tests. The BreeConnect app allows visualization and analysis of inhalation data recorded by the Breelib nebulizer and can also remind the patients when their next iloprost inhalation session is due, if this option is activated by the patients.

Table 1. Data captured by the smartphone and wearable and saved in the study app.

Source	Data saved in study app
Health Kit (only access to the listed data is preset in the study app)	Number of steps[a]
	Number of stairs
	Walking distance, m[a]
	Mean heart rate, beats per min[a]
	Number of standing up events
Core Motion (preprocessed data from motion sensors)	Walking time, s
	Stationary time, s
	Exercise time (physically active, more than walking), s
	Automotive time, s
	Cycling time, s
Core Location	Relevant position changes, leaving home location (no continuous data recording; position accuracy: 500 m)[b]
Accelerometer and gyroscope raw data	Heart rate during activity, beats per minute

[a]Steps, walking distance, and mean heart rate per min are also saved in the 6-min walk distance app.

[b]Leaving home location means leaving the 500 m circle that is flagged as *home*. Daily physical activities over a distance <500 m are detected through steps and raw accelerometer and barometer data.

The study app and 6MWD app stay in the background and do not interact with the patient or the investigator, present any obtained physiological values or results, or give recommendations. These 2 apps are neither medical nor lifestyle products as they serve only as vehicles for scientific data collection.

Data Transfer and Processing

Daily physical activity and heart rate data are sent by Bluetooth from the wearable to the study app on the smartphone (Figure 1). Sensor data from the smartphone itself are also stored by the study app. The daily physical activity and heart rate data on the smartphone are retrieved automatically at least once a day and stored pseudonymized on a secure cloud server.

Inhalation data are sent from the nebulizer to the BreeConnect app on the smartphone by a VENTAPLUS nurse (Contra Care GmbH) during a routine visit with the patient after 3 months of treatment. The data are then automatically transferred to the secure cloud server (Figure 1).

Within the cloud server, the data are processed and formatted into the required study variables (Figure 1). At the individual end of the study for each patient, the processed data are transferred from the cloud server via encrypted connection to the electronic data capture system of the CRO for final analysis. Further information is available in Multimedia Appendix 1.

Data Collection and Outcome Measures

The whole study period for each patient comprises a baseline period and an observation period (Figure 2). The baseline period is defined as the period from the initial visit and decision to use inhaled iloprost until the start of treatment with inhaled iloprost, or the last 14 days before the start of treatment, if the period from the initial visit to the start of treatment is more than 14 days. This period is variable depending on the time needed to obtain the Breelib nebulizer, fill a prescription, and schedule a visit to train the patient in the use of the device. The observation period is defined as 3 months±2 weeks starting from the first administration of inhaled iloprost.

After signed informed consent has been given, traditional clinical and patient-reported outcomes and digital 6MWD data are collected during the initial routine clinical visit and at 3 months±2 weeks (Figure 2). HRQoL is assessed using the EuroQol 5-dimensions (EQ-5D) questionnaire, and sleep quality is assessed using the Pittsburgh Sleep Quality Index. The investigator collects demographic data and clinical characteristics from the medical records, if available, or else by interviewing the patient. Similarly, the investigator collects effectiveness and safety-related data at the initial and end-of-observation visits. Daily physical activity and heart rate are monitored continuously, and iloprost inhalation data are recorded throughout the whole study (ie, the baseline and observation periods). Resting heart rate is calculated by the Apple system as the average heart rate measured at times of inactivity (on the basis of accelerometer data).

Figure 1. Data sources and processing in the VENTASTEP study. Inhalation data from the nebulizer and motion sensor data, location changes ≥500 m, and heart rate data from the wearable are transferred to the smartphone via Bluetooth and stored there temporarily by the BreeConnect app and study app. Motion sensor and barometer data from the smartphone itself are also stored in the study app. The data are sent from the smartphone via encrypted transmission to a secure cloud server for storage and processing to generate the digital study variables, which are then transferred to the electronic data capture system of the clinical research organization for final analysis. Patient- and investigator-reported outcomes are also saved and analyzed in the electronic data capture system of the clinical research organization. 6MWD: 6-min walk distance; BNP: brain natriuretic peptide; CRO: clinical research organization; NT-proBNP: N-terminal pro–brain natriuretic peptide; HRQoL: health-related quality of life; WHO FC: World Health Organization functional class.

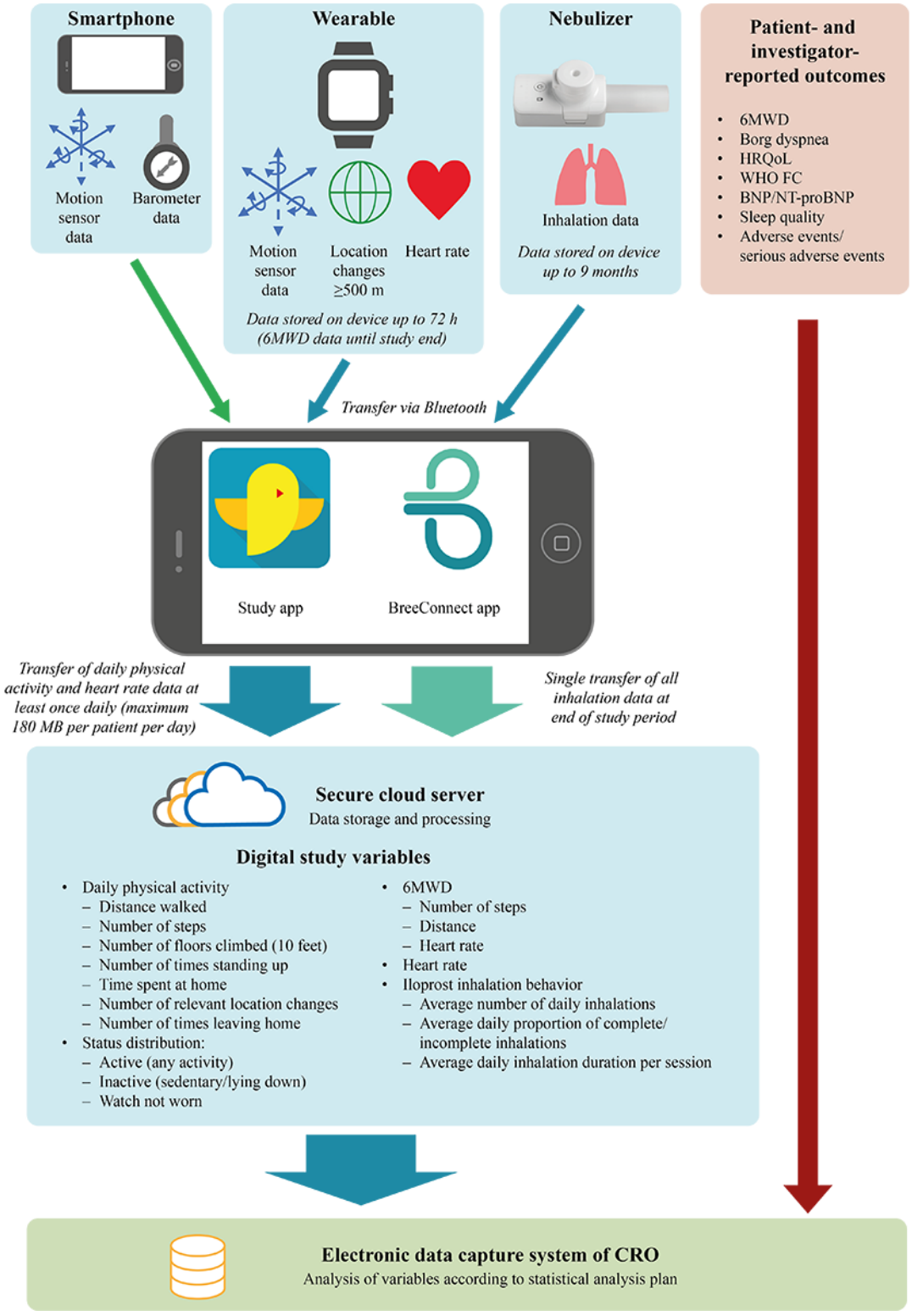
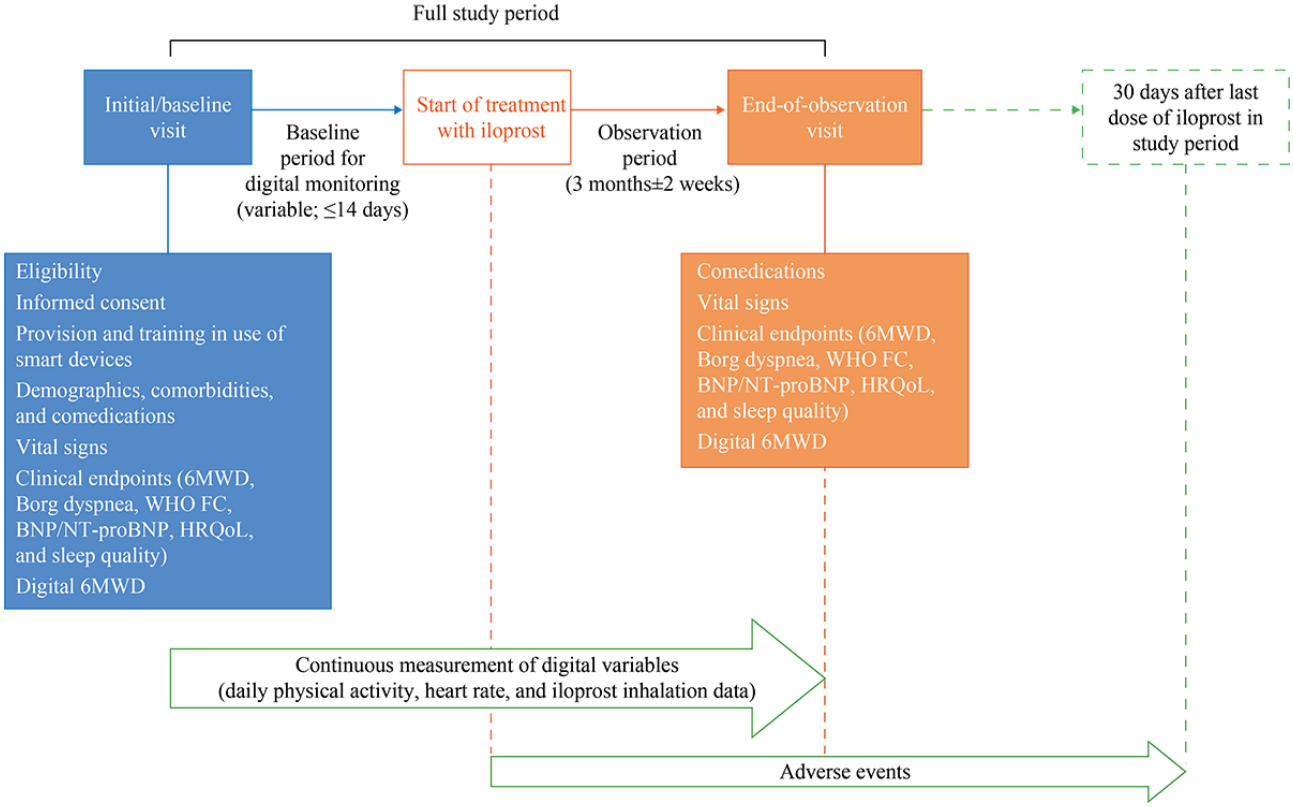


Figure 2. Study visits and data collection. 6MWD: 6-min walk distance; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro–brain natriuretic peptide; HRQoL: health-related quality of life; WHO FC: World Health Organization functional class.



Statistical Analyses

Statistical analyses of primary and secondary endpoints will be exploratory and descriptive. This study is not designed to confirm or reject predefined hypotheses. Patients receiving at least one dose of inhaled iloprost will be included in the analyses.

Primary Analysis

In total, 13 parameters are included in the primary analysis (5 routine clinical parameters: 6MWD, Borg dyspnea scale, HRQoL, WHO FC, and BNP or NT-proBNP, and 8 digital parameters: 6MWD and 7 parameters reflecting daily physical activity, as listed in Figure 1). Digital parameters reflecting daily physical activity will be summarized at baseline (median of all up to 14 device-based daily assessments before the first intake of inhaled iloprost) and during the last 14 days of the observation period (median of daily assessments). If there are no data before the first intake of inhaled iloprost or in the last 14 days of the observation period, the patient will be excluded from the primary analysis.

Patient-wise data (absolute values at baseline and the end of the observation period and changes from baseline to the end of the observation period) will be analyzed descriptively by sample statistics (ie, mean, SD, median, quartiles, and minimum and maximum values). A 95% CI of the mean will also be derived (missing values will be neglected).

For all 78 combinations of the 13 parameters included in the primary analysis, changes from baseline to the end of the observation period will be compared in a correlation analysis, and Pearson and Spearman correlation coefficients will be calculated. Each correlation analysis will be based on pairwise complete observations, with no imputation of missing values.

Other Analyses

An exploratory *t* test (2-sided alpha=.05) will be performed to evaluate the statistical significance of changes in 6MWD from the baseline to the end of the observation period. Correlation of step frequency and heart rate measured digitally during the 6MWD test will be assessed.

Regression analyses will be performed for each of the 5 primary clinical endpoints, with a change in the clinical endpoint as a dependent variable and digital endpoints as independent variables. Sensitivity analyses will include correlations of primary endpoints using the full data set rather than pairwise complete observations. The impact of nebulizing time will also be evaluated.

Patient Population Size

On the basis of results of a feasibility study conducted in 16 German sites in Q1 2017 (data not shown), the planned total sample size for this exploratory study is 80 patients (minimum value of n=50; maximum value of n=100), who are to be enrolled at about 15 sites over a 12-month period. If fewer than 50 patients are enrolled in 12 months, the recruitment period will be prolonged until 50 patients are enrolled. The minimum number of patients was determined as 50 to ensure reasonable precision of the correlation coefficients (even with 40% missing data). The maximum number of patients was determined as 100 because of financial and organizational reasons.

Results

Feasibility Survey

The feasibility of performing a digital noninterventional study was evaluated in an anonymous survey of patients with PAH at a single center (Giessen) in 2017. The patients were asked whether or not they would participate in a hypothetical digital noninterventional study, and under which preconditions.

In total, 30 patients completed the survey questionnaire. However, 15 of the patients indicated that they would not participate in such a study. The reasons for nonparticipation included the following: “too big hurdle”, “too exhausting”, “too much monitoring”, “doubts about guaranteeing patient safety and privacy”, “sitting in a wheelchair”, and “feeling too old”.

The remaining 15 patients indicated that they would participate and use digital devices such as an Apple watch and an iPhone. Of this subset, 8 patients would allow digital monitoring of all variables proposed in the questionnaire (sleep behavior, number of steps, distance traveled, number of visited places, type of movement, GPS location, heart rate, and number/time of meals per day). The other 7 patients would allow digital monitoring of subsets of the proposed variables (measurement of number of steps, distance traveled, and heart frequency were each allowed by 5 of these patients, and measurement of sleep behavior and type of movement were each allowed by 4 of these patients).

Consequences for Study Protocol

The survey responses suggested that digital monitoring of sleep behavior and energy expenditure and precise GPS tracking would not be accepted by patients; the VENTASTEP protocol therefore excluded digital monitoring of these parameters and included only rough location tracking (changes of ≥500 m). The first participant in the VENTASTEP study was enrolled on February 1, 2018, and the estimated study completion date is July 31, 2019.

Discussion

Rationale for Study Design

The VENTASTEP study will evaluate the correlation between changes in a range of digital daily physical activity parameters and changes in established clinical measures of disease course and treatment response in patients with PAH receiving treatment with inhaled iloprost. In addition, the study will provide information on iloprost inhalation behavior and relationship with daily physical activity, the association of heart rate with daily physical activity and iloprost inhalation, adverse events, the feasibility of digital assessment of 6MWD, and changes in clinical outcome measures, sleep quality, heart rate, daily physical activity, and HRQoL that occur when inhaled iloprost is added to existing PAH therapy.

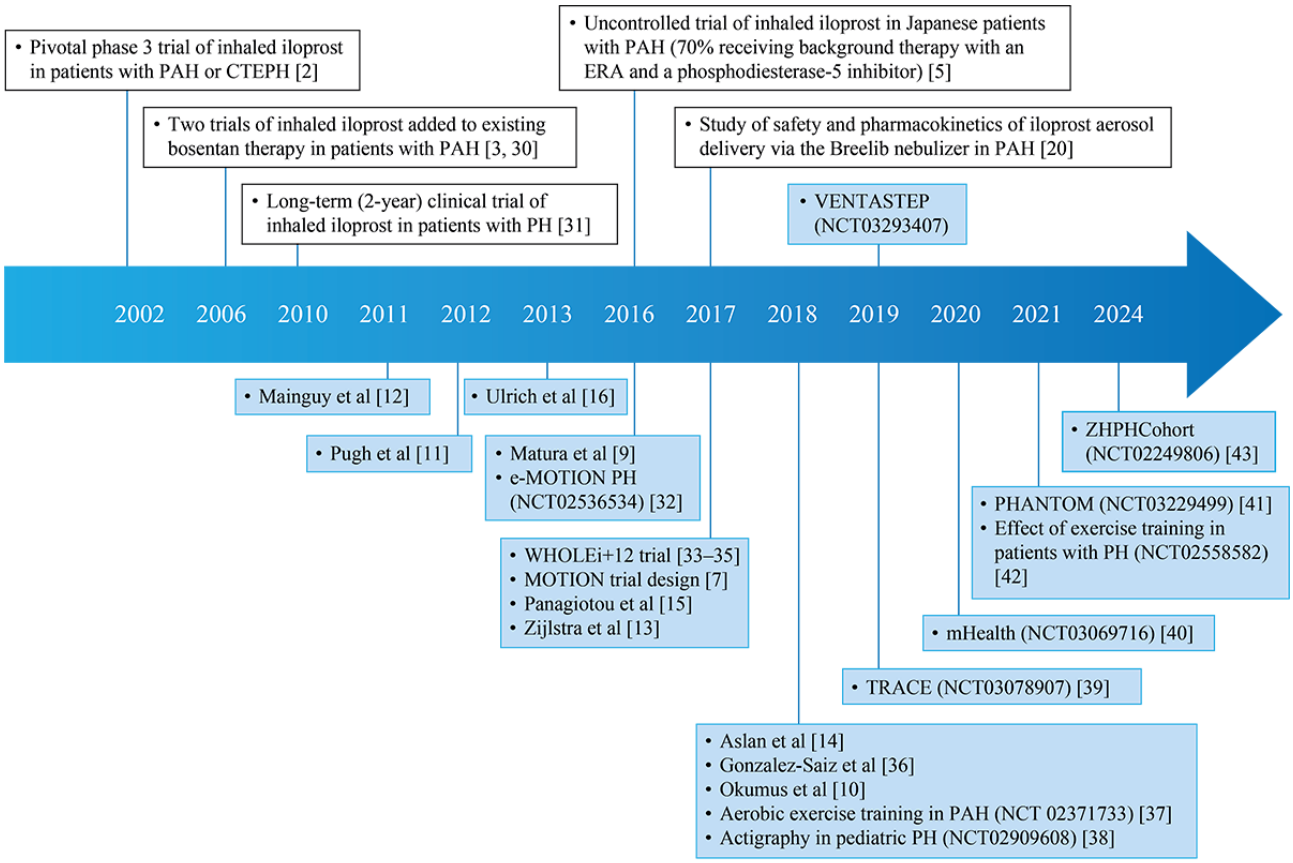
Daily physical activity can be measured using a variety of methods. Self-reporting (eg, via a diary or questionnaire) is inexpensive but subjective [22]. Video recording may be useful in a laboratory setting [23] but is unlikely to be practical for monitoring of daily physical activity in real life [22]. Mechanical pedometers are the simplest wearable daily physical activity sensors, but they provide only step counts without information on exercise intensity [22]. Accelerometers and gyroscopes provide information on linear acceleration and angular motion, respectively, which can be classified into activity types such as walking [22]. Accelerometers have undergone remarkable advances in recent years, with improvements in memory and battery capacities, acceleration range, and linearity, and reductions in size and cost. Furthermore, raw data are being made available to researchers in addition to processed, manufacturer-specific *count* data [24].

We chose to use the Apple Watch Series 2 and iPhone 6s for this study as they allow measurement of many different parameters (they are both equipped with accelerometers and gyroscopes, the watch has a GPS sensor and heart rate monitor, and the smartphone has a barometer). The watch is also simple to wear and relatively unobtrusive, which is an important consideration for acceptability in long-term use. The ActiGraph has been used in several studies in PAH but requires a chest strap to monitor heart rate (similar to some other activity trackers used in medical research), which would not be feasible for a continuous 3-month study. Consumer wearables, including Apple Watches, have been shown to provide reliable measurements of heart rate, number of steps, and distance walked [23,25,26], and the Apple Watch Series 2 was considered the most accurate available consumer wearable at the time of design of the VENTASTEP study (a recent study of 4 wrist wearables in 50 healthy adults showed that the Apple Watch was the most accurate for heart rate monitoring [27], and the ability of the Apple Watch to detect pulse irregularity is now being assessed in 419,093 volunteers in the Apple Heart Study [28]). However, it should be noted that consumer activity trackers tend to have better test-retest reliability and validity for step-counting at average and vigorous walking speed than at slow walking speed [29], which may be relevant for studies in PAH.

An overview of digital studies in PAH and a timeline of digital studies in relation to key iloprost studies are presented in Multimedia Appendix 2 and Figure 3, respectively [2,3,5,7,9-16,20,30-44].

Physical activity is becoming increasingly important in PAH, with evidence emerging that exercise training in patients with PAH leads to substantial improvements in exercise capacity and pulmonary hemodynamics [45,46]. Moreover, as shown in Figure 3, tracking of daily physical activity is gaining increasing acceptance in PAH studies. Nevertheless, it is still underrepresented as a primary endpoint in PAH clinical trials, which may change in future.

Figure 3. Timeline of key studies of inhaled iloprost and studies of digitally monitored daily physical activity in pulmonary arterial hypertension. Studies of inhaled iloprost (with traditional or digital endpoints) are shown above the timeline, and other studies in pulmonary arterial hypertension with digital monitoring of daily physical activity are shown below the timeline. Blue shading indicates studies with digital monitoring of daily physical activity. Published studies are positioned on the timeline by year of publication; unpublished studies are shown with their ClinicalTrials.gov ID numbers and positioned on the timeline by year of (anticipated) study completion. CTEPH: chronic thromboembolic pulmonary hypertension; e-MOTION PH: electronic activity level monitoring pilot in pulmonary hypertension; ERA: endothelin receptor antagonist; LONGACT: correlation of long-term wrist actigraphy recorded physical performance and 6-min walk distance in patients with pulmonary arterial hypertension; mHealth: mobile health intervention in pulmonary arterial hypertension; MOTION: measuring outcomes in patients with pulmonary arterial hypertension not on active treatment; PAH: pulmonary arterial hypertension; PH: pulmonary hypertension; PHANTOM: pulmonary hypertension and anastrozole trial; TRACE: effect of selexipag on daily life physical activity of patients with pulmonary arterial hypertension; VENTASTEP: evaluation of inhaled iloprost effects using the Breelib nebulizer, on clinical outcomes and physical activity of patients with advanced pulmonary arterial hypertension; WHOLEi+12: whole muscle exercise training in pulmonary hypertension; ZHPHCohort: Zürich Pulmonary Hypertension Outcome Assessment Cohort.



The innovative, digital methodology of the VENTASTEP study will allow simultaneous tracking of daily physical activity, heart rate, and iloprost inhalations for the first time and will provide new insights into clinical outcomes, daily physical activity, and HRQoL in patients starting inhaled iloprost in addition to existing PAH therapy. This is a key strength of this study; the simultaneous capturing of inhalation data and daily physical activity data via remote monitoring will avoid the bias associated with self-reporting and will allow objective assessment of disease course and treatment response. Moreover, it will provide insight into the association of heart rate variability with daily physical activity parameters and intake of PAH medication. The study uses a newly designed app, which harnesses technology available in a consumer wearable and smartphone to measure a wide range of digital parameters; the app is able to distinguish between different types of movement, building a realistic picture of daily physical activity in patients with PAH. The duration of the study (3 months±2 weeks) will also provide a rich digital dataset; previously published studies that included digital measurement of daily physical activity in PAH had shorter monitoring periods (≤14 consecutive days; Multimedia Appendix 2).

Furthermore, VENTASTEP includes traditional investigator- and patient-reported outcomes such as 6MWD and HRQoL (measured using the EQ-5D) alongside digital monitoring data, allowing the potential identification of new digital markers of disease progression and treatment response in PAH. The 6MWD is a widely used measure in PAH [17,18], but it reflects maximum physical activity rather than average daily physical activity. HRQoL is known to be impaired in patients with PAH [47], which might be reflected by reduced levels of daily physical activity. Assessment of daily physical activity could thus provide greater insight into the behavior of patients and the impact of PAH in real life and may allow the development of behavioral interventions to improve outcomes.

In our single-center survey of 30 patients with PAH, 50% (15/30) of the patients indicated that they would accept activity tracking. The rate of acceptance of activity tracking was previously reported as 81% (81 of 99 participants) in a US-based study using the Dynamo Activity Tracker [48] but may differ

between devices [49]. Acceptance may also decline with increasing duration of use; a study of 1258 health plan members given tracking devices in the United States found that at least 90.22% (1135/1258), 82.51% (1038/1258), and 74.80% (941/1258) of participants used their devices for at least 6, 9, and 12 months, respectively [50], whereas a study of the Fitbit Zip in France (N=711) showed continued tracking in 73.9% (526/711) and 16.0% (114/711) of participants at 100 days and 320 days, respectively [51]. The VENTASTEP study was designed considering the results of our single-center survey and will give insight into the willingness of patients with PAH to participate in a 3-month digital noninterventional study, which will involve following and accepting digital monitoring procedures over the observation period.

Limitations

An important limitation of this study is the fact that all participants are aware of being monitored. This knowledge may influence the measures being collected (Hawthorne effect). The study is being performed locally in Germany, and the VENTASTEP study population may not be representative of other countries. A population-based study showed that middle-aged German adults have very low levels of daily physical activity [52]; the difference between impaired and *normal* levels of daily physical activity in the VENTASTEP study may therefore be small. In addition, only patients willing to use wearable devices are included; therefore, the study population may not be representative of the German population with PAH. Physicians will be asked to document all patients in a screening log and record the reasons for noninclusion. All patients in this study are participating in a patient support program, which may also limit the representativeness of the results.

The VENTASTEP study is an observational study based on routine clinical practice; documentation of baseline characteristics may therefore lack detail, the duration of the baseline period will vary between patients and may be insufficient in some cases, and the follow-up visit at the end of the observation period may be delayed in some cases. In addition, patients who drop out because of deterioration cannot be included in the primary analysis. However, the potential impact of this will be estimated with a sensitivity analysis. Gaps in the daily physical activity dataset can arise if the patient does not wear the watch (this may be a particular concern for elderly patients), or if the smartphone and wearables do not work because of failure or battery lifetime. However, these states are detected and flagged by the study app and are excluded from the data evaluation.

Algorithms for classification of device data are derived from people without PAH. The categories might not be appropriate for patients with PAH. This is especially true for heart rate assessments related to parameters reflecting daily physical activity. In addition, deviations from normal heart function (eg, valve insufficiencies and pacemakers) might lead to bias. The study app and iPhone and Apple Watch tracking systems have not been tested in patients with PAH previously, and no comparison data with other activity trackers are available.

The design of this nonrandomized, single cohort study will not allow differentiation between effects induced by treatment and the natural course of disease. The study does not directly measure physical fitness, which is a separate concept from daily physical activity [53] although the 2 are related [54].

Conclusions

The design of the VENTASTEP study represents a substantial advance in the evaluation of digital monitoring of daily physical activity in PAH. The VENTASTEP study includes rigorous analysis of multiple daily physical activity parameters, heart rate, and iloprost inhalation, monitored simultaneously using digital technology in patients with PAH over a substantial period (3 months±2 weeks) in a real-world setting. Changes in traditional clinical measures of disease course and treatment response are also assessed and their correlation with changes in digital measures of daily physical activity and 6MWD will be evaluated as the primary objective. The study will thus provide a wealth of data to inform future research on the utility of digital parameters as outcome assessment tools for disease monitoring and guidance of treatment. The study will also provide insight into clinical outcomes, daily physical activity, and HRQoL in patients starting inhaled iloprost, in addition to existing PAH therapy.

Acknowledgments

This study was funded by Bayer AG (Berlin, Germany) and was conducted in collaboration with the supplier of the patient support program VENTAPLUS (Contra Care GmbH, Nürnberg, Germany) and xbird GmbH (Berlin, Germany), which created the study app (for analysis of daily physical activity and heart rate) and the 6MWD app. Medical writing assistance was provided by Dr Claire Mulligan (Beacon Medical Communications Ltd, Brighton, UK), funded by Bayer AG (Berlin, Germany).

Statistical support was provided by Frank Kleinjung (Bayer AG). Martin Kirchner (Bayer Vital GmbH) was responsible for site management activities and provided comments on an advanced draft of the manuscript.

Authors' Contributions

CM is responsible for the study design and drafting of this article and contributed to the protocol, setup, and conduct of the study. BS wrote the study protocol and is responsible for the setup, coordination, and conduct of the study. AR is responsible for the medical and scientific input and contributed to the protocol, study design, and drafting of this article. JH contributed to the protocol and was involved in the development of the study app and the 6MWD app. MJR contributed to the protocol and setup of the study

and is the principal investigator of the VENTASTEP study. All authors revised the article critically for important intellectual content and approved the final version.

Conflicts of Interest

JH is an employee of xbird GmbH (Berlin, Germany), which created the study app (for analysis of daily physical activity and heart rate) and the 6MWD app. Bayer selected xbird GmbH to join their accelerator program *Grants4Apps* in 2016. CM, AR, and BS are employees of Bayer Vital GmbH (Leverkusen, Germany), which is the local representative of the marketing authorization holder for inhaled iloprost in Europe (Bayer AG, Leverkusen, Germany). MJR has received support from United Therapeutics and Bayer Pharma AG and speaker fees from Actelion, Bayer Pharma AG, Mundipharma, Roche, and OMT.

Multimedia Appendix 1

Additional information on data transfer and processing.

[PDF File (Adobe PDF File), 30KB - resprot_v8i4e12144_app1.pdf]

Multimedia Appendix 2

Studies of digital monitoring parameters in pulmonary arterial hypertension.

[PDF File (Adobe PDF File), 84KB - resprot_v8i4e12144_app2.pdf]

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Abbreviations

6MWD: 6-min walk distance
BNP: brain natriuretic peptide
CRO: contract research organization

EQ-5D: EuroQol 5-dimensions questionnaire
ERA: endothelin receptor antagonist
GPS: global positioning system
HRQoL: health-related quality of life
NT-proBNP: N-terminal pro–brain natriuretic peptide
PAH: pulmonary arterial hypertension
WHO FC: World Health Organization functional class

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Protocol

Acute Flares of Knee Osteoarthritis (the ACT-FLARE Study): Protocol for a Web-Based Case-Crossover Study in Community-Dwelling Adults

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Abstract

Background: The cardinal feature of osteoarthritis (OA) is pain. Although heterogeneity in pain and function have been demonstrated in the long-term course of OA, the more proximate determinants of acute flare-ups remain less clear. How short-term intermittent or transient exposures trigger acute flare-ups has important implications for effective and sustainable self-management strategies.

Objective: The primary objective of this study is to identify potential triggers of acute flares in knee OA. Secondary objectives are to determine their course and consequences and describe high-risk participant profiles.

Methods: We carried out a Web-based case-crossover study. This study aims to recruit 620 community-dwelling adults aged ≥40 years, resident in England, and who have knee pain, with or without a recorded diagnosis of knee OA, and no preexisting diagnosis of inflammatory arthropathy. Participants will be recruited via 3 routes: (1) general practice registers, (2) offline community advertisement, and (3) online social media advertisement. By using questionnaires comparing periods before participants' self-reported flare-up episodes (hazard periods) with periods during the study when their knee OA symptoms are stable (control periods), triggers preceding flare-ups will be identified and examined using conditional logistic regression. Time-to-resolution of flare-up will be examined by monitoring people's daily pain, bothersomeness, and medication usage until the participant reports when their flare-up episode ends. Rates of flare-ups will be examined across different participant and flare characteristics using regression models to identify high-risk participant profiles. A study-specific Patient Advisory Group (PAG) is providing suggestion, input, and ongoing support for all stages of the research process.

Results: Participant recruitment opened in July 2018 and is anticipated to continue for 6 months. The study results will be disseminated through a number of channels, including relevant national or international conferences and peer-reviewed publication in a medical journal, via advocacy or charity organizations, such as Versus Arthritis and across social media. Findings will be fed back to members of our PAG, study participants, and clinicians from participating primary care general practices. The PAG will also take an active role in the overall dissemination strategy.

Conclusions: This study will provide empirical evidence to help patients identify common knee OA flare triggers and provide health care professionals with questions to identify patients at most risk of frequent flare-ups.

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KEYWORDS

knee; osteoarthritis; flare-up; Web-based study; case-crossover study

Introduction

Pain caused by osteoarthritis (OA) is a major cause of functional limitation and disability worldwide [1]. The course of OA pain and functional limitation is heterogeneous among people [2-8], and within different long-term trajectories, there is evidence of substantial within-person variability over time. Shorter episodes of more severe pain (acute flare-ups) deserve further investigation for a number of reasons: (1) unpredictable episodes of severe pain are distressing and disabling in themselves and become more common in the late stages of OA [9], (2) they may disrupt patterns of healthy behavior that serve to reduce the risk of OA progression (eg, weight control, keeping active, and reducing sedentary time) [10], and (3) episodic flare-ups may herald (or may even cause) a transition to less favorable long-term trajectory.

Evidence of short-term daily impact of flare-ups of knee pain is emerging internationally [11,12] as are musculoskeletal studies specifically demonstrating the utility of case-crossover designs to examine transient physical and psychological triggers of low back pain [13-15], knee OA [16-18], and hip OA [19]. Although flare-ups appear to be real phenomena experienced by people with knee OA [11], the antecedents that cause flare-ups and their consequences remain unclear. Our hypothesis is that although susceptibility to flares may be determined by a range of factors, they are ultimately triggered by short-term exposures. The etiopathogenesis of OA is believed to reflect a joint's long-term attempt to accommodate or regulate cumulative excessive or aberrant loading [20]. We postulate that intermittent or transient activity–related exposures that precipitate short-lived recurrent painful flare-ups are key to this process and related management.

The primary objective of this study is to identify the most common and consistently associated proximate causes (*triggers*) of knee OA flares to help make acute flares more predictable and therefore potentially preventable. Secondary objectives are to

1. estimate the time course of acute flares in knee OA with regard to symptoms, activities, and role interference to provide better information to patients and practitioners on the likely short-term prognosis.
2. determine whether characteristics of the participant and his or her problem can identify individuals who are susceptible to flares (*frequent flare phenotypes*) to target flare management and preventive advice in practice.

Methods

Study Design

This study is a Web-based case-crossover study [21]. This self-controlled design assembles within-person case-control comparisons to establish if transient or intermittent exposures (potential triggers) before acute or abrupt-onset events (knee OA flare-up) may explain these episodes. Case-crossover designs have been used to investigate triggers of acute-onset disease (eg, myocardial infarction [22] and stroke [23]), health care events (eg, [24,25]), and acute-on-chronic episodes (eg, gout flares [26]). In this study, the case-crossover design was chosen as an efficient method to identify recurrent *acute-on-chronic* events [27], while capturing proximate exposures. This design is particularly valuable in the context of triggers of acute flares because it controls for time invariant confounders, under the assumption that there are no time trends in exposures over the period of investigation [28]. By conducting this study using a Web-based platform, data collection is efficient in terms of time and cost, while also enabling capture of real-time information on recurrent flares [29].

Target Population

Community-dwelling adults aged 40 years and over, who are resident in England, with knee pain and/or knee OA and have daily access to email and the internet will be invited to take part in this study. A full list of eligibility criteria is presented in Table 1.

Table 1. Eligibility criteria.

Eligibility criteria	Mode of ascertainment
Inclusion criterion	
Male or female aged ≥40 years, resident in England	GPSS[a] or registration page
Registered as a permanent resident with participating general practices[b]	GPSS
Consultation for knee OA or knee OA-related joint symptoms in the last 2 years[b,c]	GPSS
Daily access to an email account and to the internet (laptop, desktop, tablet, or smartphone)	PCRF[d] or registration page
Exclusion criterion	
Known diagnosis of inflammatory arthropathy, spondyloarthropathy or crystal arthropathy (eg, rheumatoid arthritis, ankylosing spondylitis, reactive arthritis, systemic lupus erythematosus, gout, and psoriatic arthritis), fibromyalgia[c]	GPSS or registration page
Symptoms are from a knee that has been replaced	GPSS or registration page
Surgery to either knee within the past 3 months	GPSS or registration page
Unable to complete questions written in English	PCRF or registration page
Vulnerable individuals (eg, psychiatric illness, learning difficulties, dementia, terminal illness, and severe enduring mental ill health)[b]	GPSS

[a]GPSS: General practice search and screen.

[b]Applicable only to participants recruited via general practices.

[c]Based on code lists (available upon request).

[d]PCRF: patient-completed reply form.

Recruitment Procedures

Recruitment will be done via 3 routes: (1) general practice registers, (2) offline community advertisement, and (3) online community advertisement.

General Practice Registers

In total, 5000 potentially eligible adults with suspected or diagnosed clinical knee OA will be identified from up to 17 general practices across England and will be mailed a study pack (letter of invitation, Participant Information Sheet (PIS), reply form, and prepaid return envelope). General practitioners at each practice will also be invited to screen the sample list for patients whom they consider should be excluded from the invitation mailing (eg, vulnerable individuals). A reminder letter, together with a repeat PIS, reply form, and prepaid return envelope, will be sent to people who have not responded after 2 weeks. People who have not responded within 4 weeks will not be contacted again. Practice mailing will be performed in stages.

Participants who return a reply form will be providing implied consent to further contact. Those who, on their reply form, fulfill the eligibility criteria and provide their name, a valid personal email address, and mobile phone number (optional) will be sent a preconsent welcome email containing a Web link to the ACT-FLARE study website (developed using Microsoft Visual Studio). The Web link will direct them to an online copy of the PIS, and from there to the informed electronic consent (e-consent) form. For people who return a reply form with illegible, ambiguous, or invalid responses or personal details (eg, invalid email address), an attempt to clarify this information will be made with 1 follow-up email or letter, as appropriate, asking the individual to contact the study team by phone or email. If there is no response, these people will not be contacted again.

Offline Community Advertisement

Study posters, flyers, or business card advertisements will be displayed in the waiting areas and patient information points of all participating general practices; additional general practices; selected community pharmacies; patient waiting areas in community hospitals; and public libraries across England, where permission to do so is granted. Wherever possible, the study will also be publicized through local newspapers and radio.

The advertising material will include the study title, summary study information and eligibility, the Web address for the ACT-FLARE study registration webpage, and study contact email address and telephone number. Members of the public who are interested in taking part and believe they may be eligible will be invited to visit the ACT-FLARE study registration webpage where summary information, eligibility, and contact details are again displayed. Interested members of the public who deem themselves eligible will be asked to submit key data (implied confirmation of eligibility, email address, name (optional), mobile phone number (optional), postcode (to ensure they are an England resident), and how they heard about the study) to Keele Clinical Trials Unit, which will generate a unique study identification number and the preconsent welcome email containing a Web link to the ACT-FLARE study website. The Web link will direct them to a copy of the PIS and to the informed e-consent process.

Online Community Advertisement

We will use targeted social media advertising in Facebook to publicize the ACT-FLARE study. This will also include placement of adverts on selected key organizational or group

pages, such as Arthritis Research UK, Arthritis Care, Age UK, and Patient UK, as well as Keele University Research Institute for Primary Care & Health Sciences website, Facebook page, Twitter account, and blog. Interested, potentially eligible participants will be directed to the ACT-FLARE study registration page where the same subsequent process of recruitment as described in the offline route will be followed.

All participants will be invited to provide informed e-consent before setting up a username and password for login access to the ACT-FLARE study website to participate in the study.

Ethical approval has been obtained from Yorkshire & The Humber—Leeds East Research Ethics Committee (REC reference number: 18/YH/0075).

Data Collection

Data will be collected via self-complete questionnaires by the participant using a Web-based data collection platform previously developed as part of our feasibility and pilot study [30]. All participants will be followed up for a 13-week period, irrespective of how many flare-up episodes are experienced. Data collection will comprise 4 elements: (1) baseline questionnaire, (2) scheduled questionnaires, (3) event-driven questionnaires, and (4) daily questionnaires during a flare-up. Data collection has the following general features:

1. All questionnaires can be completed on a desktop, laptop, tablet, or mobile smartphone in under 15 min, in accordance with feedback from our Patient Advisory Group (PAG).
2. Questionnaires must be completed in one time point by the participant. There is no facility for partial completion and return at a later time. This approach was selected to ensure that questionnaires are completed as contemporaneously as possible.
3. Once a questionnaire has been completed and submitted by a participant through the website, the participant no longer has repeat access to the questionnaire.
4. A short onscreen *thank you* statement will be generated following the completion of each questionnaire.
5. Remembering to notify the research team about a flare-up has been identified as a critical issue. Participants who provide a mobile telephone number (optional) will be sent a reminder text message about the study once a fortnight for the duration of the study. This will be calculated from the date each participant completes their baseline questionnaire, and all texts will be sent to participants at 18:00 Greenwich Mean Time.
6. At the end of the study, participants will be invited to provide feedback on their participation in the study and whether they would be willing to additionally participate in clinical examinations during a knee flare-up, should a similar study be conducted in the future, to include magnetic resonance imaging and synovial fluid sample via knee joint aspiration.

Baseline Questionnaire

The purpose of the baseline questionnaire is to provide descriptive information on participants' history of knee pain and flare-ups, current knee features, health care use for knee pain, general health, including normal physical activity exposures, and demographics. The content of the baseline questionnaire is provided in Table 2. It includes domains and measurement instruments of potential relevance based on previous literature and critical input from a PAG.

Once participants activate their log-in with the study website, they will be directed to the baseline questionnaire, which becomes available for completion immediately. At this point, participants will also receive emailed instructions to use their username and password to log-in to the website. If participants do not complete the baseline questionnaire, an email reminder will be sent after 3 days and a repeat email reminder after a further 3 days. If no response is received after 7 days from the initial date of invitation, participants can no longer continue in the study. The participant will receive an email notification confirming this.

Table 2. Baseline questionnaire.

Concept, measurement method	Detail	Time available for completion	Reminder sent
Section A: Your knee pain			
Time since onset	Not applicable, <1 year, 1-4 years, 5-9 years, 10+ years. Left, right	7 days	Yes
Pattern [31]	5 flare pattern illustrations. Left, right	7 days	Yes
Experience of knee pain [32]	In past 6 months: No pain, predictable pain, some unpredictability, constant. Left, right	7 days	Yes
Pain, aching, stiffness in last month [33,34]	No days, few days, some days, most days, all days. Left, right	7 days	Yes
Worst and least in last week, average, current [35]	0-10 Numerical Rating Scale with anchors (no pain, pain as bad as you can imagine)	7 days	Yes
Knee injury and Osteoarthritis Outcome Score Physical Function [36]	7-items and 5-option categories for difficulties with daily activities in last week	7 days	Yes
Knee injury and Osteoarthritis Outcome Score Quality of Life [37]	4-items and 5-option categories for quality of life in last week	7 days	Yes
Bothersomeness in last 24 hours [38]	Not at all, slightly, moderately, very much, extremely. Left, right	7 days	Yes
Flare-up at present	Yes, No. Left, right	7 days	Yes
Self-reported main flare trigger	Free text	7 days	Yes
Varus-valgus malalignment [39]	Very bow legged, bow legged, normal, knock-knee, very knock-knee. Left, right	7 days	Yes
Foot rotation [39]	Very turned out feet, turned out feet, straight, turned in feet, very turned in feet. Left, right	7 days	Yes
Previous knee injury [40]	Injury induced walking problems for at least 1 week. Left, right	7 days	Yes
Family history of total knee replacement [40]	Mother, father, sister or brother. Yes, No, don't know	7 days	Yes
Section B: Health care use for your knee pain			
Medications, last week	17-option categories for drug use, tick as many boxes as apply	7 days	Yes
Health professional consultation, last year	General practitioner, practice or district nurse, physiotherapist, surgeon, rheumatologist, acupuncturist, occupational therapist	7 days	Yes
Any kind of previous knee surgery	Yes, No. Left, right	7 days	Yes
Previous knee injections last 3 months	Left, right, both, not applicable	7 days	Yes
Previous knee surgery last 3 months [40]	Left, right, both, not applicable	7 days	Yes
Previous total knee replacement	Left, right, both, not applicable	7 days	Yes
On waiting list for total knee replacement	Left, right, both, not applicable	7 days	Yes
Section C: Your general health			
Perceived general health [41]	Excellent, very good, good, fair, poor	7 days	Yes
Physical activity [42]	Work physical activity (5-response options), general physical activity in last week (5-response options, 4-option categories), walking pace	7 days	Yes
Self-reported weight	Stones and lbs or kg	7 days	Yes
Self-reported height	Feet and Inches or cm	7 days	Yes
Normal physical activities on a normal day			
Walking outside without rest	Not at all, A little, A lot	7 days	Yes
Standing for long periods without rest	Not at all, A little, A lot	7 days	Yes
Sitting for long periods without a break	Not at all, A little, A lot	7 days	Yes

Concept, measurement method	Detail	Time available for completion	Reminder sent
Moderate-to-vigorous physical activity (this may include activities that make you breath harder than normal) [43]	Not at all, A little, A lot	7 days	Yes
Going up and down stairs	Not at all, A little, A lot	7 days	Yes
Driving	Not at all, A little, A lot	7 days	Yes
Squatting or kneeling	Not at all, A little, A lot	7 days	Yes
Lifting or moving heavy objects	Not at all, A little, A lot	7 days	Yes
Going up and down ladders	Not at all, A little, A lot	7 days	Yes
Section D: About you and your circumstances			
Gender	Male, female	7 days	Yes
Date of birth	Date, Month, Year	7 days	Yes
Current employment	Paid employment or self-employed, retired, looking after home and/or family, unable to work because of sickness or disability, unemployed, doing unpaid or voluntary work, full or part-time student.	7 days	Yes

Scheduled Questionnaires

The purpose of the scheduled questionnaires is to measure activities and exposures (potential triggers) during control periods (ie, days that are not followed by a flare-up). The content for the scheduled questionnaire is provided in Table 3. It features a matrix for reporting the occurrence and amount of 21 physical, psychosocial, and environmental potential triggers on the day of questionnaire completion and the 3 days before this. These potential triggers have been selected from previous literature, PAG discussion, and clinical experience.

In total, 4 scheduled questionnaires will be sent to participants 1 week, 5 weeks, 9 weeks, and 13 weeks after completion of the baseline questionnaire. The timing of all scheduled questionnaires remains the same in the event of delayed or nonresponse to 1 or more scheduled questionnaires. All participants will be sent an email inviting them to complete each scheduled questionnaire about their activities and exposures during the last 3 days. The email will contain a direct link to the questionnaire, which will also become accessible at the correct point in time should the participant log-in to the website independently of the email link.

As a part of each scheduled questionnaire, participants will initially be asked if they are currently experiencing a flare-up of their knee pain. If *no*, they will continue to complete the scheduled questionnaire. If *yes*, the participant will be redirected to complete the event-driven questionnaire (see below).

Nonresponders will be sent an email reminder after 3 days and a repeat email reminder after a further 3 days. If no response is received after 7 days, the questionnaire becomes deactivated and can no longer be completed. The participant will receive an email notification confirming this. Nonrespondents to scheduled questionnaires remain in the study.

Event-Driven Questionnaires

The purpose of the event-driven questionnaires is to measure activities and exposures (potential triggers) during hazard periods (ie, the 3 days before experiencing a flare-up) and to gauge whether flare-ups are often anticipated by participants. The content for the event-driven questionnaire is provided in Table 4. As per the scheduled questionnaire, this features the same matrix for reporting the occurrence and amount of 21 physical, psychosocial, and environmental potential triggers on the day the flare-up started and the 3 days before this. In addition, participants will be asked about features of their flare-up.

Participants will be invited to complete an event-driven questionnaire immediately if they provide notification through the website that they are currently experiencing a self-reported flare-up. This notification can be initiated either via a Web link provided in the welcome email, scheduled questionnaire email, text message correspondence, or by logging onto the study website. There is no limit to the number of times a participant can self-report a flare-up episode during the study period.

After providing a flare-up notification, if a participant does not complete the event-driven questionnaire, an email reminder will be sent after 1 day. A repeat email reminder will be sent after a further day. If no response is received after 2 days, the event-driven questionnaire becomes deactivated and can no longer be completed. The participant will receive an email notification confirming this. Nonrespondents to event-driven questionnaires remain in the study.

Table 3. Scheduled questionnaire. Potential trigger questions answered for today, day before, 2 days earlier, and 3 days earlier.

Concept[a], measurement method	Detail	Time available for completion	Reminder sent
Knee pain			
Flare-up at present	Yes, No. Left, right	7 days	Yes
Average pain in last 24 hours [44]	0-10 Numerical Rating Scale with anchors (no pain, pain as bad as you can imagine). Left, right	7 days	Yes
Potential triggers			
Physical activities			
Walking outside without rest	Not at all, A little, A lot	7 days	Yes
Standing for long periods without rest	Not at all, A little, A lot	7 days	Yes
Sitting for long periods without a break	Not at all, A little, A lot	7 days	Yes
Moderate-to-vigorous physical activity (this may include activities that make you breath harder than normal) [43]	Not at all, A little, A lot	7 days	Yes
Going up and down stairs	Not at all, A little, A lot	7 days	Yes
Driving	Not at all, A little, A lot	7 days	Yes
Squatting or kneeling	Not at all, A little, A lot	7 days	Yes
Lifting or moving heavy objects	Not at all, A little, A lot	7 days	Yes
Going up and down ladders	Not at all, A little, A lot	7 days	Yes
Slips, trips, sprains, and strains			
Slip, trip or fall	No, Yes	7 days	Yes
Episode of buckling or giving way [45]	No, Yes	7 days	Yes
Health and health care use			
Reduce or miss medication	No, Yes	7 days	Yes
Take extra medication	No, Yes	7 days	Yes
Cough, cold, or other minor infection	No, Yes	7 days	Yes
Stress and other things			
Work-related stress [46]	No, Yes	7 days	Yes
Home-related stress [46]	No, Yes	7 days	Yes
Friend/family-related stress [46]	No, Yes	7 days	Yes
Low mood/depression	No, Yes	7 days	Yes
Feeling angry, irritable, or hostile	No, Yes	7 days	Yes
Poor night's sleep	No, Yes	7 days	Yes
Generally cold and damp weather [47]	No, Yes	7 days	Yes

[a]Questionnaire opens with orientation text: The following questions are about your knee symptoms at the moment. Please answer all questions below. Some of these questions will ask you about things you may have been doing on the last 3 days. Please can you take a moment to remind yourself what you were doing on each of these days to help you answer some of the questions below.

Table 4. Event-driven questionnaire. Potential trigger questions answered for day of flare-up, day before, 2 days earlier, and 3 days earlier.

Concept[a], measurement method	Detail	Time available for completion	Reminder sent
Nature of flare			
Knee pain			
When did this flare-up start?	Today, yesterday, 2 days ago, 3 days ago, 4 or more days ago	2 days	Yes
Was this flare-up unexpected?	Yes, No	2 days	Yes
Which knee currently experiencing a flare-up?	Left, right	2 days	Yes
Average pain in last 24 hours [44]	0-10 Numerical Rating Scale with anchors (no pain, pain as bad as you can imagine). Left, right	2 days	Yes
Changes noticed since flare-up			
More than usual: limping, swelling, stiffness, increased difficulty with activities of daily living, sleep disturbance by knee pain	Tick as many boxes as apply	2 days	Yes
Potential triggers			
Physical activities			
Walking outside without rest	Not at all, A little, A lot	2 days	Yes
Standing for long periods without rest	Not at all, A little, A lot	2 days	Yes
Sitting for long periods without a break	Not at all, A little, A lot	2 days	Yes
Moderate-to-vigorous physical activity (this may include activities that make you breath harder than normal) [43]	Not at all, A little, A lot	2 days	Yes
Going up and down stairs	Not at all, A little, A lot	2 days	Yes
Driving	Not at all, A little, A lot	2 days	Yes
Squatting or kneeling	Not at all, A little, A lot	2 days	Yes
Lifting or moving heavy objects	Not at all, A little, A lot	2 days	Yes
Going up and down ladders	Not at all, A little, A lot	2 days	Yes
Slips, trips, sprains, and strains			
Slip, trip, or fall	No, Yes	2 days	Yes
Episode of buckling or giving way [45]	No, Yes	2 days	Yes
Health and health care use			
Reduce or miss medication	No, Yes	2 days	Yes
Take extra medication	No, Yes	2 days	Yes
Cough, cold, or other minor infection	No, Yes	2 days	Yes
Stress and other things			
Work-related stress [46]	No, Yes	2 days	Yes
Home-related stress [46]	No, Yes	2 days	Yes
Friend/family-related stress [46]	No, Yes	2 days	Yes
Low mood/depression	No, Yes	2 days	Yes
Feeling angry, irritable, or hostile	No, Yes	2 days	Yes
Poor night's sleep	No, Yes	2 days	Yes
Generally cold and damp weather [47]	No, Yes	2 days	Yes
Your flare-up			
What do you think caused this flare-up of your knee pain?	Free text	2 days	Yes

[a]Questionnaire opens with orientation text: The following questions are about your current flare-up of knee pain. Please answer all questions below. Some of these questions will ask you about things you may have been doing on the 3 days before your flare-up and also on the day it started. Please can you take a moment to remind yourself what you were doing on each of these days to help you answer some of the questions below.

Daily Questionnaires During a Flare-Up

The purpose of the daily questionnaire during a flare-up is to collect information regarding the natural course of flare-up episodes. These comprise 4 brief questions on pain intensity, bothersomeness, health care use, and participant judgment on whether their flare-up has ended. The content for the daily questions during flare-up is provided in Table 5.

Upon completion of the event-driven questionnaire, participants will be invited to complete the 4 questions, starting one day later, via email until resolution of their flare-up. *Resolution* is defined as participants reporting that their symptoms have returned to their preflare *normal* state for 2 consecutive days.

There will be no reminders for the daily questionnaires during flare-up and participants can only complete questionnaires on the day they are sent, with any earlier incomplete dates becoming deactivated. Emails will be sent to participants at 18:00 Greenwich Mean Time for the duration of the flare-up episode. Broderick et al [48] have previously demonstrated that end-of-day pain measurement adequately reflects average daily pain levels. If a participant is still reporting that they are in a flare-up episode at the end of the study period, they will not be followed up to flare-up resolution beyond this time point. If a participant is having a flare-up, they will not receive a further scheduled questionnaire until the participant notifies us that the flare-up episode has resolved.

Table 5. Daily questions during a flare-up.

Concept, measurement method	Detail	Time available for completion	Reminder sent
Knee pain			
Average pain in last 24 hours [44]	0-10 Numerical Rating Scale with anchors (no pain, pain as bad as you can imagine). Left, right	6 hours	No
Impact of pain			
Bothersomeness in last 24 hours [38]	Not at all, slightly, moderately, very much, extremely. Left, right	6 hours	No
Medication use			
Pain medication taken in last 24 hours	No; yes, but less than usual; yes, about the same as usual; yes, more than usual	6 hours	No
Flare-up resolution			
Has your flare-up ended	Yes, No	6 hours	No

Patient Involvement

This study is a patient-confirmed research priority, and a study-specific PAG has assisted with the study development from inception. So far, this has included advice and suggestion on all aspects of questionnaire and website development as part of this full-scale study and our previous feasibility and pilot study [30]. Engagement has taken place through workshops, written and verbal feedback on study questionnaires, and practical hands-on trial of website utility during development. One member of our PAG has remained an active member of the study management group from inception (CP).

Outcome Definition

Self-reported flare-up of symptomatic knee OA is defined as “an event in the natural course of the condition characterized by a change in the participant’s baseline pain that is beyond normal day-to-day variation, sustained for at least 24 hours, and is sudden or quick in onset. It may impact on the ability to perform everyday activities and result in an increase in analgesic intake”. This definition was derived from our pilot study [30], which used a qualitative approach based on self-assessment, a previous literature review [49], group discussions with patients and members of the public, and findings from a previous survey and 3-month pen-and-paper daily diary study (unpublished data at time of submission).

Sample Size

A sample size of 434 participants will have 80% power at a 5% 2-tailed significance level to detect an unadjusted odds ratio of 2 for knee pain flare-up in the hazard period relative to control period if the probability of exposure (potential trigger) among control periods is at least 0.1, the correlation coefficient for the exposure between matched hazard periods and control periods is no more than 0.3 [16], and assuming a 1:1 ratio of control periods to hazard periods.

We will recruit 620 participants, allowing for approximately 30% of participants who may not experience a flare-up or drop-out during the study period [16]. We estimate a total of 17 general practices will be required for this recruitment target. This is based on 8% of adults aged ≥40 years consulting for knee OA or knee joint pain over a 2-year period [50], an average practice list size of 7000 patients, half of whom are aged ≥40 years, and a combined eligibility, response, and consent rate of 12%.

Recruitment of participants via offline and online community advertisements will efficiently supplement the above recruitment method, which will be particularly valuable in the event of lower-than-expected participation and reported flare frequency, and for reducing imprecision in important subgroup analyses, for example, restricting analysis to participants who provide early notification of flare-up and those whose flare-up proves to be more than transient.

Statistical Analysis

Summary of Baseline Data and Flow of Participants

Recruitment and Retention

Production of a Consolidation Standards of Reporting Trials–style participant flowchart and simple descriptive statistics for response rates (including age, gender, and deprivation score, derived from participant postcodes, of responders compared with eligible nonresponders at baseline) in accordance with standard definitions [51].

Summary Descriptive Characteristics of the Study Sample

Demographic and self-report clinical characteristics will be described. Participants will be compared with ineligible and nonconsenting participants on available data. Summary descriptive characteristics of flare-ups, symptoms, and consequences during the flare-up will be described.

Triggers, Course, Consequences, and High-Risk Participant Profiles

Proximate Triggers of Acute Flares (Primary Objective)

The odds of identified potential flare-up antecedents or triggers occurring in the hazard period will be compared with the relative occurrence in the control period using conditional logistic regression using m:n matching, as each participant may have multiple hazard and control periods [52]. Modeled data will be presented as odds ratios with 95% CIs. The assumption of no time-trend in exposure will be verified.

The optimal duration of the hazard (effect) period for flare-ups is unknown. Our primary analysis will be based on the scheduled questionnaires (Weeks 1, 5, 9, and 13) being the main source of control exposure measurements comparison for with the event-driven questionnaire. The relative merits of hazard periods of 24, 48, and 72 hours will be explored to test the induction period, while also protecting the analysis against rare exposures.

In the advent of low levels of completion of the scheduled questionnaire, we will explore alternative sources of control measurement: (1) normal physical activity exposure measurements ascertained in the baseline questionnaire and (2) by exposure measurement in the preceding 48 and 72 hours (for hazard period exposure defined in the preceding 24 hours) within the event-driven questionnaire.

Owing to a lack of consensus definition for a flare-up in the OA literature, our statistical analysis plan will allow for analysis of alternative definitions, for example, no defined minimum flare-up duration, or imposed knee pain change score of ≥2 on a numerical rating scale, between baseline and self-reported flare-up. We will also consider the potential for combining related exposures.

By describing the proportion of triggers during the hazard window that were reported by participants as being unanticipated, the extent to which triggers were predictable will be explored.

Time Course and Consequences of Acute Flares (Secondary Objective 1)

Using the daily questionnaires during a flare-up, time-to-resolution of symptoms will be compared across participants.

Frequency of Acute Flares (Secondary Objective 2)

The rate of acute flares reported during follow-up will be modeled using regression models. This will identify whether certain participants and flare characteristics (collected in the baseline questionnaires) are more or less likely to experience flare-ups.

The amount of missing data will be calculated and the effects on each of the analyses may be investigated using multiple imputation.

Results

Participant recruitment opened in July 2018 and is anticipated to continue for 6 months. The study results will be disseminated through a number of channels, including relevant national or international conferences and peer-reviewed publication in a medical journal, via advocacy or charity organizations, such as Versus Arthritis and across social media. Findings will be fed back to members of our PAG, study participants, and clinicians from participating primary care general practices. The PAG will also take an active role in the overall dissemination strategy.

Discussion

Recognition of the potential importance of episodic flares in the natural history of OA is gaining momentum among the clinical research community [49,53,54]. In this 13-week Web-based case-crossover study, we will combine general practice–based recruitment with social media advertising across England to identify proximate causes (*triggers*) of acute flare-ups in knee OA, estimate their time course and consequences, and describe individuals most susceptible to flares.

By embracing both digital epidemiology and within-person study design to examine OA flares, it is hoped that real-time observations of individual episodic symptom variability can provide insights into these phenomena and their potential relation to short-term prognosis. However, this endeavor is not without limitations. Major challenges of this approach are the recruitment of individuals to a Web-based data collection platform and timely capture of events and exposures. With no agreed objective measurement for an OA flare, the ascertainment of onset is reliant on participant self-report. There is also the potential for recall bias owing to differential reporting of exposure in the hazard and control periods. For example, participants answering questions about potential exposures over the last 3 days while currently experiencing a flare-up (event-driven questionnaire) may respond differently to the same questions when they are not experiencing a flare-up (scheduled questionnaire). Despite this, all comparisons are within-person, therefore eliminating time-invariant person-level confounders by design. Conditional regression is then used to

compare exposure status between the hazard and control periods within the same person. Factors that do not change over time, such as gender and genetics remain constant in all periods. In addition, inviting participants to reflect on recent experiences to help understand the behavior of their symptoms can be easily integrated into patient-oriented approaches to self-management that can occur in the community and be supported by all primary care encounters. This study will provide empirical evidence to help patients identify common knee OA flare triggers, provide health care professionals with questions to identify patients at most risk of frequent flare-ups, and inform clinical guidelines.

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Authors' Contributions

MJT and GP conceived the study. MJT, TR-M, ELP, CP, TN, and GP designed the study. TR-M developed the analysis plan in conjunction with MJT and GP. MJT and SH designed and developed the study's Web-based data collection platform. MJT drafted the paper, and all authors contributed to the paper. All authors approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

CRN: clinical research network
e-consent: electronic consent
HEE: Health Education England
NIHR: National Institute for Health Research
OA: osteoarthritis
PAG: Patient Advisory Group
PIS: Participant Information Sheet

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Protocol

A Smart Home System for Information Sharing, Health Assessments, and Medication Self-Management for Older People: Protocol for a Mixed-Methods Study

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Abstract

Background: Older adults often want to stay in a familiar place, such as their home, as they get older. This so-called aging in place, which may involve support from relatives or care professionals, can promote older people's independence and well-being. The combination of aging and disease, however, can lead to complex medication regimes and difficulties for care providers in correctly assessing the older person's health. In addition, the organization of health care is fragmented, which makes it difficult for health professionals to encourage older people to participate in their own care. It is also a challenge to perform adequate health assessments and to engage in appropriate communication between health care professionals.

Objective: The purpose of this paper is to describe the design for an integrated home-based system that can acquire and compile health-related evidence for guidance and information-sharing among care providers and care receivers in order to support and promote medication self-management among older people.

Methods: The authors used a participatory design approach for this mixed-methods project, which was divided into four phases. Phase I, Conceptualization, consists of the conceptualization of a system to support medication self-management, objective health assessments, and communication between health care professionals. Phase II, Development of a System, consists of building and bringing together the conceptualized systems from Phase I. Phase III, Pilot Study, and Phase IV, Full-Scale Intervention, are described briefly.

Results: Participants in Phase I were people who were involved in some way in the care of older adults and included older adults themselves, relatives of older adults, care professionals, and industrial partners. With input from Phase I participants, we identified two relevant concepts for promoting medication self-management, both of which related to systems that participants believed could provide guidance for the older adults themselves, relatives of older adults, and care professionals. The systems will also encourage information-sharing between care providers and care receivers. The first is the concept of the Intelligent Age-Friendly Home (IAFH), defined as an integrated residential system that evolves to sense, reason, and act in response to individuals' needs, preferences, and behaviors as these change over time. The second concept is the Medication safety, Objective assessments of health-related behaviors, and Personalized medication reminders (MedOP) system, a system that would be supported by the IAFH, and which consists of three related components: one that assesses health behaviors, another that communicates health data, and a third that promotes medication self-management.

Conclusions: The participants in this project were older adults, relatives of older adults, care professionals, and our industrial partners. With input from the participants, we identified two main concepts that could comprise a system for health assessment,

communication, and medication self-management: the IAFH and the MedOP system. These concepts will be tested in this study to determine whether they can facilitate and promote medication self-management among older people.

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KEYWORDS

assessments; medication; mixed methods; older people; self-management; smart homes

Introduction

Background

Making our world more age-friendly is a key strategy to facilitate the involvement of older persons in their own care [1]. An age-friendly world supports people of all ages in actively participating in community activities and treats everyone with respect, regardless of their age. It can also enable people to stay healthy and active as they age and provide appropriate support to those who can no longer look after themselves. Remaining at home rather than moving to assisted living seems to be important to older people, even those who are ill and/or need care and supervision [2,3]. For older adults, remaining in their homes promotes independence and well-being [4].

Over half of people aged 80 years and older suffer from two or more diseases, such as diabetes, cancer, heart disease, or mental illness [5]. The presence of multiple diseases leads to an increased use of medications and the associated risk of side effects. Moreover, one out of 10 hospitalized patients experiences some kind of harm, with medication-related errors being the most common [1].

Hence, the interaction between the aging process, diseases, medication, and related side effects leads to complex health conditions that are difficult to assess and communicate [6,7]. Moreover, since care professionals are not on-site around the clock, they receive only partial information throughout the day about older adults living at home [8]. This makes assessing and making correct decisions about the older person's health difficult. In addition, older adults themselves express their difficulty in communicating their needs and state that this is due to emotional vulnerability [9]. A further difficulty lies in the exchange of information between formal and informal caregivers. There appear to be gaps in the communication between different care professionals (eg, physicians and registered and assistant nurses) and next of kin [6,10]. This gap in communication often occurs because the various health care professionals work for different organizations, such as specialist care or outpatient care for the county council or the municipality, and lack a natural place to exchange information [6,7,10].

Research has shown that when older people self-manage their medications, there is a corresponding improvement in health status, increase in safety, and decrease in utilization and costs [8-11]. Research has also shown that medication adherence increases [8-13]. Different assistive technologies for medication compliance, such as medication dispensers, are commonly used to support independence in medication management [14]. Studies demonstrate, however, that assistive technologies for medication compliance are not suitable for older people with recurrent medication adjustments or cognitive deficiencies; this is the case because most of these devices do not include reminders or facilitate dosage adjustments and require training to operate, thus excluding the older person from the management process [8,15].

Objectives and Research Questions

The overall aim of this project is to deliver an integrated home-based system to support and promote medication self-management among older people. More specifically, the project's objectives are to design, develop, and evaluate an age-friendly smart home that uses smart technologies, such as sensors and medication dispensers, to collect and compile health-related evidence in order to support decision making and communication regarding medication treatment, which in turn could enhance medication self-management. The project itself includes four phases: (1) Phase I: Conceptualization, (2) Phase II: System Development, (3) Phase III: Pilot Study, and (4) Phase IV: Full-Scale Intervention. This paper focuses on Phase I and its results; Phases II, III, and IV are planned and will be described in upcoming publications.

The main research questions in the project are as follows:

1. How smart does a smart home need to be in order to increase knowledge about the older resident's health status?
2. Which features should a smart medication-dispensing device include to support medication management among older people?
3. How could a digitalized home documentation system support health care decision making and communicate with health care professionals and older adults?
4. Can medication self-management and medication safety for older people be supported solely by single, stand-alone systems, or are integrated systems required in order to provide the expected benefits? How should such a stand-alone and/or integrated system then be implemented in practice?

Methods

Participatory Design

Involving older adults and caregivers in the development and evaluation of health care technologies has become increasingly relevant during recent years because their perspectives and insights can reveal needs not captured by researchers and lead to solutions that are more likely to be accepted and adopted [16]. Participatory design is a method that enables involvement, active participation, and collaboration of different stakeholders (eg, older people, relatives, caregivers, and researchers) in the codesign and coresearch activities throughout the development

life cycle; the objective is a better understanding of the problem itself, reducing risks, and delivering a solution that reflects actual needs, preferences, and usage. Participatory design is also a rigorous research method and design approach [16] that draws on principles from participatory action research [17]. The method draws on the users' *tacit knowledge* —in other words, their implicit or unarticulated knowledge as learned and transmitted through experiences and apprenticeship. Participatory design uses a variety of generative tools to establish participation [18]; the process includes the following three stages [16]:

1. Stage 1: Initial exploration of work. Observations and interviews are conducted to explore uses of the technology, routines, and aspects of the work in order to assess needs.
2. Stage 2: Discovery process. Workshops and codesign activities are organized so researchers and users can define goals and the desired outcomes of the project.
3. Stage 3: Prototyping. Researchers and users engage in the cocreation of a prototype for the solution designed in Stage 2. The resulting artifact enables further discussions and understanding of the proposed solution.

In the protocol presented in this paper, the participants' involvement will be used throughout the research project and mixed methods [19] will be used for collecting their views; as well, there will be a particular focus on iterations in the design process.

Research Design

Overview

The research project mentioned in this work is being carried out in four phases: Phase I, Conceptualization; Phase II, System Development; Phase III, Pilot Study; and Phase IV, Full-Scale Intervention. In this research protocol, we describe Phase I more thoroughly and Phases II-IV only tentatively (see Figure 1).

Phase I

Conceptualization

This initial phase aims at enabling participants to familiarize themselves with how they can contribute and collaborate in the development of a home-based system to support and promote medication self-management among older people. This phase also includes exploring how technology can be used, work procedures, routines, safety, and any other aspects that might affect the users. In this phase, goals and values will be clarified in order to conceptualize the desired outcome of the project.

Participants

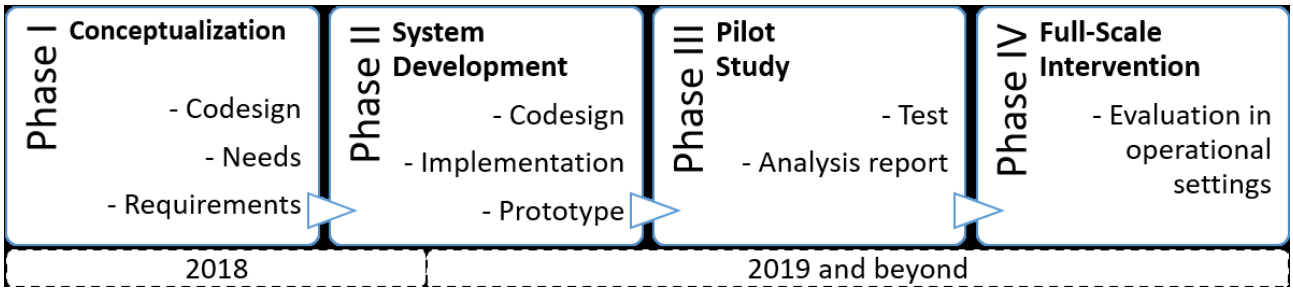
The participants were caregivers, the older people themselves, relatives, and the industrial partners. Caregivers from the municipal health care organizations in the municipalities of Halmstad and Hylte, Sweden, and the older people themselves were contacted through two different networks. The first network included the county council of the region of Halland, Sweden; the municipalities of Halmstad and Hylte, Sweden; and Halmstad University, Sweden, all of which share a mutual goal of collaborating in the development and introduction of eHealth in the region. A total of 13 people from this network participated: 9 females (69%) and 4 males (31%). Out of the 13 participants, 4 (31%) were registered nurses, 4 (31%) were assistant nurses, and 5 (38%) were managers. The second network included representatives from the National Organization of Pensioners from the county council of the region of Halland, Sweden (1 male representative), and from the Family Caregiver Association from Halmstad University (1 female representative). In addition, 2 industrial partners joined the project, contributing 7 participants to the study (3 participants from the first industrial partner and 4 from the second industrial partner). The first industrial partner produces medication-dispensing devices and had recently finished a pilot study in which its device was used by older persons in their homes and by care staff. The other industrial partner has developed Web-based questionnaires for collecting and communicating health care information.

Procedures

To explore the health care providers' and the industrial partners' tacit knowledge and way of working, they were initially visited at their workplaces. Thereafter, seminars were organized in order to create a shared understanding of pertinent issues and complexities related to medication management. Questions discussed were as follows: Can a technical solution be an alternative to the medication administration routines used today? What challenges do care professionals consider to be associated with medication administration? What challenges and solutions can technology bring? What ethical aspects are implied in introducing technological solutions for medication administration?

The participants were allowed to freely discuss these issues, and notes were taken. These were performed asynchronously, and 15 seminars were conducted in total. In addition to seminars, nine workshops were organized. Workshops differed from the seminars in that specific questions were asked relating to the participants' expert knowledge and their suggested solutions.

Figure 1. The four phases in the system development life cycle.



In order to obtain additional knowledge in the field, the research group participated in two different conferences about smart homes for older people.

Evaluation of Phase I

It became evident to both our participants and us during Phase I that the administration of medications was complex and that current routines are sometimes contradictory. Registered nurses reported that existing solutions using different kinds of drug dispensers were not safe because all tablets cannot be divided in them, all tablets do not fit into them, and one person can have many different administration systems. This made it difficult for them to have control over the medication (eg, if any interactions and side effects occur). Registered nurses reported that existing solutions using different kinds of drug dispensers were not safe for a variety of reasons; for example, the variables offered by the dispensers in terms of administration times were often insufficient to meet the needs of the patient's various complex medication schedules, or were simply not large enough to hold all of the patient's medications, resulting in difficulties for nurses in tracking the sources of interactions and side effects. At the same time, for practical reasons they were forced to delegate the medication administration to an assistant nurse, who is a nonauthorized staff member. Furthermore, they pointed out that most deviations are related to incorrect medication lists and unclear prescriptions, and there is an insufficient number of people to whom they can delegate.

The assistant nurses, on the other hand, expressed a fear of making mistakes. At the same time, it appears that relatives take a great deal of the responsibility relating to medication administration. The participants realized that a technical solution could be an alternative but also expressed concerns about whether it could solve the problem. In addition, anxiety was raised about the risk of missed social contacts for the elderly person, as staff would not have to come to their homes to administer drugs to them. During the workshop and seminars, it emerged that the care staff perceived the introduction of home-based technology as something that would support them in their daily work but would also be challenging. They lacked confidence in using technology; in addition, they feared that the older person would have fewer visits and, thus, less human contact.

With input from the participants, we identified two main concepts that could comprise a system to collect and compile health-related evidence to support decision making and communication regarding medication treatment, which in turn could enhance medication self-management: the *Intelligent Age-Friendly Home* (IAFH) and the *Medication safety, Objective assessments of health-related behaviors, and Personalized medication reminders* (MedOP) system.

Intelligent Age-Friendly Homes

Smart homes integrate home-based, network-enabled technologies that cannot only automate and control devices in the home, but also monitor the household, learn the habits and preferences of the residents over time to anticipate their needs, and take actions automatically or with minimal guidance from residents [20-22]. The extent of the autonomy of a smart home is what determines its "smarts" [22]. Over the past decades, there has been an increased interest in exploring, developing, and using smart home technologies in health care. For example, the pervasive technological infrastructure provided by smart homes has been explored in a number of projects supporting Ambient Assisted Living, which aims to provide intelligent and transparent forms of monitoring and assistance for older and disabled individuals [23].

The World Health Organization also recognizes the impact of the environment, such as home and community, on people's health and well-being at different stages of life, and particularly in later years. It proposed creating an age-friendly environment as one of its five priority areas for action concerning ageing and health, saying that such an environment "combats ageism, enables autonomy, and supports Healthy Ageing," which is defined as the "process of developing and maintaining the functional ability that enables well-being in older age" [5].

In this project, we propose the concepts of the IAFH and define them as integrated residential systems that evolve to sense, reason, and act according to individual needs, preferences, and behaviors as these change over time; in other words, a smart home that is attractive to people when they are young and is supportive of them as they age [24]. We also propose the development and evaluation of an IAFH to support medication self-management for older people. More specifically, the IAFH is envisioned to support functional monitoring (eg, activities and sleep), cognitive and sensory assistance (eg, medication reminders and drug dispensers), and personal interaction (eg, communication). Although these are the main categories of health-related smart home technologies [25], the novelty in the proposal lies in the integration of those functionalities to support medication self-management.

Medication Safety, Objective Assessments of Health-Related Behaviors, and Personalized Medication Reminders System

The MedOP system encompasses the integration of three different stand-alone systems with the objective of supporting medication safety, objective health assessment, and personalized medication reminders within an IAFH. The MedOP system integrates the following three subsystems.

Home Sensors

Various kinds of sensors, including passive infrared sensors, switch sensors, pressure sensors, smoke and gas sensors, cameras, and more, can measure different physical, motion, contact, and presence properties within a smart home. At Halmstad University, the Halmstad Intelligent Home is a fully functional, campus-based, two-room apartment that is densely outfitted with sensors and actuators. The Halmstad Intelligent Home uses a research-based, database-centric system architecture that serves as a platform for the development of smart homes with applications in health care. The system architecture focuses on different quality attributes, such as interoperability, scalability, dependability, security, and privacy.

Digitalized Home Documentation

Handling and communicating health-related information can be difficult. To overcome this issue with the use of Digitalized Home Documentation, which standardizes health-related information from the Home Sensors, we envision more accurate health assessments and communication between care receivers and caregivers, thus increasing the patient's participation in his or her own health care. We plan to achieve this standardization with the integration of nursing taxonomies. These terminologies and tools are expected to support nurses in making diagnoses and to improve education, communication, and reporting among caregivers at work. We plan to develop this component in collaboration with one of our industrial partners.

Digitalized Medication Dispenser

Physical and cognitive impairments can prevent individuals from using assistive devices or remembering the medication regimen. This part of the proposal will be developed in collaboration with our second industrial partner; this partner has previously developed a pill dispenser that can manage and schedule complex medication regimes remotely, using a cloud-based management system via different communications technologies to ensure connectivity. The proposed Digitalized Medication Dispenser system will be enhanced with objective information collected by the Home Sensors and the Digital Home Documentation systems, so that personalized scheduling and context-based medication reminders can be provided.

The three developed and integrated systems—Home Sensors, Digitalized Home Documentation, and Digitalized Medication Dispensers—form the MedOP system (see Figure 2), which will provide objective information to the care staff, allowing them to improve their decision making. The information provides an objective summary of a person's in-home activity: daily routines; current and expected location; medication dispensing; amount and quality of sleep; weight; bathroom usage; and level of, and change in, activities. The MedOP system is to be developed in a way that includes older adults in the care process by raising their awareness of their health and behaviors. Moreover, the MedOP system will help older people remember and administer their medication by tailoring medication reminders to their actual location and behaviors, as well as to their regimen.

Phase II

Development

The conceptualization of a smart system for collecting and compiling health-related evidence, supporting decision making and communication, and improving medication self-management developed in Phase I will be used to build a prototype in Phase II. This will take place in a laboratory environment at Halmstad University and the users will be involved.

Participants

Participants will be the same as in Phase I (ie, caregivers from the municipal health care organization, the older people themselves from two different ongoing networks, and the industrial partners); there will be 22 persons in total.

Procedures

Along with our participants, we will identify technical and nontechnical risks and ethical standpoints, as well as quality, design, and commercial issues. In seminars, risks and ethical standpoints will be discussed based on the following questions: Do you feel confident in your ability to use a technical solution for medication administration? How will your work situation be affected? How do you feel about a technical solution that would complement staff? These issues and those that arise during the course of the project must be considered. Other techniques will also be used to design the tool. First, a paper prototype will be used to design and test the user interface. A beta version of the paper prototype will then be built and tested in a laboratory environment. In addition, an application programming interface will be defined to facilitate and secure communication between systems. We will also identify and apply a method for software integration. Finally, the technology will be tested individually and as an integrated system in a home-like laboratory environment at Halmstad University.

Phase III

Pilot Study

In Phase III, we will pilot the implementation of the MedOP system. In the pilot study we will evaluate the functionality of the technology, adjustments, and feasibility. This will be performed by installing the MedOP system at the home of the elderly to test it in a real environment.

Participants

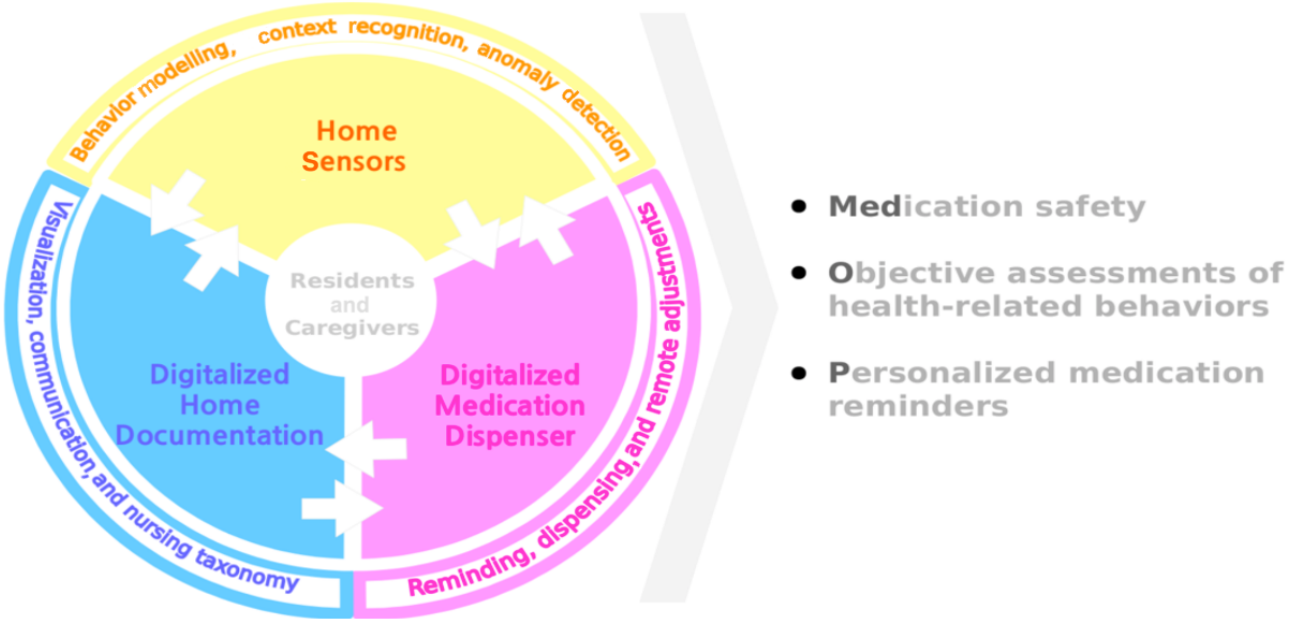
A total of 10 persons, 65 years or older, who are utilizing five or more different medications and have home help service and home nursing care will be selected. The older person will be assessed by their registered nurse to determine if they have the ability to manage their medication by themselves. The older persons will be recruited via the National Organization of Pensioners and the Family Caregiver Association. The registered and assistant nurses who are involved in the care and service of the 10 older persons will also be included in the study; this will bring the number of participants up to 15-20 persons. The registered and assistant nurses will be recruited via their managers.

Procedures

Quantitative data will be collected from the 10 older persons at baseline and at one follow-up session after 3 months using the MedOP system. The following instruments will be used for each measure:

1. Medication adherence: Morisky Medication Adherence Scale [26].
2. Well-being: Personal Well-being Index-Adult [27].
3. Self-management: *30*-item Self-Management Ability Scale [28].
4. Life satisfaction: Satisfaction With Life Scale [29].
5. Serenity: Serenity Scale [30].

Figure 2. The Medication safety, Objective assessments of health-related behaviors, and Personalized medication reminders (MedOP) system with its three integrated systems.



Qualitative data will be collected at the end of Phase III. Individual interviews will be performed with the 10 older adults who are using the MedOP system, and focus groups will be used with the nursing staff. Each focus group will consist of 6-8 participants, with separate groups for registered nurses and assistant nurses. The interviews will be analyzed using content analysis [31] and grounded theory [32,33]

Phase IV

Full-Scale Intervention

Phase IV aims to test and evaluate the MedOP system in a full-scale intervention.

Participants

All persons 65 years or older in the two municipalities participating in the study who are utilizing five or more different medications and have home help service and home nursing care will be selected and offered the opportunity to participate in the study. The older persons will be recruited via the National Organization of Pensioners and the Family Caregiver Association. The older person will be assessed by their registered nurse to determine if they have the ability to manage their medication by themselves. The registered and assistant nurses who are involved in the care and service of the older persons will also be included in the study.

Procedures

In the full-scale study, the same procedures as in Phase III will be used. By evaluating the MedOP system intervention, using both quantitative and qualitative data, the follow-up of both perceived and practical challenges will be enabled.

Ethics

Participants in Phase I were recruited via networks whose purpose is to improve and develop working methods and working conditions for care providers but also quality of care for care receivers in the municipalities. Involvement in this project can thus be seen as part of their occupational development.

Phase I of the project is not considered to have exposed the participants to danger or discomfort. Participation has been on a voluntary basis; oral and written information has been given before each session regarding the purpose of the study and that the data may be used in research.

In Phases II-IV, ethical issues are involved in the different activities of their procedures. Since the implementation of technology and high-tech care will occur in home settings, researching the unintended and ethical effects resulting from the implementation is important.

During Phase II, the researchers will collect qualitative observational and interview data in a simulated laboratory setting on healthy volunteer subjects to identify both ethical and unintended effects resulting from the implementation of new health and welfare technologies.

In Phases III and IV, a pilot study and full-scale study using similar data collection methods as in Phase II will be focused on subjects who are actually using new health and welfare technologies in their homes. As these will be elderly people needing additional support in the home, they will be treated by the researchers as vulnerable adults. In these latter phases, in addition to data collected about unintended and ethical consequences, other sensitive data will be gathered, including data on well-being, life satisfaction, and medication regimes. Special consideration will be made to limit risks associated with working with vulnerable subjects, especially in the areas of privacy and informed consent.

Approval from the Regional Committee for Medical and Health Research Ethics shall be completed to ensure that ethical aspects are handled correctly, according to Swedish law.

Results

For this study, we identified and included 22 participants that represent four different stakeholder groups (ie, caregivers from the municipal health care organizations, the two groups of older people from two different ongoing networks, and the industrial partners). The project was funded in 2016-2017 and enrollment for Phase I was completed in 2018. Parts of the MedOP system are in use and the continued work in Phase II will further develop and merge the different systems—Home Sensors, Digitalized Home Documentation, and Digitalized Medication Dispensers—with each other. Ethical approval is currently underway, and the first results are expected to be submitted for publication in mid-2020.

Discussion

The use of participatory design [16] gave us the opportunity to explore different users' perspectives and needs and propose a person-centered solution to a common and complex problem among older people, which is self-managing their medication. To better understand the problem, current approaches, and actual needs, we involved different stakeholders at the very early stages of this project. Moreover, it was expected that such an approach would lead to a consensus toward how technology could be employed to overcome the problem. However, although the care staff participating in the seminars and workshop identified and recognized the benefits of home-based technologies in their work, they also expressed concerns regarding the introduction of new methods and routines into their work. The participating health care staff also expressed a lack of confidence in using technology and feared that the older persons would have fewer visits, resulting in less human contact. Research has shown that this kind of attitude can be a barrier to the introduction of new technology systems [26]. Haken, Allouch, and van Harten [34] conclude that when introducing advanced medical technologies into the home, it is important to also provide education, clear guidelines, and information about risk management and patient safety at the same time. Developing and providing documentation and training regarding the system are requirements for Phases II, III, and IV.

In addition, and in order to ensure that the end-project results reach the intended market and users, the close collaboration with our industrial partners provided critical insights and perspectives regarding technology development and commercialization in the health care domain. We therefore argue that it is important to both understand the logic and incentives from the supply side (ie, the firms that will commercialize the technologies) and the demand side (eg, the health care professionals and older persons who will be the end users of the technologies and solutions) when operating in a networked health care system [35,36]. Moreover, it is also critical to understand who will pay for the health care innovation, both within the country and internationally, in order to ensure that the innovation will actually be implemented. We therefore propose that we also add a business model [37] perspective for our future research agenda to meet the supply and demand of innovations in health care, with a particular focus on value capture from innovations [38-40].

Acknowledgments

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Authors' Contributions

This paper was developed collaboratively by all of the authors. MNP was the project coordinator for the study and collated the completed data templates, assessed data quality, organized the workshops, drafted the individual project-evaluation protocols, applied for ethical approval, and drafted the manuscript. WOdM and JL developed and wrote the MedOP system section. HL contributed with a stakeholder perspective and wrote about the business issues. IS was the principal investigator and provided oversight for the study. All coauthors participated in the design of the project, contributed to data collection, provided comments and edits on the manuscript, and critically reviewed the manuscript for important intellectual content.

Conflicts of Interest

None declared.

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Abbreviations

IAFH: Intelligent Age-Friendly Home
MedOP: Medication safety, Objective assessments of health-related behaviors, and Personalized medication reminders

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Protocol

Evaluating the Healthy Futures Nearby Program: Protocol for Unraveling Mechanisms in Health-Related Behavior Change and Improving Perceived Health Among Socially Vulnerable Families in the Netherlands

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Abstract

Background: The persistence of health inequalities within high-income societies such as the Netherlands indicates the importance of researching effective ways to reduce those inequalities. Multiple strategies for reducing health inequalities have been identified. Specifically targeting health-related behaviors among lower socioeconomic status groups is one of those strategies. All in all, it seems relatively clear what types of approaches in general lead to health-related behavior change. However, it is still unclear *how* these approaches, in interaction with context, trigger a specific desired change. In the Netherlands, the private funding organization, Fonds NutsOhra, funded 46 small-scale projects under the umbrella of the Healthy Futures Nearby program. The projects aim to reduce vulnerable families' health deprivation by triggering lifestyle changes.

Objective: This study aimed to outline and justify the protocol for the overall evaluation of the program. The evaluation aimed to find out *to what extent* and *how* the small-scale projects and approaches within the program affect (or not) health-related behaviors and improve perceived health.

Methods: The approach to the overall evaluation of the 46 projects builds on a combination of 3 frequently used evaluation models; it is theory-based, realist informed, and uses a mixed methodology design. Methods include analysis of quantitative project data, document analysis, focus groups, and interviews. A study design has been drawn up that values and uses the multifaceted development of the projects and the influence this might have on implementation and project outcomes. Also, it respects the complex nature of the projects and is suited to studying health promotion mechanisms in depth. Finally, it optimizes the usage of all—quantitative and qualitative—project evaluation data available.

Results: This study protocol included the design of at least 4 different studies. The results will hence provide information on (1) building and defining theories of change in health promotion practice, (2) mechanisms at work in promotion of healthy behavior among vulnerable families, (3) what works and what does not in professionals' practices in health promotion among those vulnerable groups, and (4) what works and what does not in health promotion projects with a participatory approach. In addition, data will be collected on the overall effectiveness of the 46 initiatives. Data collection started in 2016. Data analysis is currently underway, and the first results are expected to be submitted for publication in 2019.

Conclusions: This overall evaluation provides a unique opportunity. The diversity of projects allows for a study protocol that answers in greater depth questions of *how* specific health promotion approaches work while also elucidating their effectiveness in a more traditional way. Using a theory-based complexity-sensitive approach that is mainly realist informed, this study also provides an opportunity to see whether combining assumptions from different evaluation perspectives yields relevant information.

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KEYWORDS

health behavior; socioeconomic status; health promotion; healthy lifestyle; Netherlands; inequalities

Introduction

Background

In the Netherlands, life expectancy has increased over the past decades. The National Institute for Public Health and the Environment also reports an increase in *healthy* life expectancy [1], meaning that people are not only living longer but also living longer *healthier* lives. However, inequalities in health between and within countries—including high-income countries such as the Netherlands—remain substantial [2,3]. Health inequalities are an issue of fairness and social justice [4,5]. People who are vulnerable to health deprivation may not reach their full potential as individuals and as a group in society. The issue is even more pressing as health inequalities appear to be reproduced from one generation to the next [6,7]. The persistence of health inequalities within societies indicates the importance of research on what the World Health Organization (WHO) has called the *social determinants* of health [8] and on policies that aim to reduce inequalities. There have been many studies on the causes of health inequalities, both within and outside the Netherlands [2,9-12].

Besides looking at what causes health inequalities, scholars, policymakers, and practitioners have dedicated themselves to finding ways to reduce those inequalities. In the Ottawa Charter, WHO stated [13], and more recently the International Union for Health Promotion and Education declared in its Curitiba statement [14], that addressing the social, environmental, and economic determinants of health is crucial for reducing health inequalities, in addition to recognizing the importance of personal skills and capabilities [15,16]. Furthermore, WHO has stated the importance of involving a range of stakeholders, including citizens, in health promotion initiatives. Multiple strategies for reducing health inequalities have been identified [5,17-19], of which specifically targeting health-related behavior among lower socioeconomic status groups is one. In the Netherlands, Beenackers et al [20] conducted a review on effective interventions for behavioral change leading toward the reduction of health inequalities, focusing on smoking, alcohol consumption, overweight, and perceived health. Overall, they concluded that approaches could be more effective in changing behavior if they are targeted specifically at the needs of those vulnerable to deprivation, if they use existing structures and the expertise of local health professionals, and if they are designed in an integrated way; this means including various perspectives and involving different sectors and stakeholders. Others have written about the effectiveness of a community-based approach in reducing health inequalities. However, for each of these measures, substantial uncertainties remain around successful implementation [21,22]. Contextual factors appear to have a major influence on whether specific approaches, or elements of approaches, work or not. Community-based approaches work in some cases but have proved much less effective in others [21,23]. Successful collaboration with local experts may be largely dependent on whether such a network actually exists, whether professionals are open or willing to collaborate, whether previous local projects have been successful and thus what the initial starting position is, and so on. All in all, even though it may be relatively clear what types of approaches in general lead to better health, it is still unclear how certain approaches, or elements of approaches, in interaction with context trigger specific outcomes.

More traditional approaches to health promotion evaluation focus predominantly on researching evidence for specific interventions by measuring (quantitatively) the effectiveness of predefined outcomes. However, evidence on the effectiveness of interventions does not provide a sufficient or workable base for future work in health promotion. As argued, varying and dynamic contexts combined with participatory approaches require in-depth study of mechanisms rather than of specific interventions. What mechanisms underlie successes in the promotion of healthy behaviors or the discouragement of health risks? What contexts enable or hinder such processes? To answer such questions, more in-depth studies and data are needed to enable researchers to look at different social and physical settings and mechanisms at play within those contexts. These studies should be designed to grasp the full interactions, relations, and influences of and between contextual factors, interventions, mechanisms, and outcomes. This paper outlines the protocol for an evaluation study particularly aimed at unraveling these mechanisms. We have made an effort to create an overall evaluation plan that does justice to the dynamics and complexity of local, community health promotion projects and results in relevant information on what works in (the process of) promoting a healthy lifestyle. The novelty of our design lies, among other things, in our flexible approach to evaluation with regard to the initiatives' plans and dynamics, creativity in collecting and combining diverse data, and the focus on *what* works instead of *which project* works.

Research Questions

A program (Textbox 1) funding 46 small-scale health promotion projects within the Netherlands [24] presented the opportunity to study what happens in different settings and contexts while also looking in depth at processes at play. These diverse, merely local initiatives have all designed their own intervention and evaluation. Information from these initiatives and evaluations is available for the overall evaluation. The combination of diverse small-scale projects offers both a very broad and an in-depth source of information on the workings of health promotion through lifestyle changes in specific contexts. This provides a unique opportunity to study mechanisms for changing socially vulnerable families' health-related behaviors. The overall evaluation aims to find answers to 2 main questions:

1. To what extent do (shared) approaches within small-scale projects affect health-related behaviors and improve perceived health (impact)?

2. How do the approaches within the program affect (or not) health-related behaviors and improve perceived health (mechanisms)?

Opportunities

There are 4 ways in which the program and projects (Textbox 1) offer a unique opportunity to study health promotion mechanisms: (1) the evaluation data from the 46 small-scale projects potentially enable the study of the projects' *effectiveness* in changing health-related behavior and improving perceived health; (2) the projects offer a diverse and in-depth source of information on how particular approaches, in different contexts, may lead to specific outcomes and thus provide a basis for *unraveling mechanisms* of health promotion; (3) partial homogeneity in approaches and desired outcomes provides the opportunity to *compare* the effectiveness and mechanisms of similar approaches in varying contexts; and (4) the timing of the overall evaluation, parallel to the implementation of the projects, allows for a strong focus during the evaluation on *learning while doing* for all stakeholders involved. These 4 opportunities, elaborated below, set the framework for the overall evaluation.

Textbox 1. The Healthy Futures Nearby program and projects.

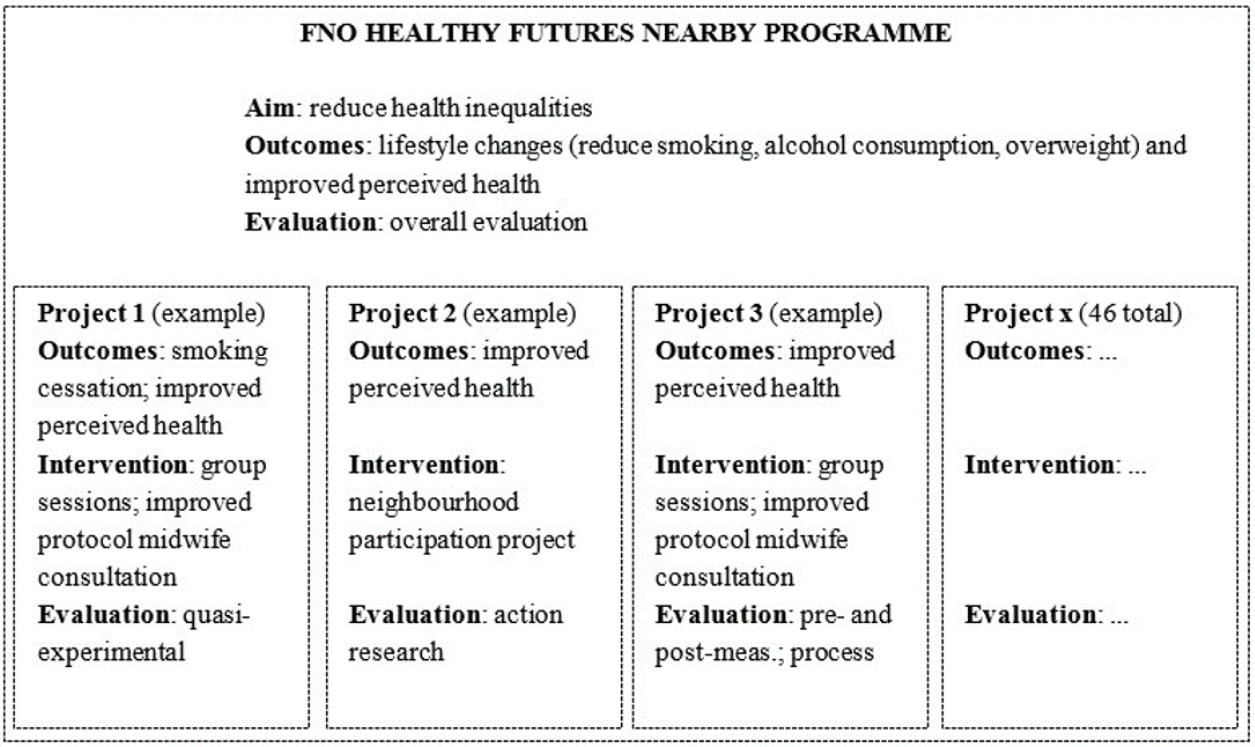
In the Netherlands, the private funding organization, Fonds NutsOhra, funded 46 small-scale projects under the umbrella of the Healthy Futures Nearby (HFN) program [24] and issued an overall evaluation of the program to learn about participation, effectiveness, and sustainability. The projects all aim to reduce health inequalities through lifestyle changes in vulnerable families.

The HFN program aims to "improve the health behaviors of vulnerable families with a low socioeconomic background to reduce health inequalities." Vulnerable families are defined as households in which at least 1 adult and 1 child live together, who experience multiple problems with finances, education, work, or well-being and who suffer health deprivation by smoking, heavy consumption of alcohol, or unhealthy weight combined with a lower perceived health.

- Projects have been awarded funding for the years 2016 to 2019 (34 projects) or 2017 to 2019 (12 projects).
- Projects use either a neighborhood-oriented (similar to community development) participatory approach or work from an intersectoral approach (similar to a systems perspective, including different stakeholders and levels) to reduce inequalities by promoting healthy lifestyles. These 2 approaches can be understood as the program's *theory of change*.
- All 46 small-scale projects focus directly or indirectly on reducing alcohol use, promoting smoking cessation, promoting a healthy weight and improving perceived health. To reach their goals, the projects develop and implement a range of strategies and activities. For instance, some employ a participatory, dynamic neighborhood-oriented approach, whereas others focus on improving social infrastructures for families facing multiple problems.

All projects conduct their own project evaluations, which almost always include pre- and postmeasurement of project-specific outcome measures (behaviors and perceived health) among vulnerable families (Figure 1).

Figure 1. Structure of the Fonds NutsOhra (FNO) Healthy Futures Nearby program.



First, the information made available by the projects is potentially of high enough quality to examine to some extent the effectiveness of their activities and approaches. Such information on effectiveness could provide relevant information at the higher program or policy level [25]. Projects conduct their own evaluations, consisting of at least a baseline and post activities measurement of relevant project-specific outcomes at the participant (family) level. However, project-specific research designs vary greatly and not all projects use a (quasi) experimental setup, meaning that for instance control groups are not included in most of the project evaluations. Considering these limitations, by examining effectiveness, we aimed to study the extent to which the projects have changed health-related behaviors and led to an improved perceived health among socially vulnerable families participating in the projects. An initial exploration of the combined project baseline data will help determine which methodological approach is best suited to combine and analyze the set of information on health-related behavior.

A second opportunity lies in the in-depth information contained in the 46 small-scale projects, which can potentially be very useful for unraveling mechanisms. Whereas effectiveness is often the central focus of evaluation, the diversity of projects under study here is suited to answering more in-depth questions on how the various health promotion approaches work (or not) in different contexts. Various projects work with similar approaches, enabling the study of these approaches in different contexts. Understanding the influence of contextual factors—social, historical, and physical—has been identified as crucial to policymakers' and practitioners' successful implementation of health promotion initiatives [26]. To generate success, it is essential to understand under what circumstances specific interventions may work or not. Evaluation should aim to generate knowledge on these context-mechanism interactions instead of focusing solely on the experimental effectiveness of interventions. Context should therefore play a major role in learning through evaluation. Also, the main challenge in learning from (community) health promotion projects is to study and define *how* and *why* communities may benefit [21]. This has often been addressed as opening the black box: it is known whether a specific project works or not, but possibilities for transferability are limited because it is not known *why* and *how* the project or approach works or does not work in relation to a specific context [27]. The 46 projects can provide that in-depth information. Looking at mechanisms and including contextual influences does, however, have implications for the evaluation design. More traditional, experimental evaluation designs do not suffice. Although the interaction between approach and context is considered an important factor in health promotion projects, designs such as randomized controlled trails deliberately exclude such contextual influences to keep causal relations *clean*. Also, these designs leave little room for variations in approaches, dynamics, and changes during implementation and valuable unexpected effects and serendipity—all very relevant in the complex reality addressed in health promotion interventions. Kok et al [22] provided 6 reasons why a more traditional, reductionist approach is not well-suited to health promotion evaluation: lack of clarity about what the approach precisely is; lack of clarity about what is expected of local contexts for effectiveness; the very diverse and open settings for health promotion; diversity in organizations and underdeveloped organizational systems; the impossibility of realizing similar configurations in different locations; and the difficulty in determining whether a project or approach works in practice as intended.

Third, the information from the projects is sufficiently diverse and substantial to look at different approaches to changing health-related behavior: promoting healthy behavior or discouraging risky behavior. Groups of projects work toward a similar outcome in varying ways, such as promoting smoking cessation (outcome) by offering one-on-one counseling or organizing group sessions (approaches). Also, some projects appear to be working along the lines of similar approaches but aim at different outcomes—for instance, the development of a participatory project together with neighborhood residents to raise awareness of risky health-related behaviors or to increase active citizen participation in neighborhood activities. The existence of similar approaches and outcomes within projects allows us to additionally compare groups of projects.

A fourth opportunity resides in the fact that the development and evaluation of the 46 projects are themselves relevant processes. A range of different stakeholders have been and will be involved in development, implementation, and evaluation. Almost half of the project designs imply the dominance of community participation. Most projects have been inspired and shaped by policy, science, and practice. Also, timewise, the overall evaluation will be conducted parallel to the implementation of the projects. These 2 characteristics, participation of diverse stakeholders and timing of the evaluation, mean that the overall evaluation could be very much a *learning* opportunity for all involved.

Methods

Study Design

For the overall evaluation of the 46 projects, a protocol was designed that respects the criteria set by the program. It takes into account the multifaceted development of the projects and the influence this might have on implementation and project outcomes, and the complex nature of the program and projects [25]. The aim of the protocol was to enable researchers to study mechanisms of health promotion in depth. Finally, the design sought to optimize the usage of all—quantitative and qualitative—project evaluation data available.

The 4 opportunities, or program and project characteristics, mentioned in the previous paragraphs guided the study design. In addition, the program's main principles that have guided the design of projects shaped the evaluation design: promotion of healthy lifestyles to reduce health inequalities, a participatory approach, an intersectoral design, and a community development approach. The evaluation design should fit these project design guidelines, if only to ensure that the potential of the information offered is harnessed. In addition, we believed that research in health promotion should ideally be oriented toward also improving practices in health promotion [28]. The methods selected for evaluation should furthermore be most likely to

illuminate relevant issues, both success factors and barriers, within projects and programs and be sufficiently diverse to reflect the individual, social, cultural, organizational, and economic factors at play [28]. The overall evaluation of the 46 projects builds on a combination of 3 frequently used approaches to evaluation; it is theory-based, realist informed, and uses a mixed methodology design. We recognized the complex nature of the health promotion projects by combining these approaches. In the study, a theory-based perspective on evaluation provided opportunities to involve views from all relevant stakeholders, including those who offer more practical experience and knowledge (professionals) and those who offer knowledge from the lived experience (target group), as well as stakeholders who offer a more scientific, more abstract, or theoretical view (researchers). The theory-based perspective is important throughout the study. Frequent updating of the project theories will remind the researchers to maintain an open view on the dynamic nature of the projects' settings, contexts, and activities. As the study was realist informed, the realist perspective was used to guide the in-depth search for mechanisms by means of realist case studies [29].

The overall evaluation will be conducted by a team of researchers from 3 organizations: Wageningen Economic Research, the Verwey-Jonker Institute, and Wageningen University, Chairgroup Health and Society.

The study design encompassed 4 steps: A to D, presented in Figure 2. A is an ongoing first step to identify the theoretical assumptions about—not necessarily linear—causal pathways underlying each project. After that, step B is performed to measure effectiveness, and steps C and D are performed to study and unravel mechanisms. Each step is used to support, provide feedback into, and verify the other steps in the design. In combination (data triangulation), all steps lead to answers to both the main research questions. Each step is discussed in detail in this section.

Step A: Identify Theoretical Models and Assumptions

The first step in the overall evaluation is to identify the (theoretical) assumptions on causal pathways for each project. Identifying and using these assumptions (theory-based evaluation) can strengthen program design and implementation and promote policy and practice learning about the effectiveness of interventions [30]. The assumptions about pathways that lead to desired outcomes in a project have been referred to in many different ways [25,31]. In this paper, we use *theoretical models and assumptions* and *presumed causal pathways* interchangeably. Following Rogers [31], both refer to "a variety of ways of developing a causal model linking program inputs and activities to a chain of intended or observed outcomes, and then using this model to guide evaluation." The models will be identified using project proposals and, additionally, group interviews in an *Effectenarena* format [32]. This interview format is designed to facilitate participatory decision making through multistakeholder discussions. The method uses a few key concepts to streamline the group discussion: investors (stakeholders that *invest* time, money, and knowledge in the project), expected activities and conditions for those activities, and expected effects and *collectors* (those who benefit in any way). It enables the researchers as well as the project stakeholders to gain more insights into the desired outcomes, assumed causal pathways, contextual factors, and possible drivers and barriers. Focusing solely on project proposals may provide a biased result (because they are often written by project leaders). Specifically, for this study, the group interview ensures that all stakeholders involved *have their say* when it comes to assumptions relevant to the project. A group session in the *Effectenarena* format will thus be organized with each project, involving all relevant stakeholders including the vulnerable target group when possible. Two researchers will facilitate the discussions and draft a short report of the meeting, which will then be presented to the respective project leader for approval. In addition, the researcher involved will draw a visualization of the model for each project. The research team will use the sessions and reports and any other relevant documentation such as project proposals to extract for each project the underlying theoretical models and assumptions. This will be both a list of assumptions and a visual map. Given the complex, dynamic, and not necessarily linear nature of the projects, initial theoretical models and assumptions will serve as a basic set of assumptions that are open to adjustments as the projects develop. Over the course of the years, regular monitoring through interviews, group sessions, and administrative reports will build on and test these initial sets of assumptions. Insights into how HFN program principles (Textbox 1) have translated into project models and assumptions may offer valuable lessons for the implementation of future health promotion policies.

Step B: Quantitative Data Collection and Analysis

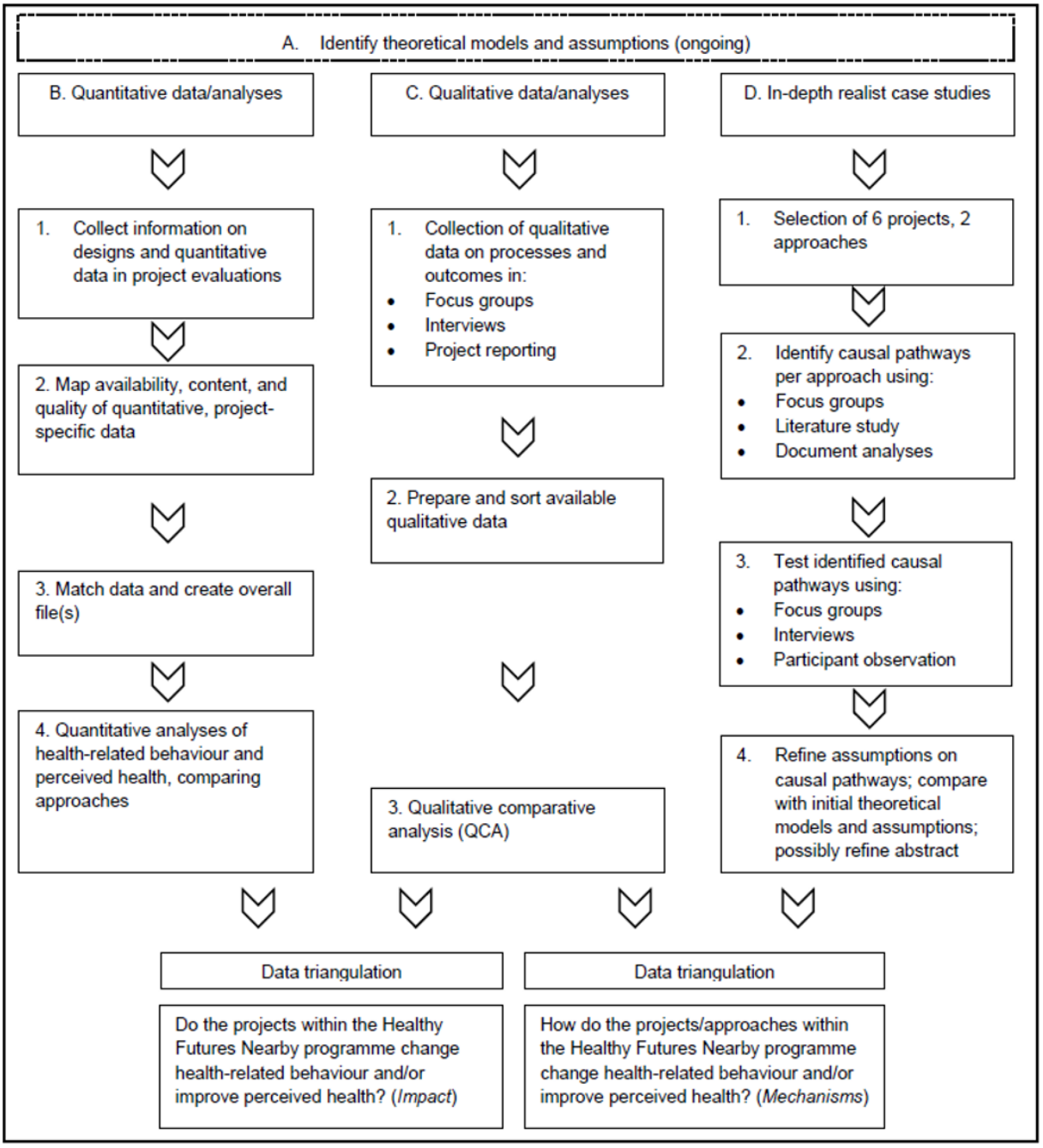
All projects (taking place over the years 2016 to 2019) will conduct their own project-specific (primary) analysis and evaluation. Step B, in this study, includes the *overall* collection and secondary analysis of quantitative project-specific data throughout 2016 and 2019 to study program impact. Complete project-specific data and publications on desired outcomes among vulnerable families will only be available during the last stage of the overall evaluation. Also, the project-specific evaluations and the overall evaluation will be conducted in parallel. This may offer opportunities for collaboration and mutual learning, but it also requires careful planning to avoid heavy participant burden. As already mentioned, all 46 projects have their own specified evaluation design. From these project evaluations, we aim as much as possible to use the information already gathered. More specifically, our focus will be on data on perceived health and health-related behavior outcomes at the individual level of vulnerable family members. Although the projects' evaluation designs range from randomized controlled trails to participatory action research, most conduct some form of pre- and postmeasurement of these health-related behavior outcomes. In total, 4 main activities have been distinguished in this step:

1. Collection of information on designs and quantitative data in project evaluations. Project proposals, available research proposals, and *Effectenarena* sessions will be used to collect information on the quantitative data collected in each project, by whom, for which specific target group, and using which methods and instruments. This step also includes an

exploration of possibilities to combine and match data from different projects.

2. Map content and quality of quantitative project-specific data. A substantial number of project baseline measurements will take place over the first 1.5 years of the funding period. After this, we shall gather the data available from these baseline measurements. An initial exploration of the quality of the datasets will be conducted in close consultation with the (local) researchers involved in the projects.
3. Match data and create overall file(s). Statistical software R [33] will be used to match project data and thus create the overall file(s). The matching exercise will examine possible effects and compare those effects on health-related behavior and perceived health between *approaches*. Theoretically and ideally, this should lead to a number of files combining information from different projects on perceived health, weight, physical activity, smoking, and drinking behavior. Exploration of the available data as described in steps 1 and 2 will show which comparisons are possible at which levels of aggregation.
4. Quantitative analyses. Statistical software (R) will be used to compare projects and approaches relating to effects on health-related behavior and perceived health.

Figure 2. Steps in the protocol to unravel effects and mechanisms in the Healthy Futures Nearby program.



Step C: Qualitative Data Collection and Analysis

A parallel step (C) in the design concerns the collection and use of qualitative data. This step entails primary data gathered by the researchers on the overall evaluation from each individual local initiative. The qualitative data will provide information to direct and support the quantitative analysis and contribute to answering *which* questions about mechanisms. In total, 3 sources of information will be included:

1. Information gathered in 46 group interviews—*Effectenarena* sessions as well as 2 *audit* sessions per project, scheduled at half term and at the end of the subsidiary period. The aim of the audits is twofold: to provide the researchers with information on outcomes and (preliminary) results, processes, and developments in the different projects, while creating space for project teams to reflect on developments and collaboration and learn from experiences and results so far. All relevant stakeholders for each individual project will be invited to the audits, including the vulnerable target group when possible. The discussions will be semistructured, including topics on participation, outcomes, mechanisms, collaboration, and sustainability, but leaving room for discussions tailored to project-specific issues and developments. A timeline exercise [34-36] will be used to involve all participants in the discussion. A guideline for a semistructured group interview will be developed covering the aforementioned topics. Audits will be facilitated by a researcher, preferably the researcher who has led the *Effectenarena* session for this specific project. A second researcher or research assistant, present during the sessions, will draw up a short report, which will in turn be presented to the project leader. This person will be asked to judge how accurately the report reflects the group sessions.
2. Information collected through yearly rounds of interviews with all 46 projects leaders. Telephone interviews will be scheduled yearly with all project leaders. The interviews will be conducted by a member of the overall research team. Each interview will follow a predefined semistructured format, thereby ensuring that data are collected on results, participation, mechanisms, and sustainability, but leaving room for project-specific tailoring. Furthermore, the structure and the content of the interviews are dependent on the timing: the first round will focus more on participation and collaboration, whereas later rounds will focus more on results, mechanisms, and sustainability. Project leaders will be notified beforehand about the aim of the interview, the main topics, and the (anonymous) way in which the information will be used. Before the interview, their permission will be requested to record the conversation. All recordings will be transcribed, and both audio files and transcriptions will be stored at a secure site.
3. Information collected through project reporting forms. Project leaders will be regularly asked (approximately twice every year) to fill out a reporting form on developments and results within their projects. To minimize the research and accounting and administrative burden for project leaders, these forms will be drafted in collaboration with Fonds NutsOhra (FNO). FNO requires project leaders to regularly fill out reports, so combining these will be efficient.

Qualitative comparative analysis (QCA) [37-39] will be used to analyze the qualitative data from group interviews, interviews with project leaders, and project reporting forms. QCA is an analytic approach and a set of research tools that combines formalized cross-case comparisons with detailed within-case analysis [39]. QCA will be carried out using R QCA software [33].

Step D: In-Depth, Realist Informed Case Studies

In our 46 projects, altogether, and for a substantial number of specific projects, outcomes and results are uncertain as well as emergent. That is why, following Glouberman and Zimmerman, we regard them as complex rather than simple or complicated situations [40], although this does not mean that the projects do not have simple or complicated components in them as well [31]. The complex nature of the projects requires an appropriate evaluation design. To deal with this complexity and the related importance of context [41], realist informed case studies will be executed in a fourth step (D). Unraveling mechanisms for health-related behavior change and improved perceived health is the main aim of these in-depth studies. The case studies will be designed to look at specific *approaches* or situations instead of studying specific projects or interventions. An approach or situation exists within projects; a project is often more than just this situation, for instance, building a relationship between a (care) professional and a family member or organizing a participatory session for a specific group of vulnerable families. In other words, the level of evaluation within the case studies is that of specific relevant situations rather than that of the complete intervention. This will ensure that the evaluation results are relevant to all stakeholders instead of just a few projects. Also, choosing some *projects* as a main subject of study might be discouraging for others, whereas choosing *approaches* may spark interest and learning for everyone and encourage far more projects. The case studies include 4 steps:

(1) Selection of 2 approaches and, per approach, 3 projects working with these approaches (a total of 6 projects). The selection of approaches is based on possibilities to study the approaches within the 46 projects and theoretical and societal relevance. Possible approaches are community participation, the role of health professionals in promoting healthy lifestyles, improving local networks, and so on. Project selection will be finalized in consultation with project leaders and program management. (2) Identification of possible causal pathways for each selected approach using a realist perspective. These causal pathways are often called C (Context), M (Mechanism), and O (Outcome) configurations [41,42]. Mechanisms are determinants of behavior that work to generate an intended or unintended outcome. In so doing, mechanisms depend strongly on context. Jagosh et al [43] refer to context as the *backdrop* of programs and research and can thus include cultural norms and history of a community, geographic location, the nature of existing social networks, and neighborhood infrastructure. Outcomes are the result of an interaction between mechanisms and context. Methodologies for the case studies include literature review, interviews, document analysis, and focus groups. (3) Identified

causal pathways are translated into more abstract-level theories. Further field study, using focus groups, interviews, and participant observation, will test identified and alternative causal pathways. (4) Translation of findings into a more abstract level and possible refinement of the abstract-level theory. These realist case studies will provide information to answer the main research question on mechanisms (research question 2).

Data Triangulation and Analysis

Steps A to D as described above ensure the collection of information on the overall impact of the program and on mechanisms of health-related behavior change at work in the projects. Using source triangulation (combining views from different stakeholders and perspectives) and method triangulation (combining qualitative and qualitative sources) can support better understanding. Data triangulation will combine the available information toward answering both research questions.

1. Results from the quantitative analysis will be compared with results from qualitative methods to provide answers on *impact*. The QCA as described above provides information that supports or contradicts the patterns derived from quantitative data analysis. Qualitative analysis will also include thematic coding and content analysis. The qualitative data will be used to complement, but also to question and test, the insights from quantitative analysis. In turn, the quantitative information will be used to inform further qualitative analysis.
2. Information from qualitative sources combined with realist informed case studies will provide insights into how the approaches within projects may bring about change: the *mechanisms* at play. A realist informed analysis, exploring and testing context mechanism outcome configurations such as those described above, is the basis. Mechanisms at work within approaches (eg, how does involving local professionals work in promoting physical activity) will be identified and tested. Further qualitative data, collected in addition to the case studies, may be used to further understand and explain these identified and tested mechanisms.

Results

The overall evaluation project was funded in 2016. This study protocol included the design of at least 4 different studies. The results will hence provide information on (1) building and defining theories of change in health promotion practice, (2) mechanisms at work in promotion of healthy behavior among vulnerable families, (3) what works and what does not in professionals' practices in health promotion among those vulnerable groups, and (4) what works and what does not in health promotion projects with a participatory approach. In addition, data will be collected on the overall effectiveness of the 46 initiatives. This will yield insights into possibilities for comparisons using diverse, quantitative, and qualitative data. The first data collection—the gathering and defining theories of change for each separate project—started in 2016, and data collection is currently ongoing. According to Dutch law, this study did not require formal ethics committee approval. However, special attention is paid in all activities to inform respondents and protect their privacy. All participants are provided with information about the purpose and contents of the research. Participation is voluntarily, and participants are able to withdraw from the study at any time for any reason. The collected data are treated confidentially and anonymously. Data analysis is currently under way, and the first results are expected to be submitted for publication in 2019.

Discussion

Opportunities

The 46 small-scale projects—which can be described as very diverse but with common principles—provide a unique opportunity for research on mechanisms in health promotion. They offer an extended range of relevant cases, instead of just one or two. To our knowledge, not many program evaluations have the same potential to provide such rich material on multiple cases in varying contexts. The availability of project-specific evaluation data provides the possibility to study the *impact* of different approaches with regard to changes in health-related behavior and perceived health. Similarities in strategies for health promotion as well as differences between projects enable such analysis. However, the diversity in the projects allows for a study protocol that also answers in greater depth questions of how specific health promotion approaches work, what we have called unraveling *mechanisms*. The multitude of contexts under study combined with various projects implementing similar approaches and activities potentially provides the opportunity to compare impact and mechanisms in interaction with contextual factors. Last but not least, the timing and the participatory approach applied in the overall evaluation enables all stakeholders to maximize learning throughout the 4 years of funding. Using a theory-based, complexity-sensitive approach that is predominantly realist informed, this study will also provide an opportunity to see whether combining assumptions from different approaches yields relevant information. This proposed combination of approaches in one evaluation design could theoretically open up black boxes while also elucidating more traditional measures of effectiveness.

Challenges

In addition to the great opportunity provided, we acknowledge that the overall evaluation includes some challenges. The 3 important remarks are as follows: (1) the evaluation is shaped by the information available in the HFN program, (2) there is a difference between the program's distal aim and the projects' proximal focus, and (3) the possible weaknesses in the evaluation designs of the individual projects may lead to low-quality data on the overall level. We have briefly explained these remarks below.

First, FNO has laid out multiple guidelines as well as suggestions for project leaders to use in the design of their projects. Guidelines have been issued about the focus of the projects—health-related behavior or perceived health—and about target groups—socially vulnerable families. On the one hand, it seems that project leaders have been following these guidelines; all say they will focus on smoking cessation, the reduction of alcohol consumption, promoting healthy weight

through feeding practices or exercise, or improving perceived health. On the other hand, regarding target groups, projects often seem to have been less compliant. Target groups are all classified as vulnerable families but range from single mothers with a low income or education to multiproblem households in specific urban areas. Also, the focus on health-related behavior may cause projects to ignore outcomes at the intermediate level. The diversity in target groups may complicate combined analyses of project data at the overall level. This means that, however rich the information offered by the program is, it may at times prove either too diverse or too focused for the researches to be able to analyze its effectiveness and processes at the higher program level. In this study, we addressed this issue by not only looking at effectiveness but also broadening the scope of the research to in-depth mechanisms of health promotion. In addition, we explored alternative ways of analysis to address effectiveness.

A related second limitation lies in the fact that, even though the programs aim to reduce health inequalities, a specific focus on health-related behavior among socially vulnerable families has been prescribed for the projects. Graham [17] has distinguished 3 approaches to reducing health inequalities. Targeted programs may improve the health of those in the worst socioeconomic position without making any effort to improve the health of those in higher socioeconomic positions. Other programs may target the health gap between low and high socioeconomic groups by improving the health of the poorest groups fastest. Another last approach Graham mentions is to explicitly address *gradients* in health inequalities [17,44]. Most HFN projects are designed to target specifically, and in several cases only, those in the lowest socioeconomic position. By not addressing the gradient, the projects may thus fail to improve the health of intermediate groups [44]. However, the information that this study may produce on mechanisms among the most vulnerable groups could be an important contribution to shaping future health promotion initiatives. As mechanisms operate in specific contexts—that is, for specific groups—results may even prove more valuable when restricted to a group, place, or time.

The gap in levels between the program's aim and the projects' focus may be seen as the difference between proximal and distal factors [28]: factors contributing to health that are on a level closer to the individual, such as behavior, and factors or differences that emerge at a level further away from the individual, such as societal inequalities. The program appears to build on the notion that positive outcomes on causes at the proximal level, behavioral changes, may indicate successful outcomes at the distal level: reducing health inequalities. Although the usage of the terminology of proximal and distal in an evaluation framework has certain advantages [45], especially in clarifying theoretical models, it also complicates matters [46]. One complication relevant to the program under study is that embracing the notions of proximal and distal may lead to considering 1 factor (in this case, the proximal: behavior change) as more important than others at the distal level in explaining and reducing health inequalities. Previous research indicates that, although behavior change is certainly related to changes in health inequalities, it is not considered the one most important explanation [20,47]. In-depth information on for whom, when, and where certain behavior change interventions work or not can, however, still contain valuable tools for the design of future health promotion interventions.

Finally, the proposed study design is not tailored to measure changes in inequalities per se in a traditional, experimental way. There are few possibilities to include control groups in the evaluation design. The projects' geographical and target group boundaries are often vague and dynamic. Therefore, expected outcomes may appear at different levels and in a variety of sizes. In many projects, the project-specific evaluation design has been tailored to such dynamics and complexity, using quasi-experimental, nonexperimental, participatory, process-focused or mostly qualitative designs. The consequent limited possibilities for conducting a randomized experiment at the project level will complicate the aggregation of quantitative data at the higher level. We cannot change the fact that we have to work with a diverse range of data. Optimizing communication with project leaders and project researchers and starting off with an exploration of the possibilities for data aggregation, we still hope to make as much use as possible of the information available.

It is very valuable that the information from multiple relevant cases is combined and that all projects address the same proximal indicators for health. This evaluation enables us to study effectiveness in addition to mechanisms. Its timing, parallel to the implementation of the projects, allows for continuous learning by all stakeholders involved. The diversity in contexts and approaches additionally holds promise for the transferability of successful mechanisms, thereby informing future programs.

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Authors' Contributions

LH was the first author of the manuscript and participated in the design of the study. LV and MK designed the study. All authors have read and approved the final manuscript and contributed to the drafting and revision of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-reviewer report from the Wageningen School of Social Sciences.

[PDF File (Adobe PDF File), 807KB - resprot_v8i4e11305_app1.pdf]

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Abbreviations

FNO: Fonds NutsOhra
HFN: Healthy Futures Nearby
QCA: Qualitative Comparative Analysis
WHO: World Health Organization

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Protocol

A Capacity Building Program to Improve the Self-Efficacy of Key Workers to Support the Well-Being of Parents of a Child With a Disability Accessing an Early Childhood Intervention Service: Protocol for a Stepped-Wedge Design Trial

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Abstract

Background: Early childhood intervention services support children with disabilities or developmental delays from birth to school entry with the aim to achieve optimal outcomes for children and their families. A transdisciplinary approach to delivering early childhood intervention, particularly the key worker model, is considered the best practice, where allied health professionals (eg, speech pathologists, physiotherapists, occupational therapists, psychologists, and special educators) and the family work together as a collaborative team to share information, knowledge, and skills across disciplinary boundaries, with a key worker coordinating and delivering most of the intervention to achieve the goals for the child and their family. Initial qualitative research demonstrated parents want their key worker to also support their mental well-being. Poor mental well-being of parents of a child with a disability is of relevance to key workers because of its association with poor child-related outcomes. One of the major challenges key workers report in supporting families is managing parent distress and, because of lack of confidence, is a secondary negative impact on their own well-being.

Objective: This trial has been developed in response to the negative cycle of low professional confidence to support parents' mental health, increased key worker stress, and high turnover of employees working within a disability service setting.

Methods: A stepped-wedge design is used to deliver and evaluate a capacity building intervention program, over a 9-month period, for key workers to improve both parent and staff mental well-being. The primary outcome is key workers' self-efficacy in supporting parental mental well-being. Secondary outcomes include manager self-efficacy in supporting key workers and staff perceptions of supervisory support, staff job-related mental well-being, parental satisfaction with their key worker, parental mental well-being, and cost-consequence of the program.

Results: This study was funded in October 2014, supported by an Australian National Health and Medical Research Council Partnership Project grant (Grant number 1076861). Focus groups and individual face-to-face interviews were conducted from February to November 2015 with 40 parents who have a child with a disability and 13 key workers to gain insight into how the disability service could better promote child and family health and well-being and to inform about the development of the trial.

Conclusions: The stepped-wedge study design is practical and ethical for research with a vulnerable population group of parents of a child with a disability, providing high quality data with all participants exposed to the intervention by the end of the trial.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12617001530314; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=372578 (Archived by WebCite at http://www.webcitation.org/76XjDavnG)

International Registered Report Identifier (IRRID): DERR1-10.2196/12531

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KEYWORDS

mental health; early intervention; allied health; health services for persons with disabilities; capacity building; cost analysis

Introduction

Background

In 2015, 4.3 million Australians were reported as having a disability, including 327,400 children (7.6%) aged 0 to 14 years [1]. Early Childhood Intervention Services (ECISs) are an Australian government–funded service that supports children with disabilities or developmental delays from birth to school entry and their families [2]. These services aim to provide families with the knowledge, skills, and support to meet the needs of their child and to optimize their child's development and participation in family and community life.

A transdisciplinary approach to delivering early childhood intervention, particularly the key worker model, is considered the best practice, where allied health professionals (eg, speech pathologists, physiotherapists, occupational therapists, psychologists, and special educators) and the family work together as a collaborative team to share information, knowledge, and skills across disciplinary boundaries, with a key worker coordinating and delivering most of the intervention to achieve the goals for the child and their family [3-5].

Theoretical Framework

Family-centered practice (FCP) is important to the delivery of care in ECISs. This is a broadly defined philosophy which places families in central and pivotal roles in decisions and actions involving the child, parent, and family priorities and preferences [6]. Implicit in the philosophy of FCP is the need for services to be responsive to the family situation and to mobilize support that can produce optimal child, parent, and family benefits [7,8]. FCP and the key worker model have been linked with increased parent satisfaction, decreased parent stress, and improved child outcomes [9-14]. However, applying FCP principles has been difficult with the criticism of it being espoused rather than enacted in everyday practice and areas being deemed important for families and professionals varying slightly [15-17].

Research on the mental well-being of parents of children with a disability is of particular relevance to FCP within ECISs. Mental well-being is defined as "a dynamic state that refers to individuals' ability to develop their potential, work productively and creatively, build strong and positive relationships with others, and contribute to their community" [18]. Several aspects of parental mental well-being can be adversely impacted when caring for a child with a disability, including mental and physical health, marital relationships, and participation in social and economic life [19-26]. Poor mental well-being is of relevance to key workers within ECISs because it is a significant risk factor for poor child-related outcomes [27-30]. Furthermore, given that the principles of FCP acknowledge the needs of the family holistically, parental mental well-being is of high relevance to ECISs. However, in the few research studies available, those that have investigated support for parental mental well-being suggest that disability services for children do not adequately accomplish this [31-34]. Our own data also support this. A recent review found limited training or support for staff in transdisciplinary teams to work confidently outside their disciplinary boundaries, with this issue needing to be addressed for the model to truly be considered best practice [35]. For the transdisciplinary model to work well for families, the professional competencies of the key worker go beyond discipline-specific knowledge and include personal qualities such as empathy, sensitivity, listening effectively, interpersonal communication skills, and interacting with authenticity [5].

Setting

This research study was codeveloped by a cross-sectoral team of academics and clinicians in partnership with a major Victorian nongovernment disability service provider in Victoria, Australia, and included an initial qualitative scoping study to identify what

children with a disability and their families required to optimize their health and well-being and how staff can facilitate this through the service. The disability service provider offers a wide range of support services to people of all ages who either are born with or acquire a disability. The *Pursuit of Wellbeing* program involves staff within their ECIS, which provides services to children aged up to 6 years, who vary in their severity of disability or developmental delay, family circumstances, and cultural background. The service has 6 different ECIS sites across metropolitan Melbourne which for the purpose of this study are known as *hubs*. They are geographically spread, approximately 25 kilometers apart, to service the suburban population. Each family has a key worker assigned to them from a transdisciplinary team of allied health professionals. Across the 6 hubs, there are approximately 60 key workers supporting 600 families. The disability service provider will implement the program across the 6 hubs using a phased process over a 9-month period, and all key workers and managers will receive the program as part of the trial, which is supported by the executive management team at the service.

Phase 1: Identification of Family and Staff Needs

In the first phase of development of this trial, a combination of focus groups and individual face-to-face interviews were conducted with 40 parents who have a child with a disability and 13 key workers to gain insight into how the disability service could better promote child and family health and well-being. Parents reported they were satisfied with the professional advice and support that their child received; however, they felt that they did not receive adequate support for their own mental well-being [36]. Concurrently, key workers also reported that one of their major challenges was managing the high rates of parental distress and their need for greater confidence and skills in supporting parental mental well-being. They did not feel confident to refer parents to relevant support services as key workers were unclear whether addressing parents' mental well-being during a home visit to the family fell within the boundaries of their role, prioritizing support for the child only, an additional barrier being the lack of knowledge of local services to support parents of a child with a disability. The staff also identified that it would be useful for each team to have access to a key worker with a background in psychology on the team. Ideally, key workers with a psychology background would be available within all teams, but this is dependent on successful recruitment to these positions by the organization.

Phase 2: Development of the Pursuit of Wellbeing Program

A new capacity building program, titled *The Pursuit of Wellbeing*, was then codeveloped based on the findings identified in phase 1 of the research and the current literature, with the aim to build the self-efficacy of key workers to better support the mental health and well-being of parents (Textbox 1). A capacity building framework was selected as it encompasses actions aimed at strengthening the skills and capabilities of the individuals, organization, systems, and wider community [37,38]. Increased capacity at the individual level is likely to increase the self-efficacy of key workers. Self-efficacy is an aspect of empowerment relating to how people perceive their ability to manage challenging situations and accomplish goals. By building the self-efficacy of key workers to support parental mental well-being, we anticipate their own well-being will be impacted by increasing their confidence in how to manage challenging situations and providing a sense of personal accomplishment in their service to the parents and carers [39]. This is important given that high staff stress and poor morale has been linked to burnout, absenteeism, and high staff turnover [40,41], and critically, these factors may in turn result in a lack of support for parents. This trial thus seeks to disrupt the current negative cycle of low professional confidence, increased stress and high turnover of employees, and continuing unmet needs of parents [24,42].

Phase 3: Delivery of the Pursuit of Wellbeing Program

The intervention program will be implemented by a disability service provider as part of an organizational system change involving all key workers and managers providing an ECIS to families with children aged 0 to 6 years with a disability or developmental delay. The training will be facilitated by an internal senior manager who is also a clinical psychologist. An internal position was chosen not only because of their understanding of the intricacies of mental health promotion but also to tailor the program to suit the organizations needs and embed the program into existing organizational operations. The training is designed to include educational modules, discussion, and provision of a toolkit of psychological resources to support key workers in discussing well-being with parents and for managers to provide well-being support to their staff. Managers of each hub will then assume responsibility for the ongoing implementation of the program to their staff, with ongoing support and advice available from the facilitator. In this way, the program, if effective, will be sustainable. This protocol outlines the methodology of the evaluation of the *Pursuit of Wellbeing* program undertaken by the research team.

Textbox 1. The Pursuit of Wellbeing capacity building program to support staff efficacy in managing the mental wellbeing of parents in an early childhood intervention service.

Training program

- Key workers and managers
  - Module 1: Strengthening capacity to support parental mental wellbeing. Topics covered include: Importance of family-centered practice to promote wellbeing of child with a disability; How to open up conversation around parental wellbeing; Identifying red flags for poor mental health; Identifying coping types; How to refer to appropriate supports.
  - Module 2: Staff wellbeing and role boundaries. Topics covered include: How to identify and manage stress in the workplace; Self-care strategies; Outline of key worker roles, responsibilities and boundaries, and balancing the role; Available team and organizational support strategies, such as promoting debriefing, and counseling options if staff are experiencing heightened stress or distress.
- Managers
  - Module 1: Strengthening support for key workers. Topics covered include: How to identify, support, and manage stress in the workplace (in others and in self); Clarification of key worker role boundaries; How to debrief with staff; How to promote staff self-care. It is anticipated that managers will be a key resource for staff seeking expertise in addressing parental mental well-being. Managers will also discuss the support required for a senior staff member in their team acting as parental well-being champion (further details below). This role will likely be assumed by a key worker appointed also as a team leader position.

Resources

- For key workers and managers
  - The following are provided as hard copies and Web-based via the staff intranet after completion of the study: Organisational Practice Framework incorporating the key messages of the training; Toolkit of positive psychology activities and resources; Tailored referral pathway of local support services; Well-being for parents and carers resource [43].
  - A formalized debriefing process for staff includes: Building the capacity of managers to improve their approach to debriefing during monthly supervision meetings; Developing of a flow chart for staff to know their immediate options to access debriefing and counseling.
  - The appointment of a senior staff member in each team to act as a parental well-being champion. Additional training will be provided to support the champion in their conversations with key workers on supporting parental mental well-being.
- For parents
  - The following are provided as hard copies: Tailored referral pathway of local support services; Well-being for parents and carers resource [43].

Methods

Objectives

The objective of this study is to trial a capacity building program that aims to increase the self-efficacy of key workers to support parental mental wellbeing. The research questions are outlined in Textbox 2.

The predicted outcomes and impacts of the intervention are presented in a logic model (Figure 1).

Trial Design

This study employs a stepped-wedge design to evaluate the program. The design was chosen so that each hub would eventually receive the program and be provided with the new professional development opportunity. The intervention will be rolled out progressively over 9 months. The clusters for randomization will be the hubs (N=6). Randomization will be conducted by a statistician who is independent of the administration of the intervention [44]. The first 2 hubs will not be randomly selected, as senior management advised against this because of the large amount of ongoing organizational change at the service. These 2 hubs will be selected based on readiness to undergo the trial and will receive the program immediately after baseline is established with the remaining 4 hubs randomized 2 at a time, every 3 months thereafter. In this way, hubs that were previously acting as control hubs will progressively receive the program. All hubs are assessed at baseline and every 3 months thereafter. The stepped-wedge design is suitable for a phased evaluation approach such as this, in which there is an imperative to allow all participants to have access to the new program. The design also allows each hub or cluster to act as its own *pre versus post* control and, in the first 2 periods, there are at least 2 hubs acting as controls and at least 2 hubs receiving the program (Table 1). The statistical analysis (see below) will combine the *between-* and *within-* hub information on the effect of the program. We seek to minimize potential bias by not revealing to the key workers when the new program is scheduled to be allocated to their hub. However, this will be self-evident to the key workers in the last 2 hubs. Key workers that operate across multiple sites will be requested to refrain from sharing learnings or materials from the training with fellow staff at other sites who have not received the intervention. Although there is a risk of contamination, this is not anticipated to have a large effect as the number of key workers that work at multiple sites is very small.

Textbox 2. Research questions.

1. Does the capacity building program increase:
   - Key workers' self-efficacy in supporting parental mental well-being (primary outcome);
   - Managers' self-efficacy in supporting staff and parental well-being;
   - Parental mental well-being;
   - Key workers' and managers' job-related wellbeing and mental wellbeing;
   - Parental satisfaction with the service provided by their key worker; and/or
   - Key workers' and managers' perceptions of supervisory support?
2. Are the program and evaluation methodologies appropriate and feasible for key workers, managers, and parents?
3. Is the program good value-for-money?
4. Is it affordable?

The cost of the capacity building program will be estimated to help determine whether this program is *value-for-money*. Simple dominance would establish this—that is, compared with current practice, is it cheaper with improved effectiveness or cost neutral with improved effectiveness. Similarly, on the flip side, if the program is dominated, then it is not value-for-money—that is, more expensive and less effective or more expensive with no improvement in effectiveness. If the program is both more expensive and more effective, then more complex tests of efficiency are required that establish value-for-money by reference to established guidelines using a metric that enables comparison across alternate uses for limited budgets (eg, a return on investment >5% and a cost per quality-adjusted life-year <AUD$50,000). Value-for-money considerations, together with affordability considerations, will inform the program's potential to be scaled-up and adopted by other disability organizations.

Figure 1. Program logic.

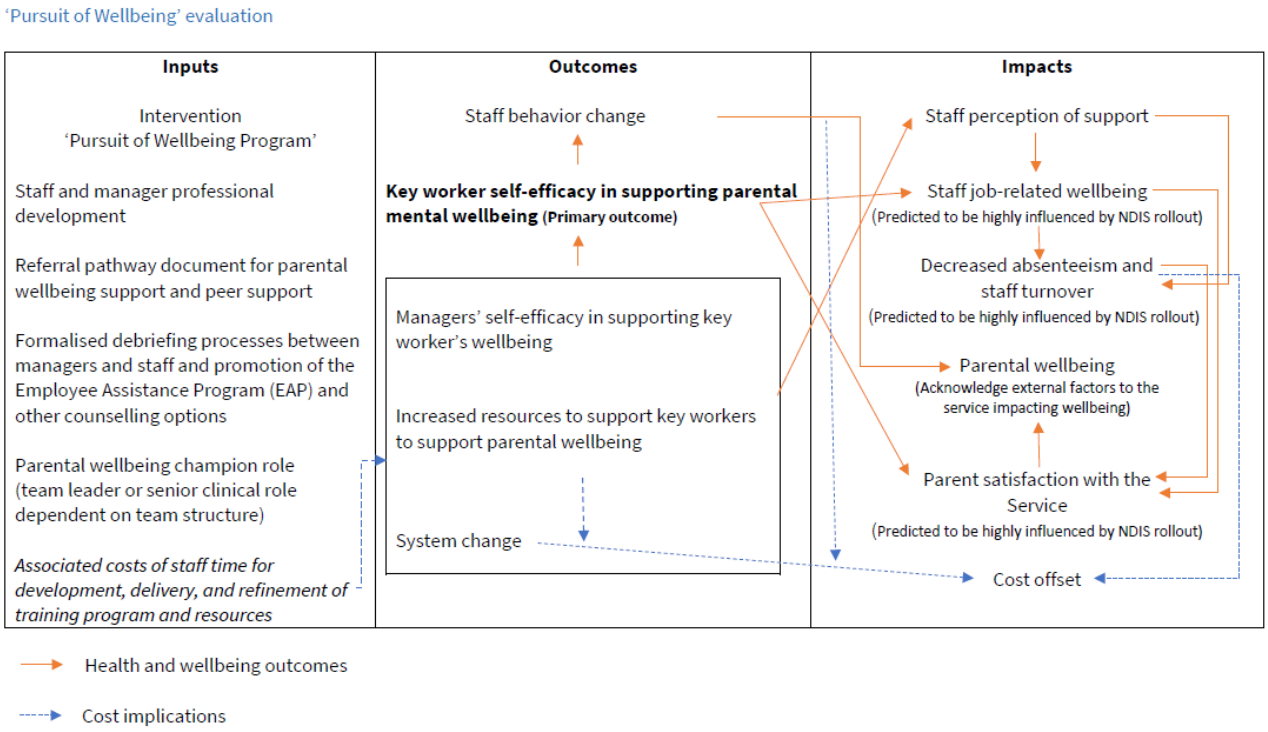

Table 1. The stepped-wedge design (partially randomized).

Hub	Baseline (0 months)	Period 1	3 months	Period 2	6 months	Period 3	9 months
1	X[a]	I[b]	X[c]	I[c]	X[c]	I[c]	X[c]
2	X	I[c]	X[c]	I[c]	X[c]	I[c]	X[c]
3	X	C[d]	X	I[c]	X[c]	I[c]	X[c]
4	X	C	X	I[c]	X[c]	I[c]	X[c]
5	X	C	X	C	X	I[c]	X[c]
6	X	C	X	C	X	I[c]	X[c]

[a]X: assessment.

[b]I: intervention (ie, the new program).

[c]Hub is receiving the program.

[d]C: control.

Participants and Recruitment

All key workers and managers at each hub have the opportunity to participate in the intervention and this will be strongly encouraged by the management. All key workers and managers at each hub, and families that they support, are eligible and will be invited to participate in the evaluation. To recruit staff, the researchers will attend a staff meeting to talk about the study and commitments involved. Staff will be given a plain language statement and consent form. The manager of each hub will be blinded to which key workers are taking part in the evaluation of the trial to allow key workers to feel comfortable in providing feedback on their current management and any adverse experiences they may have had. Reminder emails will be sent to managers to distribute to all staff to enhance recruitment until the intervention begins. To recruit parents, all key workers, regardless of their involvement in the evaluation, will be requested to give the plain language statement and consent form to parents in their regular fortnightly visits. Many parents do not act immediately on this type of survey because of their day-to-day pressures. To enhance recruitment and reach all parents, key workers will remind each parent in subsequent visits, email reminders will be distributed by an administrator at each site, and the information sheets will be left at the entrance of each service. If a parent requires an interpreter, this can be arranged both to explain the study and, if they consent, to assist them to complete the questionnaires. Parents will be informed and reassured that the service their child receives will not in any way be impacted by their participation in this evaluation. All participants will return their signed consent form directly to the researchers.

Data Collection

A mixed-methods approach will be employed to gain an understanding of the process and outcome of delivering this program. Researchers will send the consenting participants a link to the online survey at baseline and each 3-monthly time point. Online surveys will be used to collect quantitative data from all consenting key workers and managers to assess their confidence in supporting parental mental well-being, their perceptions of supervisory support, their work-related well-being, and their own mental well-being. Online surveys will also be sent to all consenting parents to assess their mental well-being, their satisfaction with their key worker, and health care resource use. Paper-based surveys were offered as an alternative for parents. Survey data will be collected at baseline and every 3 months for 9 months to reassess these variables pre- and postdelivery of the program. The survey data collected across the intervals will provide information on the program's impacts and the practical contribution of the program to the service. Survey data will be collected and managed using Research Electronic Data Capture (REDCap) tools hosted at the University of Melbourne [45]. Reminders to complete the online survey will be sent up to 4 times to all participants via email generated by the REDCap program.

Qualitative data will be collected by conducting focus groups at the 9-month time point. A total of 1 focus group at each hub (N=6) will be conducted with key workers to explore their experience with the program, discussing their perceptions about the usefulness of the program and any challenges they faced implementing their learnings and strategies with parents post training. In addition, 1 focus group at each hub (N=6) will also be conducted with parents to explore the impact of the program on their interaction with their key worker and their mental well-being. Semistructured interviews will be conducted with parents if focus groups are unable to be organized. Moreover, 1 focus group will be conducted with hub managers from the different sites to explore their view on the impact of the program on their staff, clients, and on their management role.

Outcomes

Primary Outcome

Key Workers' Self-Efficacy in Supporting Parental Mental Well-Being

We have developed a set of items to measure how confident key workers are in supporting parental mental well-being. A total of 10 items measured on a visual analogue scale (VAS; Multimedia Appendix 1) assess perceived confidence in understanding and supporting parental mental well-being; their knowledge about how to support parents' well-being and refer parents for additional help; and to communicate with parents about their well-being based on Bandura's [46] recommendation

that self-efficacy questionnaires are task-specific. The items tapping the same domain of efficacy will be correlated with each other and averaged. The primary analysis will be conducted on the average, with each item given equal importance for each individual at each assessment, of the 10 VAS measurements denoting key worker confidence (KWC).

Secondary Outcomes

Managers' Self-Efficacy in Supporting Key Workers' Well-Being

We also developed a set of items, using the scale recommended by Bandura, to measure the perceived confidence of managers in supporting key workers' well-being in the workplace and to support their staff to adequately support parental mental well-being (Multimedia Appendix 1). A total of 10 items measured on a VAS assess their perceived confidence in understanding, identifying, and supporting staff well-being and workplace stress and in initiative debriefing after a potentially stressful workplace event. The items tapping the same domain of efficacy will be correlated with each other, summed, and averaged. The primary analysis will be conducted on the average, with each item given equal importance for each individual at each assessment, of the 10 VAS measurements denoting manager confidence.

Parental Mental Well-Being

Parental mental well-being will be measured using the shortened Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS; Multimedia Appendix 2). The WEMWBS, although less sensitive, has been shown to be reliable and valid [47], and the short 7-item version of WEMWBS was found to satisfy the strict unidimensionality expectations of the Rasch model and be largely free of bias [48]. This scale differs from other scales of mental health in that it covers only positive aspects of mental health, which was an important factor in choosing this scale to assess mental well-being in this vulnerable population. The scale uses a 5-point Likert scale and scores ranging from 1 to 5 for each item will be summed and averaged.

Key workers' and Managers' Job-Related Well-Being

Job related well-being will be measured using 2 scales as reported by Warr [49,50] (Multimedia Appendix 1).

Job-Related Affective Well-Being Scale

The first instrument measures job-related affective well-being using the Institute of Work Psychology Multi-Affect Indicator and includes 12 items. The staff are questioned using a 6-point Likert scale of agreement about how their job has made them feel across the multiple domains. Domain scores are provided on job related anxiety-contentment and depression-enthusiasm; this 2-dimensional model of job-related affects provides a more comprehensive view of emotional states at work than current measures of job satisfaction [51]. This scale reported acceptable internal consistency with a coefficient alpha of .78 [49].

Job-Related Mental Well-Being

For the second scale assessing job-related mental well-being, 9 items were selected from 2 out of 5 domains within the scale. These items were selected based on relevance to the intervention to assess self-reported job competence and negative job carry-over for staff. Excluded domains were deemed not appropriate for this evaluation. The scores between the 2 measures will be correlated, higher scores indicating greater contentment and enthusiasm as well as greater competence and negative carry-over.

Parent Satisfaction With Key Workers

New items were developed for this study to assess parental satisfaction with the service provided by the key workers, based on previous assessments utilized by Yooralla (Multimedia Appendix 2). A total of 5 items assess parents' perception of support from their key worker for their social and emotional well-being and their degree of overall satisfaction with the service received from the disability provider.

Key Workers' and Managers' Perceptions of Supervisory Support

Supervisory support will be measured using some of the high-loading items of the Perceived Supervisor Support scale [52,53]. The Perceived Supervisor Support scale has 8 items based on perceptions of value and support from supervisors. A total of 3 items were chosen to assess perceived support regarding staff goals and help with problems and well-being, with most items from the scale deemed inappropriate for this evaluation. It has a high internal reliability coefficient (0.88) and has been widely used in research, including a recent project examining burnout in therapists working with children with autism [54]. These items will be averaged with each item given equal weighting.

Process Evaluation

Process data will be collected from staff at each 3-month time point via the online survey to assess attendance, usefulness, and uptake of the intervention components, such as support-seeking behavior and use of the toolkit resources provided. Researchers will also collect data on the fidelity of the training via observation and meetings with the trainer. In addition, the focus groups being conducted at 9 months postintervention with key workers, managers, and parents will provide an opportunity to explore barriers and facilitators to the delivery of the training and translation of the skills learnt within the training to current practice. Any unanticipated outcomes will be discussed in the focus groups with staff.

Costing of the Intervention

Cost data will be nested within the program and will be closely coordinated with the purpose and data collection of the study. The primary perspective will be that of the service provider, but health sector and client impacts will also be assessed. Cost analysis of the program, comparator, and any cost offsets will be measured based on service activity and resources required for the services to take place. Program cost will reflect the service provider's accounting practice, for example, cost category and routine cost data collection. A template to standardize the cost data collection will be completed by each hub manager in consultation with the finance manager at baseline and repeated at 3, 6, and 9 months later. Cost offsets refer to the potential for improvement in staff productivity and/or the service provider's revenue. Staff productivity includes staff turnover rates, absenteeism, and associated implications. The

absenteeism and turnover rates can be obtained from the service provider's records, whereas self-reported absenteeism will be measured using the short version of the World Health Organization Health and Performance Questionnaire [55,56], which will be used in conjunction with staff well-being assessment questionnaires. In addition to the key worker economic-related outcomes, the economic-related implications of parent well-being on health care system utilization will also be quantified by collecting health system resource use.

Sample Size

The sample size (6 hubs) is pragmatically determined by the number of hubs at the service and the roll-out period for the intervention. We expect approximately 8 out of 10 key workers located at each hub to consent to be repeatedly assessed (at 0, 3, 6, and 9 months) following the start of the study and approximately 3 out of the 10 families that they each support to consent to be surveyed during the study. The effect of the pragmatically determined sample size on the power of the study was investigated as follows. With 6 hubs randomized 2 at a time every 3 months starting after baseline (0 months), we have a replicated (at the cluster or hub level) stepped-wedge design with 3 periods and we have made provision for between 6 and 8 key workers in each cluster to be repeatedly assessed across the periods. Accordingly, we expect to have between 144 and 192 observations of the primary outcome variable (KWC). KWC is measured on a bounded continuous outcome scale from 0 to 100. As a contingency, we assume that approximately 10% of the variance of a measurement on a randomly selected adult is *between-hub* variance and the remaining component of the variance of a randomly selected adult splits into *between* and *within* individual variance subcomponents according to either of the 2 scenarios—an *optimistic* intraclass correlation (ICC) of 0.5 or a *less optimistic* ICC of 0.25. As an example, the baseline mean for KWC may be 70, the total variance may be 18, and the variance components for hubs, individuals, and assessments within individuals may be 2, 4, and 12, respectively (ICC=0.25). We intend to use the method of restricted maximum likelihood (REML) to fit a linear mixed model to the observations of KWC. The model will have random effects terms for hubs, key workers within hubs and assessments within key workers (within hubs), and fixed effects terms for time (0, 3, 6, and 9 months, which span the three 3-month periods) and condition (control or intervention). On the basis of 2000 simulations of the trial for each of the 4 scenarios, we find that the minimum effect sizes that can be detected with 80% power range from 0.49 to 0.68 (Table 2). For each of the 4 scenarios, the minimum detectable effect size was calculated from 2000 simulations of the trial in which restricted maximum likelihood was used, in each simulation, to estimate the variance components, and an F test was used to compare the predicted means. As a contingency against an overall system improvement over time, each scenario also included an underlying trend over time (an increase of 2 units in key worker confidence (KWC) from the first to the last assessment). Simulations assumed baseline KWC=70, total variance=18, and between-hubs variance=2 (11.1% of the total variance) with a corresponding coefficient of variation (CV)=6.1%. Simulations were also repeated with total variance=49 and between-hubs variance=5 (10.2% of the total variance) with a corresponding CV=10%. As expected, the minimum detectable effect sizes (not shown) were very similar—a consequence of standardizing the effect difference by the square root of the total variance. Accordingly, we conclude that this study has moderate-to-high power to detect moderate effect sizes for outcome variables that are measured repeatedly on key workers.

Data Analysis

Quantitative Analysis

The repeated measurements (4 in total) on individuals in the 6 hubs over the three 3-month periods will be analyzed using linear mixed models. For measurement scales that are not too coarse (eg, more than 7 distinct values), the statistical analyses will make use of the REML algorithm to fit the mixed model. This algorithm will take account of missing (at-random) assessments and also allows the exploration of various autocorrelation models for the repeated measurements. Comparison of the *control* and *new program* means (adjusted for period effects) will be assessed with an *F* test. If required, after inspection of diagnostic plots of residuals and fitted values, an empirical logit transformation will be used to reanalyze any item scales that are bounded and coarse. Generalized linear mixed-model techniques will be used to analyze binomial or other categorical data. Cumulative effects of exposure to the new program on key outcome variables will also be explored using the same methods. The final analysis will be conducted after all participants have had adequate opportunity to be assessed at the end of the third period (ie, at 9 months), and the database has been locked. Process evaluation will assist in the assessment of factors that impact on the feasibility, success, and sustainability of the intervention strategies and new program. A detailed statistical analysis plan can be accessed by contacting the corresponding author.

Table 2. Minimum effect sizes.

Key workers per hub[a,b]	Intraclass correlation[c]	Minimum detectable effect size
6	0.25	0.68
6	0.5	0.56
8	0.25	0.59
8	0.5	0.49

[a]Effect size is the expected difference between the 2 conditions (intervention-control) divided by the SD (ie, the square root of the total variance).

[b]Detectable with 80% power for the proposed stepped-wedge design with 6 hubs, 3 periods, and 4 assessment time points.

[c]Intraclass correlation: between individual variance divided by the sum of the between and within individual variances.

Economic Analysis

The economic analysis includes a cost analysis, together with efficiency analyses based on either of the following: (1) simple *dominance* (intervention cheaper/outcomes better or no different) or *dominated* (intervention more expensive and outcomes same or worse) and (2) more complex analyses that examine cost in relation to different definitions of value.

Simple dominance will be established using cost-effectiveness analysis that compares program costs with physical outcomes (based on primary and secondary outcomes for parents and key workers collected in the trial). The cost analyses will be conducted to determine whether the capacity building program is cheaper or more expensive than current practice, primarily from the service provider perspective but also from the perspective of parents and the health care system.

If the costs of the capacity program are not cheaper and the program is more effective, then *value* has to be analyzed to establish *value-for-money*. One way is to list the range of primary outcomes and secondary outcomes that have policy meaning to stakeholders (so called *cost-consequences analysis*) and/or express these as a series of cost-effectiveness ratios (eg, *net cost per parent satisfaction score* and *net cost per unit of staff well-being score*). A judgment call could then be made by key staff as to whether these benefits constitute sufficient return on the investment.

Another way is to place a dollar value on these outcomes to establish a return on investment using cost-benefit analysis. There are various methods available to do this (eg, value of *statistical lives* where premature death is prevented; human capital methods; and scenario-based techniques such as willingness-to-pay or conjoint analysis). A decision on the most appropriate technique, if the trial yields this result, will be made in conjunction with the service provider senior management.

Qualitative Analysis

The focus groups will be recorded and transcribed verbatim. Qualitative data will be analyzed and coded using an inductive, thematic approach informed by grounded theory [57]. NVivo12 software will be used to manage the data during the analysis of results [58]. Similarities and differences will be compared within and across focus groups to identify emergent themes. This will be used to generate a conceptual analysis which will be aligned with strengths and gaps in current theory, evidence, and practice to increase understanding of key issues relating to the feasibility and impact of the intervention strategies.

Results

This study was funded in October 2014 supported by an Australian National Health and Medical Research Council Partnership Project grant (Grant number 1076861) and cash and in-kind contribution from Yooralla as the associated partner organization. This is a multiyear study, and the final year comprises the trial outlined in this study. The trial is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617001530314), retrospectively registered on 3 November 2017. Results are expected to be available by the end of 2019.

Discussion

Overview

Strategies to improve the mental health and well-being of parents of children with a disability are urgently needed [59] and are timely given the current rollout of the National Disability Insurance Scheme (NDIS) in Australia. The NDIS aims to improve the lives of individuals with a disability and their families. To our knowledge, there are currently no evidence-based interventions delivered within an ECIS to directly support the mental health of parents and carers of children with a disability. However, supporting mental health as well as providing child-related input is a key factor on the pathway to enabling their own, as well as their child's, full participation in society and their community and to achieve positive health outcomes [60-62].

This study will pilot an intervention program embedded in a capacity building framework to increase ECISs' support for the mental health of parents of children with a disability. Providing professional development about the importance of recognizing and supporting parental distress, the implications on positive child development, and the importance of seeking support for their own well-being is novel to this key worker cohort. Evidence for the effectiveness and cost of this type of intervention is lacking in the literature but is urgently needed to further understand the best models of care by staff to achieve well-being outcomes for families and children with a disability. It is anticipated that the capacity of their key worker and thus their confidence and job satisfaction may lead to improvements in their own mental well-being. The training is specifically designed to build the capacity of key workers to understand when a parent is struggling and would like to be connected with additional supports and that they are supporting an at-risk population group for poor mental health. There is a strength in providing training to all key workers to be able to identify and assist parents in the first instance of becoming aware of any psychological stress or distress as the availability of a key worker with a psychology background on each team is subject to recruitment by the service. The trainings focus on providing resources to staff and helping them to identify when the parent's needs are out of their scope, we anticipate, will raise their awareness of when they need to refer customers to external supports. The focus of the early childhood intervention service is to aid the development of the child and to empower the family so key workers do not provide ongoing support for parental mental health but rather refer as appropriate.

On the basis of the research findings that emerged from the exploratory phase of this research, it is imperative to intervene at not only the key worker level but also to introduce and trial strategies at the organizational level to achieve sustainable change for families accessing the service for their child. A partnership between academics, clinicians, and the delivery organization allowed the development of a program that was feasible and relevant to the service that could be embedded in the service delivery system and addressed a current gap in the literature. The study design is practical and ethical for research in this space, with each hub of staff and parents exposed to the

intervention by the end of the trial. A knowledge translation plan is in place to embed successful components of the program into policy documents to support the ongoing accessibility of the program for current staff and upskilling of new staff. Successful components of the intervention will be made accessible online via the staff intranet for ease of access and to allow content to be updated as new evidence of best practice arises and external support details require updating. The participatory method taken to develop and deliver the intervention is ideal for the proposed sustainability of the program, with the potential to embed within the organization's professional development schedule. The scalability of the program is possible for other disability organizations that support parents of a child with a disability, once the trial has assessed if the intervention produces significantly improved self-efficacy and mental health for staff and parents. In addition, if service improvements and increased parent satisfaction have been shown to occur, the service will be more closely aligned with the NDIS.

Strengths and Limitations

A strength of this study is the stepped-wedged design, which allows the collection of mixed-method data, including quantitative data, also including economic data, and qualitative data from key workers and parents, which historically are a difficult cohort to involve in longitudinal research because of family demands. Particularly, the inclusion of the economic evaluation provides a model for future studies involving service delivery organizations. The design also addresses the ethical issue of conducting a blinded randomized control trial with a vulnerable population, as we deem it inequitable to provide care for mental well-being to only a cohort of parents accessing the service. A limitation of this study is that it is conducted within a changing policy and funding context, with the NDIS roll out underway in Australia, which is having an ongoing impact to service delivery within the partner organization and which we anticipate will be a potential confounder on the outcome measurements. For organizational reasons, the first 2 hubs are not randomly selected. This is not a major issue for assessment of the impact of the program on the partnering organization as we will use both this intrahub (each hub as its own control) as well as the interhub information when estimating the effect of the new program on the organization. Incomplete randomization does, however, impact on the external validity of the program. We seek to minimize potential bias by not revealing to the staff when the new program is scheduled to be allocated to their hub, although this may become self-evident in the last 2 hubs. Owing to this research being conducted in a real-world service delivery context, there is possible contamination because of a small number of key workers working across multiple sites that will receive the intervention at varying times which may not be overcome by the methods introduced to minimize contamination impact on results. Although methods to minimize the impact of this are in place, it is possible that training at 1 site will influence their service delivery approach to parents at their alternative work place that has not yet received the intervention and other staff may observe and learn, particularly because of the transdisciplinary approach. This will be addressed through discussions with relevant key workers who will be asked to avoid talking about their learnings with staff from hubs yet to receive the intervention to minimize contamination as much as possible. A further limitation of the research was that it was not feasible to have a third group that received only the well-being materials that are provided in conjunction with the face-to-face training to assess their impact independent of the impact of the training on parental well-being.

Conclusions

This research will investigate a strategy to help break the negative cycle of poor mental health in parents of children with a disability that leads to poorer short and long-term outcomes for themselves, their child, and their family and their ability to contribute to the community and workforce. It is also urgently needed to provide staff training and clear work roles for the provision of support to parents to reduce worker stress, improve staff retention, and decrease stress for coworkers and families. Through building the knowledge and confidence of health professionals to support parents, it is likely that health professionals will feel increased self-efficacy and job-related well-being, which may also increase productivity and reduce job turnover. Furthermore, by improving the provision of mental health support for parents, it is likely children will benefit in terms of their own health, particularly mentally and socially, and their development because of the increased capacity of parents to care for their children.

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Authors' Contributions

ED was the principal investigator of the study until October 2017, with LG assuming the principal investigator role. ED, DY, K-MG, JR, RCart, and UT drafted the paper. Specifically, JR contributed to the data analysis considerations, and RCart and UT contributed to the economic evaluation and analysis considerations. KW, LG, RM, DR, JT, JM, and PI contributed to considerations of research with families of children with a disability and the completion of the manuscript. All the coauthors contributed to the study design. All authors read and approved the final manuscript.

Conflicts of Interest

JM, CK, PI and R Carr were employees and members of the executive management team at Yooralla, the partnering organization on the grant received to conduct this study.

Multimedia Appendix 1

Staff survey.

[PDF File (Adobe PDF File), 52KB - resprot_v8i4e12531_app1.pdf]

Multimedia Appendix 2

Parent survey.

[PDF File (Adobe PDF File), 41KB - resprot_v8i4e12531_app2.pdf]

Multimedia Appendix 3

NHMRC Partnership Project Grant Review Panel Report.

[PDF File (Adobe PDF File), 40KB - resprot_v8i4e12531_app3.pdf]

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Abbreviations

ECIS: Early Childhood Intervention Service
FCP: family-centered practice
KWC: key worker confidence
NDIS: National Disability Insurance Scheme
REDCap: Research Electronic Data Capture
REML: restricted maximum likelihood
VAS: visual analogue scale
WEMWBS: Warwick-Edinburgh Mental Wellbeing Scale

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Protocol

Safety of Intranasal Ketamine for Reducing Uncontrolled Cancer-Related Pain: Protocol of a Phase I/II Clinical Trial

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Abstract

Background: Approximately 12 million Americans are affected with cancer. Of these, 53% experience pain at all stages of cancer. Pain may remain uncontrolled despite high-dose opioid therapy, and opioids have many well-documented harmful side effects. Intranasal ketamine has been shown to be effective in controlling breakthrough noncancer pain in a double-blind randomized control trial (DBRCT) by Carr et al in 2003 as well as to help with depression in a DBRCT by Lapidus et al in 2014. We seek to obtain preliminary data on the safety, feasibility, and utility of this novel technique for the treatment of uncontrolled cancer pain.

Objective: This study aimed to obtain preliminary data via a clinical trial addressing the safety, feasibility, pharmacokinetics, and pharmacodynamics of intranasal ketamine. These initial findings will be applied to a subsequent trial to determine the effectiveness and associated toxicities of ketamine in a larger sample of cancer patients and to address the compelling need to identify new, successful management therapies for cancer pain.

Methods: This is an institutional review board– and investigational new drug–approved, prospective phase I/II trial to investigate the safety and use of intranasal ketamine in patients with uncontrolled pain related to cancer or cancer treatment. Informed consent will be obtained prior to all study procedures. All patients will be assigned to the same investigational treatment arm. After patient selection via inclusion/exclusion criteria, patients will be seen over 5 visits, with each visit conducted 2-7 days apart. Patients will be administered ketamine on visits 1-4 and monitored for 240 minutes with continuous pulse oximetry and regular blood pressure checks. Blood samples as well as patient-reported outcomes will be collected at set time points at baseline and after drug delivery. Patients will receive 10 mg intranasal ketamine on visit 1, 10 mg intravenous ketamine on visit 2, 30 mg intranasal ketamine on visit 3, and 50 mg intranasal ketamine on visit 4. On visit 5, an addition blood sample will be drawn.

Results: As of March 2019, enrollment is in progress, and a total of 7 subjects have completed the study. Enrollment is expected to be completed by April 2019. Final data analysis will commence soon after, and the results are expected to be submitted for publication in 2019.

Conclusions: If intranasal ketamine can be utilized for pain control in cancer patients, it could provide superior analgesia and better quality of life, without the risk of significant respiratory depression and constipation associated with opioid medications.

These findings will be an important initial step toward testing the effectiveness of intranasal ketamine as a nonopioid medication for cancer pain and as potential maintenance outpatient therapy.

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KEYWORDS

cancer pain; intranasal ketamine; chronic pain

Introduction

Background and Rationale

About 11.9 million Americans are affected with cancer, of which 53% experience pain at all stages of cancer. This proportion increases to 58%-69% among patients with advanced cancer [1]. Depression often coexists with cancer pain. Patients with cancer pain often require high dosages of opioids that make them too sedated to effectively participate in day-to-day activities and have a good quality of life. Occasionally, even after high-dose opioids, their pain remains uncontrolled in the setting of opioid tolerance or opioid-unresponsive pain. An epidemiological study revealed that 10%-15% of these patients fail to achieve acceptable pain relief with opiates alone or in combination with conventional adjuvant analgesics [2-4].

In the search for improved therapies for chronic cancer pain, medications with novel mechanisms of action have been sought. One such promising pharmacologic approach is ketamine. Ketamine is a Food and Drug Administration (FDA)–approved anesthetic with amnesic, analgesic, dissociative, and sedative properties. It is unique among anesthetic agents, as it does not depress the cardiovascular and respiratory systems. Ketamine is a noncompetitive, antagonist of *N*-methyl-D-aspartate (NMDA) receptors that blocks the NMDA channel in the open state by binding to the phencyclidine site located within the lumen of the channel. Antagonism of NMDA receptors produces antinociception of persistent or neuropathic pain in animal models and analgesia in pain states in humans. The NMDA receptor is believed to play a role in the development of opioid tolerance, and ketamine has been shown to prevent fentanyl-induced hyperalgesia and subsequent acute morphine tolerance in a rat model [5]. Ketamine also interacts at a number of other receptor sites to block pain, including voltage-sensitive calcium channels. Some other effects of ketamine are depression of sodium channels, modulation of cholinergic neurotransmission, and inhibition of serotonin and norepinephrine uptake. Ketamine also interacts with kappa and mu opioid receptors; however, in humans, naloxone, an opioid antagonist, does not antagonize the analgesic effects of ketamine. Safety and efficacy of ketamine as an anesthetic and analgesic agent are well documented [6-8]. Ketamine is not labeled as an analgesic agent by the FDA. Low (subanesthestic) doses of ketamine have minimal adverse impact upon cardiovascular or respiratory function but produce analgesia and modulate central sensitization, hyperalgesia, and opioid tolerance. Ketamine is typically administered intravenously, but the intravenous route is not convenient for use in an ambulatory setting. Although ketamine has been administered orally, its oral bioavailability is low due to hepatic first pass, limiting the application of this route for chronic use. The intranasal route has several advantages such as higher bioavailability due to avoidance of first-pass hepatic metabolism, no need for venous access, ability to repeat doses quickly, and rapid absorption [9-10].

Intranasal ketamine is effective in controlling breakthrough pain, as shown in a double-blind randomized controlled trial (DBRCT) by Carr et al in 2003 [11], as well as in helping with depression, as shown in a DBRCT by Lapidus in 2014 [12]. The Carr study [11] was a DBRCT including 20 patients with breakthrough pain and noted pain relief within 10 min, lasting up to 60 minutes with 10-50 mg of intranasal ketamine (2.65 point average decrease on the Numerical Pain Rating Score [NPRS] scale). The pain scores were only recorded until 60 minutes after drug administration, and the patients were allowed to determine the dose themselves, without precise description for the dose in the study. The study by Lapidus et al [12] was performed in 20 patients with major depression and noted significant improvement in depressive symptoms (7.6 point average decrease on the Montgomery-Asberg Depression Rating Scale [MADRS] scale) in 44% of patients at 24 hours after administration of 50 mg intranasal ketamine. There are limited data regarding the use of ketamine as an adjuvant to opioids for the management of *cancer* pain [13]. We seek to obtain preliminary data on the safety, feasibility, and utility of this novel technique for the treatment of uncontrolled cancer pain.

Objectives

If intranasal ketamine can be utilized for pain control in patients with cancer, it could provide superior analgesia and a better quality of life without the risk of significant respiratory depression associated with opioid medications. We seek to obtain preliminary data via a clinical trial addressing the safety, feasibility, and utility of this novel technique for the treatment of persistent uncontrolled cancer pain. These findings would be an important initial step toward testing the effectiveness of intranasal ketamine as a nonopioid medication for cancer pain and as potential maintenance outpatient therapy. These initial findings will be applied to a subsequent trial to determine the effectiveness and associated toxicities of ketamine in a larger sample of cancer patients and to address the compelling need to identify new, successful management therapies for cancer pain.

Methods

Trial Design

This is a prospective clinical trial aimed to investigate the use of intranasal ketamine in patients with uncontrolled pain related to cancer or cancer treatment (Figure 1). All patients will be assigned to the same investigational treatment arm.

Participants, Interventions, and Outcomes

Study Setting

The trial will be conducted at the Phase I Unit of the Winship Cancer Institute, an academic hospital in Atlanta, Georgia, United States. Subjects will be recruited at the supportive oncology, oncology, and pain clinics at an academic institution located in Atlanta, Georgia. Subjects may be identified and contacted via telephone with information about the study prior to their next clinic appointment in order to allow time for them to consider the study.

Eligibility Criteria

Patients will be eligible to participate if they are (1) men or women of at least 18 years of age; (2) patients with uncontrolled pain related to cancer or cancer treatment (uncontrolled pain will be defined as (i) pain that persists for more than 7 days and is rated ≥4 on the NPRS or (ii) use of breakthrough medication more than 4 times in 24 hours or receiving treatment with oral morphine ≥50 mg/day); (3) patients who are able to follow-up in person during the trial; (4) patients on a stable analgesic regimen for >7 days without escalation during the study period, receiving rescue or immediate-release medication every 3 or more hours; (5) patients who are willing and able to maintain a daily pain diary; (6) patients who are able to understand written and verbal English; and (7) patients who weigh ≥50 kg.

Patients will be excluded from the study if they have any of the following:

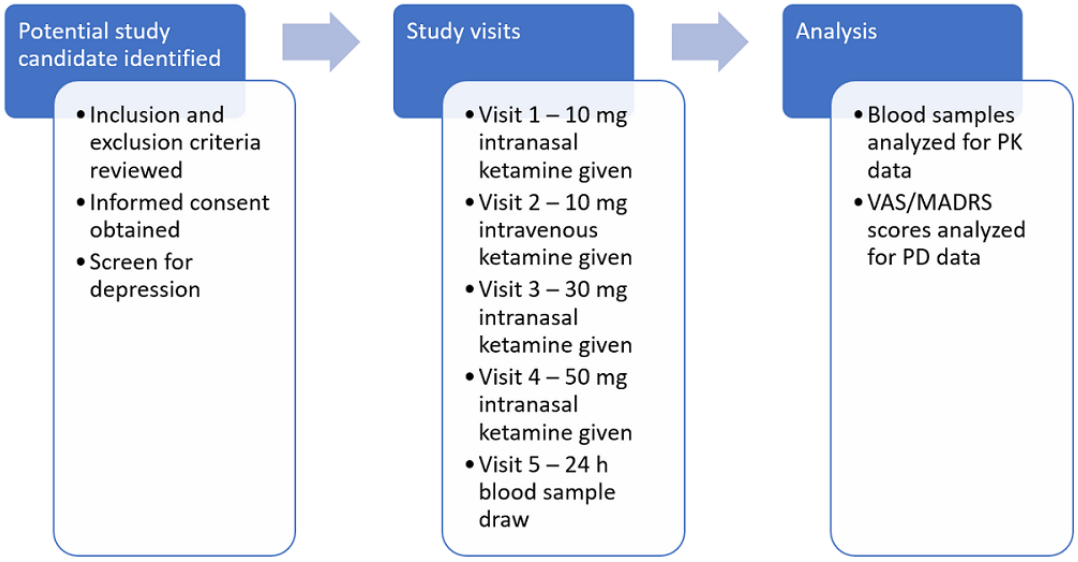
- Transportation issues interfering with return study visits
- High disposition of laryngospasm or apnea
- Severe cardiac disease
- Conditions where significant elevations in blood pressure would be a serious hazard
- Stage 2 or higher hypertension (systolic blood pressure>160 mmHg or diastolic blood pressure>100 mmHg)
- Baseline tachycardia (heart rate>100 beats/minute)
- History of seizures, elevated intracranial pressure, or cerebrospinal fluid obstructive states (eg, severe head injury and central congenital or mass lesions)
- Conditions that may increase intraocular pressure (eg, glaucoma and acute globe injury)
- History of uncontrolled depression or other psychiatric comorbidity with psychosis
- History of liver disease
- History of interstitial cystitis
- History of nasal or sinus anomalies or dysfunction (eg, allergic or infectious rhinitis)
- Lesions of the nasal mucosa
- Pregnancy, ongoing nursing, and childbearing potential but no use of contraception known to be highly effective. Highly effective contraception methods include a combination of any two of the following: use of oral, injected, or implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine system; barrier methods of contraception such as condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository; total abstinence; and male/female sterilization
- Illicit substance abuse within the past 6 months
- Documented history of medication abuse/misuse (eg, unsanctioned dose escalation and broken opioid agreement)
- Clinical requirement for medications that are concurrent inducers or strong inhibitors of CYP3A4. CYP3A4 substrates are allowed.
- Porphyria (the possibility of triggering a porphyric reaction)
- Severe active anemia (hemoglobin level<8 g/dL documented by laboratories; blood drawn within 3 months of the first study treatment)
- History of difficult intravenous access
- Intractable vomiting

Interventions

Written informed consent will be obtained prior to the conduct of study procedures, either while recruiting subjects prior to study visit 1 or during the first study visit prior to the beginning of the study. Subjects must meet all study eligibility criteria on visit 1 prior to study treatment. Intranasal ketamine will be prepared from a 100 mg/mL vial to be delivered nasally with a nasal atomizer. We will deliver 0.1 mL to provide 10 mg of atomized ketamine. Alternating nares will be used to deliver 0.1 mL at a time until the full dose is delivered. Christensen et al [14] reported the safety of intranasal doses of 10 mg, 30 mg, and 50 mg ketamine. Therefore, for the purpose of this study, 10 mg, 30 mg, and 50 mg of intranasal ketamine will be administered. Each visit will be conducted 2-7 days apart to avoid any accumulation of study doses. Patients will be asked to return to the Phase I Unit for a total of five study visits. All study visits will take place within 6 weeks or less.

On the first study visit, 10 mg of intranasal ketamine will be given to make sure that the study patients are able to tolerate a small dose of intranasal ketamine. On the second visit, 10 mg of intravenous ketamine will be given to help establish bioavailability of intranasal ketamine, with patients serving as their own controls. On the third and fourth visits, higher doses of ketamine, specifically, 30 mg and 50 mg, respectively, will be given, if the patients did not have severe adverse events with the smaller dosage. On the fifth study visit, no ketamine will be administered.

Figure 1. Participant timeline. PK: pharmacokinetic; PD: pharmacodynamic; VAS: Visual Analoge Scale; MADRS: Montgomery Asberg Depression Rating Scale.



Licensed study personnel will administer the ketamine. The intranasal ketamine will be administered in the following process: First, the mucosal atomization device (MAD) will be primed, and the appropriate dose will be loaded into the syringe. The patient will be seated in a chair and clear his/her sinuses using a tissue, if needed. The patient's head will be tilted backward. The MAD will be inserted into a nostril and aimed directly posterior, leveling with the floor of the nare and slightly lateral. A total of 0.1 mL (10 mg) ketamine will be administered. The patient will be asked to keep his/her head tilted backward for 5 minutes, if tolerable, in order to ensure that the medication does not run out of the nares. If medication visibly runs out of the nares or if the patient reports feeling the medication trickling down his/her throat, the event will be noted. If more than 0.1 mL (10 mg) needs to be delivered, steps 3-5 will be repeated in the contralateral nare, alternating until the full dose is delivered. After a short break of 30 seconds, ketamine will be re-administered into the same nare.

Patients may continue to take their usual pain medication as needed. Since the effect of most of the oral immediate-release opioid medications peaks between 30 and 90 minutes, ketamine will be given at least 120 minutes after the last dose of immediate-release opioid medication, so that the reduction in pain score is not confounded with the results of immediate-release opioid medications.

A family member/friend must transport the patient home following drug administration, as driving for 24 hours after drug administration is discouraged. A telephone call will be placed 14 days after the last dose of medication is administered to follow up any ongoing adverse events that occurred during the study period. If there are no ongoing adverse events at the end of visit 5, the subject's participation will end at that time. Provided all eligibility requirements are met, subjects may be reconsented to participate if they withdrew early, at the discretion of the investigator.

As the study subjects will have uncontrolled pain, it is likely that they might be on opioid medications during the study. Patients may continue their opioid and pain medication as prescribed. The Georgia prescription-monitoring database will be searched by the investigators, and an opioid pill count will be performed at each visit to monitor the opioid intake during the study.

If there is any hospitalization related to the study drug administration, the study will be put on hold for a formal review by the principal investigator and the Data and Safety Monitoring Committee (DSMC). The principal investigator or delegated person will communicate the event details to the DSMC for their review and determination of approval to continue the study. The study will be discontinued if there is more than one hospitalization related to administration of the study drug.

Outcomes

Primary Outcomes

The primary outcomes are as follows: (1) To conduct a clinical trial of intranasal ketamine in a sample of patients with cancer-related pain, the pharmacokinetics of intranasal ketamine will be measured through analysis of ketamine and its metabolite norketamine to determine pharmacokinetic variables including peak concentration after each dose and route (C_{max}), time to peak concentration, total area under the concentration time curve (AUC_{0-t}), half-life, and clearance. (2) To evaluate (pharmacodynamic) the effects of intranasal ketamine on patient-reported outcomes such as pain scores, side effects, depression, health-related quality of life, and functional status, the patient-related outcome will be assessed as measured by the NPRS, Side Effect Rating Scale for Dissociative Anesthetics (SERSDA), MADRS, Edmonton Symptom Assessment (ESAS), Eastern Cooperative Oncology Group (ECOG), and Patient-Reported Outcomes Measurement Information System (PROMIS) scales.

Secondary Outcomes

To determine the opioid-sparing effect of intranasal ketamine, we will (1) document the use of rescue medications prior to and during the study and (2) evaluate the total opioid consumption prior to and during the study.

Measurements

The following assessments will be documented in the patient research study record (Table 1):

- Height and weight at the first study visit
- Pain intensity on the NPRS prior to and at 5, 10, 15, 30, 45, 60, 120, 180, and 240 minutes after medication is given
- Vital signs including heart rate, blood pressure, respiratory rate, and pulse oximetry at baseline and 5, 10, 15, 30, 45, 60, 120, 180, and 240 minutes. Vital signs and pulse oximetry will be monitored continuously for a minimum of 30 minutes after drug administration. Vital signs will be measured more frequently if they are unstable
- The ECOG and ESAS scores at baseline and on each visit
- Sedation level on the Richmond Agitation-Sedation Scale (RASS) scale prior to and at 30, 60, and 240 minutes after medication is given. If the RASS score is between +4 and –3, sedation/delirium assessment on the Confusion Assessment Method for the Intensive Care Unit scale will be performed prior to and at 30, 60, and 240 minutes after medication is given
- Side effects using the SERSDA prior to and at 30, 60, and 240 minutes after medication is given
- Olfactory assessment before and after study drug administration to determine if the study medication has impacted the sense of smell
- Intake of any rescue medication; if taken, we will determine if it was taken at the usual interval or after a longer interval
- Patient response to the intervention if anything besides change in NPRS is reported
- Patient and family education regarding maintaining a pain diary (Multimedia Appendix 11) and reviewing discharge instructions, including when to call the study coordinator or report to the emergency department
- PROMIS functional scale on the first and last days of the study
- Any change in health status during the duration of study
- Opioid medication pill count at the beginning of each visit
- Only for visits 1, 3, and 4: If the patient reports symptoms of a significant upper respiratory tract infection (eg, rhinorrhea or congestion), the study visit will be canceled and rescheduled at a later date
- If changes in the sense of smell are noted, a study investigator will be notified, and additional olfactory assessments will be performed, with the frequency and number of assessments at the discretion of the investigator
- The frequency of the assessments may be increased at the discretion of the investigator

The study nurse will notify the attending physician if any of the following occur:

- Baseline heart rate>100 beats/minute, blood pressure>160/100 mmHg, or pain score≤5 on the NPRS. The physician will make the decision of whether to proceed with the study visit or cancel it based on the inclusion/exclusion criterion
- Any side effects or unexpected results or the vital signs change more than 20% from baseline (heart rate<50 beats/minute or >110 beats/minute, systolic blood pressure<90 mmHg or >180 mmHg, diastolic blood pressure<30 mmHg or >100 mmHg, respiratory rate<8 or >24 breaths/minute, or oxygen saturation <90%) after the study medication is given
- Sedation on the RASS scale is between –1 and –5 at any time
- Positive results for delirium on the Confusion Assessment Method for the Intensive Care Unit scale at any time
- Presence of any possible side effects from the study drug administration

Patients will be deemed eligible for discharge after the 240-minute assessment if their vital signs are within 10% of the baseline values; their RASS score is between +1 and –1; and side effects, as noted on the SERSDA scale, are ≤2 or no more than 1 point greater than their baseline value (the investigator must be notified if the value is greater than 2).

If the patient does not meet these criteria at the end of the 240-minute assessments, the study nurse will contact the research physician for further evaluation and assessment.

Sample Size

A sample size of 7 from a population of 20 (in the study by Carr et al [11]) yields a power of 91% to detect an NPRS difference of –2.7 between the null hypothesis mean of 0.0 and the alternative hypothesis mean of 2.7, with an estimated SD of 1.9 and a significance level (alpha) of .05 using a two-sided Wilcoxon test, assuming that the actual distribution is normal.

A sample size of 7 patients is needed based on statistical analysis observed in the study by Carr et al [11]. We will include 10 patients to account for the possibility that the observed pain reduction in this study may be different from that reported by Carr et al [11], as in this study, patients were given ketamine for breakthrough pain, not for baseline pain. We will enroll up to 25 patients in the study to account for potential dropouts. If a higher dropout rate is observed, we will enroll more patients until we have at least 10 patients who complete the entire study.

Any subject who does not complete the intravenous dosing and at least one intranasal dose will be replaced and followed up for safety, as needed, or receive a telephone call at 14 days. Enrolled subjects who discontinue the study early will be replaced. If a subject misses more than one treatment visit during the study period, the subject will be withdrawn and replaced to achieve a minimum of 10 subjects who are maximally treated with study medication (four study visits).

Table 1. Assessment schedule.

Assessments	Screening	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Telephone call
Review of inclusion/exclusion	✓						
Informed consent	✓						
Medical history/demographics	✓						
Hemoglobin level (if none in patient records within 3 months of visit 1)		✓					
Urine pregnancy test - within 1 week of planned visit (women of child-bearing potential)		✓	✓	✓	✓	✓	
Depression screening using PHQ-9[a]	✓	✓[b]					
Completion of the PROMIS[c] questionnaire		✓				✓	
ECOG[d] scale		✓	✓	✓	✓	✓	
ESAS[e] scale		✓	✓	✓	✓	✓	
MADRS[f, g, h]		✓	✓	✓	✓	✓	
Height		✓				✓	
Weight		✓	✓	✓	✓	✓	
Intravenous access		✓	✓[i]	✓	✓		
Study medication administration		✓	✓	✓	✓		
Vital Signs (heart rate[j], blood pressure, respiratory rate, pulse oximetry[k])		✓[l]	✓[l]	✓[l]	✓[l]	✓[m]	
Blood samples (pharmacokinetics		✓[m]	✓[n, o]	✓[n, o]	✓[n, o]	✓[o]	
Hepatic function test		✓				✓	
Urinalysis		✓				✓	
Pain scores using NPRS[p]		✓[l]	✓[l]	✓[l]	✓[l]	✓[m]	
RASS[q] scale		✓[r]	✓[r]	✓[r]	✓[r]	✓[m]	
CAM ICU[s] scale for RASS score between +4 to –3		✓	✓	✓	✓	✓	
SERSDA[t] scale		✓[r]	✓[r]	✓[r]	✓[r]	✓[m]	
Olfactory assessment - before and after drug administration		✓	✓	✓	✓		
Adverse events		✓	✓	✓	✓	✓	✓[u]
Details of rescue medication use		✓	✓	✓	✓	✓	
Pain diary[v]		✓	✓	✓	✓	✓	
Opioid pill count		✓	✓	✓	✓	✓	

[a]PHQ-9: Patient Health Questionnaire - 9 items.

[b]If not previously recorded during the screening visit or within 3 months of planned visit one, and no history of depression.

[c]PROMIS: Patient-Reported Outcomes Measurement Information System.

[d]ECOG: Eastern Cooperative Oncology Group.

[e]ESAS: Edmonton Symptom Assessment.

[f]MADRS: Montgomery-Asberg Depression Rating Scale.

[g]If screened positive for depression, questionnaire to be administered before medication is given.

[h]Questionnaire to be repeated between 180 and 240 minutes after medication is given.

[i]Two intravenous access points are needed at visit 2—One for study medication and one for blood draws.

[j]Monitoring will occur continuously for a minimum of 30 minutes after drug administration.

[k]Pulse oximetry monitoring will occur continuously for a minimum of 30 minutes after drug administration.

[l]To be recorded at baseline and 5, 10, 15, 30 (±5), 45 (±5), 60 (±5), 120 (±15), and 240 (±15) minutes after medication administration.

[m]On arrival for study visit.

[n]Samples will be obtained at 2, 30 (±5), 60 (±5), and 240 (±15) minutes after medication administration on visits 1-4.

[o]Baseline samples will be drawn on visits 2-5.

[p]NPRS: Numerical Pain Rating Score.

[q]RASS: Richmond Agitation-Sedation Scale.

[r]Assess at baseline and 30 (±5), 60 (±5), and 240 (±15) minutes after medication administration.

[s]CAM ICU: Confusion Assessment Method for the Intensive Care Unit.

[t]SERSDA: Side Effect Rating Scale for Dissociative Anesthetics.

[u]Ongoing adverse events will be followed up by a telephone call 14 days after the last day of study medication administration (±1 day).

[v]Patient to record data throughout study enrollment. Data are collected at final visit.

Recruitment

Subjects will be recruited at the supportive oncology clinic, oncology clinics, the pain clinic, and the Acute Pain Service at Emory by research coordinators and investigators. Subjects may be identified and contacted via telephone with information about the study prior to their next clinic appointment in order to allow time for them to consider the study.

Data Collection, Management, and Analysis

Data Collection Methods

Pharmacokinetics

Blood samples will be drawn at 2, 30, 60, and 240 minutes. Baseline blood samples will be drawn on Visits 2 through 5. The specimen requirements for laboratory testing are 3 mL serum or plasma in EDTA-containing vacuum tubes. We will draw 6 mL blood per sample to allow for adequate serum/plasma samples. The total blood drawn during one visit would be 24-30 mL. Samples will be promptly centrifuged, and serum or plasma will be separated into a plastic cryovial and frozen. The plastic containers will be preservative free. All samples will be sent to National Medical Services within 3 months. The samples are valid for 7 months at –20°C and for 30 days when refrigerated or stored at room temperature. Samples will be destroyed immediately after analysis. Gas chromatography with mass spectrometry analysis of the samples will be performed to determine the concentrations of ketamine and its metabolite, norketamine. Plasma concentration-time curves for ketamine and norketamine will be generated for each subject and compared among subjects for the variables of route and dose, with intravenous administration serving as the basis for comparison.

Pharmacodynamics

All assessment forms are provided in Multimedia Appendices 1-10.

Pain will be measured using the NPRS. This scale is the most responsive tool to document pain intensity as compared to the Visual Analogue Scale and Visual Rating Scale for measuring pain and shows higher compliance rates, better responsiveness, easier use, and better applicability than the latter scales [15,16]. In general, improvements of ≤1.5 points for pain severity on NPRS could be seen as clinically irrelevant [17-20]. Above that value, the cutoff point for “clinical relevance” depends on patients’ baseline pain severity and ranges from 2.4 to 5.3 [19-21]. Higher baseline scores require larger raw changes to represent clinically important differences [22].

Patients will maintain a pain diary for the entire study period until the final study visit and record how often they took their usual breakthrough medication during the trial. Patients will log pain scores three times a day.

The 10-item PROMIS questionnaire will be filled out at the first (baseline) and fifth (final) study visit to assess global health.

Participants will fill out a Patient Health Questionnaire - 9 items (PHQ-9) scale during the screening visit or the first study visit. The PHQ-9 scale ranges from 0 to 27 points and can be used for screening of depression. Patients who are on antidepressants or score more than 4 points on the PHQ-9 scale will be assessed for depression during the study. Depression will be assessed based on the MADRS on each visit. This is a 10-item questionnaire designed to be particularly sensitive to treatment effects [23]. Higher MADRS scores indicate more severe depression, and each item yields a score of 0-6 points. The overall score ranges from 0 to 60. Participants who screen positive for depression and are not on any treatment for depression will be offered a psychiatry consult as a part of their routine healthcare, if interested.

The performance status will be assessed by ECOG grading at baseline and throughout the study, which ranges from 0 to 5, where 0 is fully active and 5 is dead.

ESAS will be used to assess 9 common symptoms (pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being, and shortness of breath) experienced by cancer patients. Each symptom is rated from 0 to 10 points on a numerical scale, with 0 indicating that the symptom is absent and 10 indicating that the symptom is at its worst possible severity.

Side effects will be assessed using the SERSDA questionnaire prior to and at 30, 60, and 240 minutes after medication is given. The SERSDA questionnaire rates fatigue, dizziness, nausea, headache, feeling of unreality, changes in hearing, changes in vision, mood change, generalized discomfort, and hallucination on a scale of 0-4 points.

Data Management

The privacy of the research subjects will be ensured through the standard procedures for securing research data, including data encryption, limiting data access to trained personnel, and de-identification of subjects. All records identifying the subject

will be kept confidential and, to the extent permitted by the applicable laws and regulations, will not be made publicly available. If the results of the study are published, the subject's identity will remain confidential. Data will be stored in two locations: Hard copies will be kept in a secure and locked location, and soft copies will be stored electronically via a secure server.

Statistical Methods

Pharmacokinetics

To determine the pharmacokinetic characteristics such as bioavailability, peak effect, and elimination of intranasal ketamine, concentrations of ketamine and its metabolite norketamine will be analyzed.

Pharmacodynamics

To determine the pharmacodynamics of intranasal ketamine in terms of patient-related outcomes, pain scores on NPRS will be analyzed using the Wilcoxon signed-rank test, as the study sample size is too small to be analyzed by paired *t* test. A generalized Linear Model will be used to model any time trend for pain score change and to test if the trend is significant. A Wilcoxon signed-rank test will be used to compare any changes in depression severity on MADRS. A Chi-square test will be used to test the presence/absence of any side effects. A Wilcoxon signed-rank test will be used to assess the severity of all side effects (including SERSDA), if needed; to determine any changes in functional status on the PROMIS scale; and to compare any changes in the ESAS and ECOG scores.

Pharmacokinetic-Pharmacodynamic Relationships and Opioid-Sparing Effect

To determine the pharmacokinetic-pharmacodynamic relationships of intranasal ketamine delivered, we will compare the timing, degree, and duration of change in pain scores with individual and group pharmacokinetic parameters in order to assess potential relationships between the measures of exposure (C_{max}, and $AUC_{0\text{-}t}$) and pain relief. Multivariate modeling including patient-specific data (age, sex, weight, body mass index, and morphine equivalents) will be performed using initial pharmacokinetic parameters and goodness-of-fit analyses for compartmental model selection. If applicable, data from vital sign measurement changes will also be used for comparison with pharmacokinetic data.

To determine the opioid-sparing effect of intranasal ketamine, a Chi-square test will be used to compare the frequency of rescue medication use and a Wilcoxon signed-rank test will be used to compare the total opioid consumption.

Monitoring

Data Monitoring

Data will be monitored by the Winship Cancer Institute DSMC. The DSMC oversees internal monitoring functions by reviewing study conduct for consistency with Good Clinical Practice, compliance with federal regulations, and production of high-quality scientific data. The DSMC comprises physician investigators, internal monitors, and administrative staff. Initial study monitoring will occur within 6 months from the date of the first subject accrued, with two of the first five subjects already reviewed. Therefore, subsequent monitoring will occur in 6-month intervals, if any subjects are accrued. The population continuing to receive the intervention will be monitored as determined by the DSMC. At minimum, 10% of the subjects accrued since previous monitoring will be reviewed. An additional subject (or subjects) may be selected based on previously noted monitoring deficiencies or at the DSMC's discretion. Continued monitoring will occur in 6-month intervals for the population continuing to receive the intervention as determined by the DSMC. The DSMC will review pertinent aspects of the study conduct including patient safety, protocol compliance, data collection, and efficacy. The principal investigator or designee will be responsible for notifying the DSMC of patient accrual and status updates within 2 months of the planned review. The DSMC is independent from the study sponsor; however, the chair of the DSMC (DV) is a coinvestigator. DV steps out of DSMC meetings whenever the study is being discussed, and the vice-chair of the DSMC assumes the role of chair.

Harms

The following methods will be used to avoid harms:

1. A monthly meeting of investigators, clinical research coordinators, and regulatory personnel will be held to review the clinical data.
2. Adverse event reporting will utilize the Common Terminology Criteria for Adverse Events, version 5.0. The grading scale for these adverse events is as follows:
    - Grade 1 - Mild: asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated
    - Grade 2 - Moderate: minimal, local, or noninvasive intervention indicated, limiting age-appropriate instrumental activities of daily living (ADL)
    - Grade 3 - Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated, disabling, limiting self-care ADL
    - Grade 4 - Life-threatening consequences: urgent intervention indicated
    - Grade 5 - Death related to an adverse event
    - A serious adverse event is an adverse event or suspected adverse drug reaction that fulfills one of the following criteria: it results in death; it is immediately life-threatening (life-threatening in the definition of serious adverse event refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe); it requires in-subject hospitalization or prolongation of existing hospitalization; it results in persistent or significant disability or incapacity; it is a congenital anomaly or birth defect; it is an important medical event (important medical event in the definition of "serious" refers to an event that may not be immediately life threatening, or result in death or hospitalization, but from medical and scientific judgment, it may jeopardize the subject or require

medical or surgical intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization. Development of cancer or drug dependency/abuse will normally be considered serious as per this criterion)

3. Study progress in terms of enrollment and activity of current patients will be reviewed during the monthly meeting of the investigators, clinical research coordinators, and regulatory personnel. The principal investigator may increase the frequency of this meeting, if necessary.
4. As the investigational new drug sponsor-investigator, unexpected fatal or life-threatening suspected adverse reactions will be reported using the Medwatch FDA form 3500A via FedEx to the FDA no later than 7 calendar days after the initial receipt of information (21CFR 312.32(C)(2)). Additionally, serious unexpected suspected adverse reactions and a clinically important increase in the rate of a serious suspected adverse reaction will be reported no later than 15 calendar days after determining that the information qualifies for reporting (21 CFR 312.32(C)(1)) in paper format using FDA form 3500A. Finally, an annual progress report will be provided within 60 days of the anniversary date that the investigational new drug became active (ie, January 20, 2017 (21 CFR 312.33)).
5. Adverse events will be recorded. An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product or study treatment and that does not necessarily have a causal relationship with this administration. An adverse event can therefore be any unfavorable and unintended sign (including any abnormal laboratory findings), symptom, or disease temporally associated with the use of a medicinal (investigational) product, irrespective of whether it is related to the medicinal (investigational) product. Adverse events will be captured from the time of the first study drug administration through the fifth study visit. Ongoing adverse events at the fifth visit will be followed with a telephone call 14 days (plus or minus 1 day) after the last medication administration. Adverse events will be reported to the principal investigator by Emory email or telephone. All adverse events will be documented in an adverse event log. The reporting policy of the Emory Institutional Review Board will be followed.
6. The study will be put on hold after any hospitalization that is related to study drug administration for a formal review by the principal investigator and the DSMC. The principal investigator or delegated person will communicate the event details to the DSMC for their review and determination of approval to continue the study. The study will be end if there is more than one hospitalization related to administration of the study drug.
7. The Emory University School of Medicine Department of Anesthesiology will conduct this study according to national rules, regulations, and guidelines governing human clinical research. In addition, procedures cited by the US Code of Federal Regulations (Title 21) will be followed, as these apply to the principles of Good Clinical Practice and approval by the Emory University Institutional Review Board.

Auditing

This study will be followed by the Winship Cancer Institute Data Safety Monitoring Committee (DSMC) for local review and confirmation of proper study execution and safety measures. See the “Data Monitoring” section for further details.

Ethics and Dissemination

Research Ethics Approval

Institutional review board approval has been obtained, and the specified policies and procedures will be followed.

Protocol Amendments

All protocol changes will first be approved by the DSMC and Institutional Review Board. Approved important protocol changes (eg, changes to eligibility criteria, outcomes, and analyses) will be disseminated to relevant parties (eg, investigators, study staff, trial participants, trial registries, and journals). The following protocol amendments have been made and approved by the institutional review board (all changes reflected in this protocol):

- Amendment 1: Feb 13, 2017 to May 2, 2017
  - Corrections to Table 1. The assessment schedule has been modified as follows: A negative pregnancy test is required for child-bearing women within 1 week of study drug administration and may therefore require repetition at any point during the study visit period depending on the schedule of the visits. Continuous monitoring will be performed, and the requirement for telemetry will be removed. The word “Opioid” has been added to pill count. ECOG and ESAS have been removed from screening assessments. The missing 10-minute pain score assessments have been added
  - A goals/outcomes section has been expanded
  - More detail has been added to the Statistical Methods section
- Amendment 2: May 2, 2017 to Feb 23, 2018
  - Additional study identification has been included
  - Minor grammatical errors have been corrected
  - Potential subjects may be contacted by telephone in advance of the next scheduled clinic appointment
  - Clarification has been added that eligibility requirements must be confirmed at visit 1. A hemoglobin test may be ordered if required to meet the eligibility criteria in visit 1
  - Replacement/reconsent of subjects has been addressed
  - Requirement to notify the investigator of side effects has been added
  - Treatment strategy for central nervous system side effects has been added
  - Enrollment has been increased up to 25 people in order to achieve 10 treated patients
  - Clarification of the FDA reporting process has been provided
- Amendment 3: Feb 23, 2018 to May 24, 2018

- Visit days may be up to 7 days apart versus the previous 5 days apart, and the total time to study completion may be up to 6 weeks
- The follow-up phone call will only occur if there are ongoing adverse events on visit 5
- Clarification of the telephone call visit has been added
- Use of the CAM ICU scale has been corrected
- Subject monitoring parameters for patients #15, #16, and #17 have been added
- A more detailed description of study drug-administration process has been added
- Requirement of research physician notification for baseline pain score value has been added
- Morphine equivalent requirement has been reduced from 100 to 50 in the eligibility criteria

- Amendment 4: May 24, 2018 to Jan 2, 2019
  - The acceptable pain score for study inclusion has been reduced from 6 to 4 points

Consent or Assent

Written informed consent will be obtained by a research team member delegated to do so by the principal investigator, prior to conducting any research procedures. This process will include a discussion of risks and benefits as well as answering patient questions. If patients are able to provide their own medical history, they will be deemed capable of providing informed consent for research participation. The process will be free of coercion. Study patients will be paid a small amount as reimbursement for travel expenses for each visit completed. They can withdraw from the study at any time without penalty to their ongoing care.

Confidentiality

The privacy of the research subjects will be ensured through the standard procedures for securing research data. All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and regulations, will not be made publicly available. Subjects will be identified by a study number. If the results of the study are published, the subject's identity will remain confidential.

Access to Data

Access to study data will be limited to trained study personnel specifically delegated to do so. Logs of personnel training and role delegations will be maintained.

Ancillary and Posttrial Care

A telephone call will be placed 14 days after the last dose of medication is administered, to follow up on any ongoing adverse events that occurred during the study period. If there are no ongoing adverse events at the end of visit 5, the subject's participation will end at that time.

If a patient becomes ill or injured due to participation in the study, Emory University will help the patient obtain medical treatment. Emory University has not, however, set aside any money to pay for this medical treatment. The only exception is if it is proven that the patient's injury or illness is directly caused by the negligence of an Emory employee. "Negligence" is the failure to follow the standard duty of care.

If a patient becomes ill or injured due to participation in this study, the patient's insurer will be billed for the associated treatment costs. If the patient does not have insurance, or if the insurer does not pay, the patient will have to pay the costs.

A compensation of US $50 per visit will be provided to each patient for each completed visit as reimbursement for travel expenses to and from the institution.

Dissemination Policy

Results of the trial will be submitted for publication to major peer-reviewed scientific and medical journals. If no peer-reviewed journal accepts the manuscript for publication, it will be submitted to an open access journal for publication. The results will also be reported in the Clinicaltrials.gov database. Publication will be listed in PUBMED Central for public access. The protocol will be submitted for publication to peer-reviewed journals.

Results

Initial funding was approved by the Emory University Department of Anesthesiology in August 2016. Investigational new drug approval was obtained in January 2017. Institutional review board approval was obtained in April 2017. Recruitment began in July 2017. Additional funding was approved by the National Center for Advancing Translational Sciences of the National Institutes of Health in August 2018. As of March 2019, enrollment is in progress and expected to be completed by April 2019. Thus far, 10 subjects have been enrolled: 7 subjects have completed the protocol (target of 10) and 3 subjects were withdrawn early by the principal investigator, as they did not meet the eligibility criteria by the time of their first visit. Final data analysis will commence soon after, and the results are expected to be submitted for publication in 2019.

Discussion

Although intranasal ketamine has been shown to be effective in the treatment of chronic breakthrough pain, there are limited data regarding the use of ketamine as an adjuvant to opioids for the management of *cancer* pain. If intranasal ketamine can be utilized for pain control in patients with cancer, it could provide superior analgesia and a better quality of life without the risk of significant respiratory depression associated with opioid medications. These findings will be an important initial step toward testing the effectiveness of intranasal ketamine as a nonopioid medication for cancer pain and as potential maintenance outpatient therapy.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Numerical pain rating scale.

[PNG File, 10KB - resprot_v8i4e12125_app1.png]

Multimedia Appendix 2

Side Effects Rating Scale for Dissociative Anesthetics.

[PNG File, 13KB - resprot_v8i4e12125_app2.png]

Multimedia Appendix 3

Eastern Cooperative Oncology Group performance status.

[PNG File, 27KB - resprot_v8i4e12125_app3.png]

Multimedia Appendix 4

Edmonton Symptom Assessment System.

[PNG File, 36KB - resprot_v8i4e12125_app4.png]

Multimedia Appendix 5

The Richmond Agitation-Sedation Scale, used to assess sedation.

[PNG File, 252KB - resprot_v8i4e12125_app5.png]

Multimedia Appendix 6

The Confusion Assessment Method for the Intensive Care Unit, used to assess for delirium.

[PNG File, 546KB - resprot_v8i4e12125_app6.png]

Multimedia Appendix 7

Patient Health Questionnaire - 9 items.

[PNG File, 50KB - resprot_v8i4e12125_app7.png]

Multimedia Appendix 8

Montgomery-Asberg depression scale.

[PNG File, 141KB - resprot_v8i4e12125_app8.png]

Multimedia Appendix 9

Patient-Reported Outcomes Measurement Information System questionnaire (part 1).

[PNG File, 51KB - resprot_v8i4e12125_app9.png]

Multimedia Appendix 10

Patient-Reported Outcomes Measurement Information System questionnaire (part 2).

[PNG File, 23KB - resprot_v8i4e12125_app10.png]

Multimedia Appendix 11

Weekly pain diary. Completed by the subject each week during participation in the study.

[PNG File, 114KB - resprot_v8i4e12125_app11.png]

Multimedia Appendix 12

Peer-reviewer report #1 from ACTSI/Georgia CTSA KL2 and K12-BIRCWH.

[PDF File (Adobe PDF File), 171KB - resprot_v8i4e12125_app12.pdf]

Multimedia Appendix 13

Peer-reviewer report #2 from ACTSI/Georgia CTSA KL2 and K12-BIRCWH.

[PDF File (Adobe PDF File), 175KB - resprot_v8i4e12125_app13.pdf]

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Abbreviations

ADL: activities of daily living
AUC_{0-t}: total area under-the-concentration-time curve
CAM ICU: Confusion Assessment Method for the Intensive Care Unit
C_{max}: peak concentration after each dose and route
DBRCT: double-blind randomized controlled trial
DSMC: Data and Safety Monitoring Committee
ECOG: Eastern Cooperative Oncology Group
ESAS: Edmonton Symptom Assessment
FDA: Food and Drug Administration
MAD: mucosal atomization device
MADRS: Montgomery-Asberg Depression Rating Scale
NMDA: N-methyl-D-aspartate NMDA
NPRS: Numerical Pain Rating Score
PHQ-9: Patient Health Questionnaire - 9 items
PROMIS: Patient-Reported Outcomes Measurement Information System
RASS: Richmond Agitation-Sedation Scale
SERSDA: Side Effect Rating Scale for Dissociative Anesthetics

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Protocol

A Medication Synchronization Program and Blood Pressure Levels in a Community Pharmacy: Protocol

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Abstract

Background: The lack of adherence to prescribed antihypertensive medication occurs in 50% of patients and leads to poor health outcomes and increased medical costs. Consistent use of antihypertensive medications among patients with hypertension is essential to the reduction of short- and long-term cardiovascular complications. Strategies to improve medication adherence include syncing prescription medications in the pharmacy, which allow patients to retrieve chronically prescribed medications in one visit. The adoption of medication synchronization has been shown to improve adherence to medications; however, there is a lack of data showing if the intervention reduces blood pressure and improves long-term health outcomes.

Objective: This study aims to determine the association between participation in an appointment-based medication synchronization service and blood pressure levels among patients on antihypertensive medications.

Methods: This longitudinal prospective cohort study will observe changes in blood pressure among individuals in a medication synchronization program and those in a usual care group. Patients on at least two antihypertensive medications and four total medications have been recruited to participate in the study. All participants will be required to have at least a 6-month history of filling prescriptions at the pharmacy prior to enrollment in the study. Based on an estimated standard deviation of 14 mmHg, a sample size of 70 participants provides approximately 80% power with a two-sided .05 significance to detect a difference of 9 mmHg blood pressure between the two cohorts.

Results: As of the publication of this paper, patients are completing final blood pressure visits at the pharmacy and medication data are being collected from the pharmacy. Once patients complete all blood pressure visits, data analysis will begin.

Conclusions: This study will link medication synchronization and changes in blood pressure levels among individuals with hypertension. This study will provide preliminary data for a randomized clinical trial that will assess the impact of medication synchronization on blood pressure.

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KEYWORDS

pharmacy practice; medication synchronization; hypertension

Introduction

Background

Despite the multitude of treatment options for the management of hypertension, heart disease and stroke remain the leading causes of death attributed in part to high blood pressure. Among the 75 million Americans with hypertension, 74.9% of patients are being treated and only 52.5% of patients are under control [1]. Although effective medications to lower blood pressure have been around for decades, lack of medication adherence occurs among 50% of patients and leads to poor health outcomes [2]. Medication nonadherence is attributed to multiple factors, including lack of health system coordination, asymptomatic disease, patient-specific factors, and complexity of drug regimens [3].

Pharmacy-based strategies to improve medication adherence include the incorporation of synchronization, which enables patients to retrieve multiple medications systematically on one predetermined date [4-6]. Currently, there is limited literature suggesting medication synchronization might improve health outcomes in chronic conditions such as hypertension. One study examined the effect of medication synchronization or an education program on hypertensive health outcomes of patients in a community pharmacy setting [7]. After 4 months of enrollment in medication synchronization, patients achieved an average systolic blood pressure (SBP) reduction of 4 mmHg (P=.04) [7]. However, it is important to note that the control and education groups both achieved significant reductions in SBP (9 mmHg, P=.001 and 10 mmHg, P<.001, respectively) [7]. These significant findings may have been due to the feedback patients received, as all groups had their blood pressure taken and were educated when picking up their medications [7]. A review of participants recruited for the study indicated that baseline blood pressures were low at the start of the study—average baseline SBP of 138 mmHg and diastolic blood pressure (DBP) of 79 mmHg—which may have contributed to a lack of change at the conclusion of the study [7]. Additionally, there was no change in the patients' reported self-adherence to medications within any groups [7]. This may suggest that ensuring patients have their medications by implementing medication synchronization alone may not be enough to improve patient adherence and, in turn, health outcomes.

Other literature may not specify medication synchronization as the intervention used. Although other studies may not be identically comparable to medication synchronization, there are some similarities to the interventions performed that merit investigation. One such example is the Federal Study of Adherence to Medications in the Elderly (FAME) study, which examined the effect of a pharmacy care program on patient adherence and persistence [8]. This study also examined the pharmaceutical care program's effect on blood pressure and cholesterol outcomes. The authors found that improved adherence was associated with improvements in SBP, with the pharmaceutical care group achieving greater SBP reduction than usual care (-6.9 mmHg and -1.0 mmHg, respectively, P=.04) [8]. The pharmaceutical program consisted of providing medication education, dispensing of medications using blister packaging, and regular follow-up with a pharmacist every 2 months. Individualized education was provided to teach patients about drug names, indications, strengths, adverse effects, and instructions for use during visits [8]. Medication education is commonly performed by pharmacists and can be a component of the medication synchronization intervention along with regular follow-up. Medication synchronization requires pharmacists to go over the medication list with the patient each month. In doing so, regular follow-up occurs and the patient or pharmacist may have questions that lead to medication education or more comprehensive medication therapy management services.

Though there are similarities between medication synchronization and the FAME study intervention, the key difference is the use of blister packaging in the study. Thus, the study cannot directly be compared to a medication synchronization intervention due to the inclusion of compliance packaging. Although medication synchronization has been shown to indirectly improve medication adherence, it is not known if utilization leads to reduced blood pressure. Therefore, we aim to determine the association between participation in a medication synchronization service and blood pressure levels among patients on antihypertensive medications.

The overall objective of this project is to determine the association between participation in an appointment-based medication synchronization service and blood pressure levels among patients on antihypertensive medications. Other study objectives are to examine whether the effect of an appointment-based medication synchronization service on patients' blood pressure vary based on time-invariant demographic characteristics and time-variant characteristics of the subjects. Data generated from this study will determine the appropriate study size for a larger clinical trial of the intervention.

Aims and Hypothesis

Aim 1 is to examine the association between enrollment in an appointment-based medication synchronization program and study participants' blood pressure levels. Hypothesis 1 is as follows: consistent enrollment within a medication synchronization service will be associated with lower blood pressure measurements. This hypothesis will be tested using blood pressure ascertained over a follow-up period of up to 10 months.

Aim 2a is to examine whether the effect of an appointment-based medication synchronization program on patients' blood pressure varies based on time-invariant demographic characteristics of patients, such as gender, age, education, income, and ethnic origin.

Aim 2b is to examine whether the effect of an appointment-based medication synchronization program on patients' blood pressure varies based on time-variant characteristics of patients, such as weight, lifestyle change, adverse health behavior, ethanol use, frequency and intensity of exercise, adverse drug reaction, the number of medications, and adherence rates.

Aim 3 is to describe the level of patient satisfaction with enrollment in an appointment-based medication synchronization program.

Methods

Study Design

This is a longitudinal prospective study to observe whether enrollment in an appointment-based medication synchronization program will change SBP and DBP levels in patients with hypertension (ie, SBP/DBP of 140/90 mmHg or more) [9]. Two cohorts of patients will be recruited from pharmacy patrons who will volunteer to enroll in the study.

Group 1 (medication synchronization group) comprises patients voluntarily participating in the study and who will enroll in the appointment-based medication synchronization program.

Group 2 (traditional pharmacy medication pick-up group) comprises patients voluntarily participating in the study and who refuse to participate in the appointment-based medication synchronization program.

Human Subjects

All procedures, informed consent protocols, and study documents were approved by the University of Toledo Biomedical Institutional Review Board. Study procedures were all approved by the pharmacy practice site.

Informed Consent

All research subjects will sign written informed consent forms prior to participating in the study.

Study Population

Recruitment will occur among patients that utilize an independent pharmacy for prescription services in Toledo, Ohio. The pharmacy's computer software will be screened for patients that potentially meet the inclusion criteria (see Figure 1). Up to 100 patients eligible to participate based on inclusion and exclusion criteria will be enrolled in the study. Textbox 1 describes inclusion and exclusion criteria. A flyer describing the study will be posted in the pharmacy to recruit individuals. The flyer will emphasize that participation is voluntary and that a participant may withdraw at any time during the study. The flyer encourages potential participants to call the principal investigator or a coinvestigator if they are interested in learning more about the study. A script was developed that describes the nature of the phone call. Patients interested in the study will be asked to visit the pharmacy to meet with a study investigator who will provide more information about the study. Risks and benefits of the study will be discussed with the patient. If, after meeting in person, the individual is interested in participating in the study, they will be invited to complete the informed consent document. Subjects may withdraw from the study at any time without prejudice to their care.

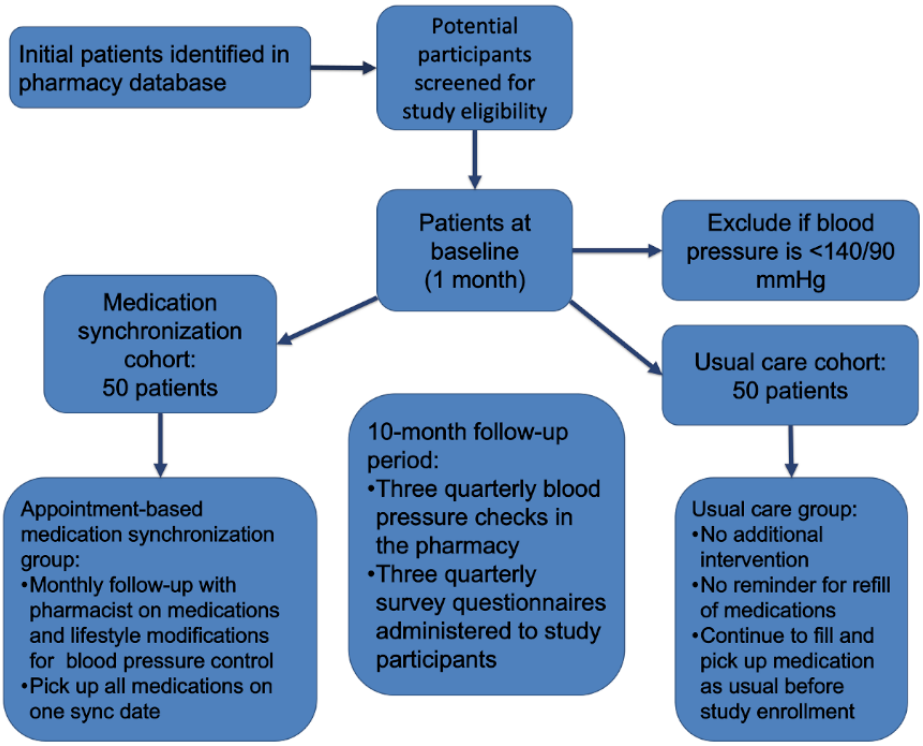
Study Procedures

After the baseline clinic visit, patients that meet the study inclusion and exclusion provisions will be followed by cohort depending on the services they decide to utilize in the pharmacy. Participants will be categorized as participating in medication synchronization or traditional medication pick-up group. Participation in any of these pharmacy services are voluntary and are a part of care offered by the pharmacy. Participants will notify investigators as to which cohort they would like to participate in at the month-1 research visit.

The baseline visit procedure includes confirmation that all inclusion and exclusion criteria are satisfied, verification of participant consent and contact information, and completion of baseline data survey, including obtaining blood pressure for analysis. The follow-up visit schedules for data collection do not differ by cohort groups. Table 1 provides more detail about scheduled research visits and information that will be collected. For data collection in both groups, all participants will have visits at months 1, 4, 7, and 10. For event ascertainment, participants in both groups will be queried regarding the occurrence of a possible event on the same schedule, specifically every 3 months. Follow-up in-person visits at the pharmacy will involve gathering of blood pressure data. Follow-up phone call surveys will involve gathering data on changes in health status and satisfaction with pharmacy services.

A multitude of physical measures and medication data will be collected throughout the study via five research pharmacy visits or four phone call surveys. A one-time medical history will be collected at baseline to serve as a screening tool as well as an eligibility and stratification factor. The following physical measures will be collected at baseline: seated blood pressure, weight, height, gender, age, medical history, sociodemographic data, and smoking and alcohol usage. Seated blood pressure, physical measures, and questionnaires will be gathered during pharmacy visits, while all other information, including health status and satisfaction with pharmacy services, will be collected via phone call surveys. Sociodemographic information will reflect age, race, date of diagnosis, ethnicity, gender, level of education, marital status, persons living with participants, and US postal code. This data will be used to identify eligible participants and to characterize the final study population. Baseline medication data include the number of medications, type of medications, and adherence. *Proportion of days covered* will be utilized to assess medication adherence. Monthly medication data will be collected to evaluate prescription records to assess adherence. Seated blood pressure, weight, sociodemographic data, and smoking and alcohol usage will be collected every 3 months starting from the first month of the study.

Figure 1. Study diagram.



Textbox 1. List of inclusion and exclusion criteria for study.

Inclusion criteria:

- Subject is an adult, 18 years of age or older.
- Subject is able to read, understand, and sign a written informed consent form to participate in the study.
- Subject has systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg during the baseline period.
- Subject has been an established patron of Toledo Family Pharmacy Inc for at least six previous refills of blood pressure medications.
- Subject has filled more than four prescriptions at Toledo Family Pharmacy each month for the past 3 months.
- Subject has a history of hypertension and has been prescribed at least two antihypertensive medications.
- Subject possesses an active phone number where they can be reached.
- Subject is willing and able to comply with the study protocol.

Exclusion criteria:

- Subject is participating in another clinical trial within four weeks of the baseline period involving an intervention that could affect the outcome measures of this study.
- Subject has end-stage renal disease and is on dialysis.
- Subject had a heart attack in the previous six months.
- Subject had a stroke in the previous six months.
- Subject is currently enrolled in an auto-delivery program or medication packaging program.
- Subject has a psychiatric or mental disorder that, in the judgment of the investigator, could interfere with provision of informed consent or completion of survey questionnaires.
- Patient has a designated power-of-attorney that signs for medications, which renders them not competent to sign the informed consent form.

Table 1. Study timeline and data collection.

Data to be collected	Baseline	Month									
		1	2	3	4	5	6	7	8	9	10
Physical measures											
Seated blood pressure	x	x			x			x			x
Weight	x	x			x			x			x
Height	x										
Questionnaires											
Gender	x										
Age	x										
Medical history	x										
Sociodemographic data	x	x			x			x			x
Smoking and alcohol use	x	x			x			x			x
Medication data											
Number of medications	x	x	x	x	x	x	x	x	x	x	x
Cost of medications	x	x	x	x	x	x	x	x	x	x	x
Type of medications	x	x	x	x	x	x	x	x	x	x	x
Adherence	x	x	x	x	x	x	x	x	x	x	x

The pharmacy will supply the research team with medication data on each of the participants enrolled in the study each month. Data provided will include the number of medications, names of medications, costs of medications, the date when the prescription was filled, and the date when the prescription was picked up from the pharmacy. For each drug, the quantity filled, days' supply, and prescription number will be obtained. Protected health information collected in the study will be maintained on a key code sheet. This code sheet will be locked in the principal investigator's office at the University of Toledo. A code will be on all data collection forms to refer to each participant in the study. These efforts will maintain research participants' confidentiality throughout the study. Data collected on data forms will be maintained in a locked cabinet in the principal investigator's office, separate from the key code sheet. Data collected on code sheets will also be transcribed to electronic format using REDCap provided by the University of Toledo.

Data Analysis

By assuming a medium effect size of 0.75 times standard deviation for the intervention and set power at 0.8 with a two-sided alpha of .05, the sample size needed is 70 participants, with 35 in each group, allowing for up to 20% attrition. Based on the estimated standard deviation of 14 mmHg, the proposed sample size will provide approximately 80% power to detect a difference as small as 9.5 mmHg between intervention and control groups [7]. Descriptive statistics will be presented as mean (SD) for continuous data and percent frequency (interquartile range) for categorical data to describe patients' characteristics.

Given the observational nature of the study and patients' self-selection of the treatment arms, inverse-probability -of-treatment weighted (IPTW) estimation of marginal structural models (MSMs) will be employed in this study. This estimation addresses both sources of potential bias, such as confounders or covariates (eg, age, income, and medication profiles) and missing data under the missing-at-random (MAR) assumption, the most popular informative mechanism in practice. MSMs are a class of statistical models used for causal inference in epidemiology and use a multi-step estimation strategy to control for the effect of confounding variables, allowing the investigator to obtain unbiased estimates [10-12]. Among the several methods that have been proposed to estimate the parameters in MSMs, IPTW is the most commonly used one to address confounding variables [13]. It tries to control for confounding variables by assigning each observation a weight and uses this to create a *pseudo-population*, where treatment arm and control arm are balanced over the confounder [10]. When applied to our study, an MSM consists of three submodules that models the following: (1) the probability of receiving treatment (ie, synchronized arm) for each participant and the weights of the IPTW estimator are simply the inverse of those probabilities; (2) the probability of missing data under MAR and the inverse of those probabilities are used as weights to account for missing values; and (3) the effects of synchronization on blood pressure using reweighted samples. Logit link will be used in both auxiliary modules for the treatment arm and missing data. By controlling for observed confounders and missing data mechanisms through the two auxiliary modules, the main module will provide valid inference about treatment differences in the absence of hidden bias. Statistical significance is set at an alpha of .05 for all analyses.

Results

Funding was provided on May 12, 2017. As of the publication of this paper, patients are being enrolled in the study and

completing follow-up visits in the pharmacy. Also, as of the publication of this paper, investigators are collecting prescription data provided by the pharmacy for all participants in the study. Data collection and analysis will be completed by May 2019.

The medication synchronization service will be delivered as described in the American Pharmacists Association Foundation's *Pharmacy's Appointment-Based Model Implementation Guidefor Pharmacy Practices* [14]. There are three major components of medication synchronization, which include (1) prescription synchronization, (2) a monthly call to the patient, and (3) scheduled monthly appointments. For the prescription synchronization step, a patient should be assigned a sync day for all medications in the pharmacy. Additionally, the pharmacy may have to facilitate short or long fills, so medications can be synced for the assigned date.

Once a sync day has been assigned, a pharmacy staff member will call the patient at least a week before the sync date. This is to ensure there are no medication changes prior to filling medications and for the pharmacy staff to confirm if there have been any new medications added or medications that have been discontinued. Once the patient comes to pick up medications that have been synced, the pharmacist will briefly counsel the patient.

The monthly appointments are times when patients will come in to retrieve their prescriptions. This is also a time the pharmacist can provide some education to the patient on blood pressure management. This encounter is not meant to go beyond the usual patient consultation that occurs when a patient picks up a prescription. The intent of this consultation is to provide a focused means of providing patients with education on hypertension and medication use. A brief topic outline described in Table 2 has been developed to facilitate talking points for patients enrolled in the medication synchronization group of the study.

Table 2. Outline of counseling points for medication synchronization cohort.

Month	Pharmacist guide for counseling patients
1	Give American Heart Association sheet, *What is High Blood Pressure?* and discuss basic information about blood pressure: it is a silent disease.
2	Discuss multiple way to control blood pressure, including with diet and medications; discuss lifestyle.
3	Discuss treatment goals. What are my blood pressure targets?
4	How do my blood pressure medications work? Discuss each medication and how they each work.
5	Discuss my lifestyle and how it impacts blood pressure control. Is there one goal I can make to improve blood pressure control?
6	Discuss medication side effects. Review medications again and risks of side effects.
7	Discuss lifestyle and physical activity. What can I do to improve my fitness?
8	Discuss future goal to maintain or improve blood pressure levels.
9	Discuss future goal to maintain or improve blood pressure levels.
10	Discuss future goal to maintain or improve blood pressure levels.

Discussion

Although there are studies that demonstrate medication synchronization has an impact on adherence metrics, there is still need for data to connect it with a clinical measure such as blood pressure. Data generated from this study will provide an association between medication synchronization and blood pressure levels. It will also determine effect size and the appropriate sample size for a future clinical trial of the intervention. Limitations of this study include lack of randomization at the point of entry in the study. Study investigators will use MSMs to overcome self-selection bias.

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Conflicts of Interest

None declared.

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Abbreviations

DBP: diastolic blood pressure
FAME: Federal Study of Adherence to Medications in the Elderly
IPTW: inverse-probability-of-treatment weighted
MAR: missing at random
MSM: marginal structural model
NACDS: National Association of Chain Drug Stores
SBP: systolic blood pressure

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Protocol

Development of a Phone Survey Tool to Measure Respectful Maternity Care During Pregnancy and Childbirth in India: Study Protocol

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Abstract

Background: Respectful maternity care (RMC) is a key barometer of the underlying quality of care women receive during pregnancy and childbirth. Efforts to measure RMC have largely been qualitative, although validated quantitative tools are emerging. Available tools have been limited to the measurement of RMC during childbirth and confined to observational and face-to-face survey modes. Phone surveys are less invasive, low cost, and rapid alternatives to traditional face-to-face methods, yet little is known about their validity and reliability.

Objective: The primary objective of this study was to develop validated face-to-face and phone survey tools for measuring RMC during pregnancy and childbirth for use in India and other low resource settings. The secondary objective was to optimize strategies for improving the delivery of phone surveys for use in measuring RMC.

Methods: To develop face-to-face and phone surveys for measuring RMC, we describe procedures for assessing content, criterion, and construct validity as well as reliability analyses. To optimize the delivery of phone surveys, we outline plans for substudies, which aim to assess the effect of survey modality, and content on survey response, completion, and attrition rates.

Results: Data collection will be carried out in 4 districts of Madhya Pradesh, India, from July 2018 to March 2019.

Conclusions: To our knowledge, this is the first RMC phone survey tool developed for India, which may provide an opportunity for the rapid, routine collection of data essential for improving the quality of care during pregnancy and childbirth. Elsewhere, phone survey tools are emerging; however, efforts to develop these surveys are often not inclusive of rigorous pretesting activities essential for ensuring quality data, including cognitive, reliability, and validity testing. In the absence of these activities, emerging data could overestimate or underestimate the burden of disease and health care practices under assessment. In the context of RMC, poor quality data could have adverse consequences including the *naming and shaming* of providers. By outlining a blueprint of the minimum activities required to generate reliable and valid survey tools, we hope to improve efforts to develop and deploy face-to-face and phone surveys in the health sector.

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KEYWORDS

maternal care; text messages; phone surveys; India

Introduction

Background and Rationale

In 2015, nearly 90% of the estimated 302,000 global maternal deaths occurred in 2 regions: sub-Saharan Africa (201,000) and Southern Asia (66,000) [1]. Although the global number of maternal deaths in 2015 corresponds to an absolute decline in the maternal mortality ratio (MMR) of 44% since 1990, it too masks wide variation within and across countries as nearly 30% of countries assessed globally have not achieved significant declines in MMR [1]. Historically, efforts to achieve reductions in mortality have sought to bolster the frequency and timeliness of health service utilization across the continuum of care, with particular emphasis on pregnancy care and institutional delivery. Although this has led to increases in the overall utilization of care in many settings [2,3], the lack of momentum in realizing declines in maternal mortality raises important questions about the underlying quality of care received during pregnancy and childbirth.

The treatment of women during childbirth has emerged as a key component of overall quality of care. Building off of research on obstetric violence from Latin America, the closely related term *disrespect and abuse* has been used in recent years to describe varying typologies of the mistreatment of women during childbirth [4,5]. Emerging evidence on disrespect and abuse suggests that poor treatment of women during childbirth may be widespread and a barrier to improving maternal health outcomes and continued engagement with the health sector [6].

Ensuing calls to action have framed the mistreatment of women as a violation of human rights and emphasized the right of every woman to respectful maternity care (RMC) [5]. In 2014, the World Health Organization (WHO) issued a statement advocating for the prevention and elimination of disrespect and abuse during facility-based childbirth, stating that “every woman has the right to the highest attainable standard of health, which includes the right to dignified, respectful health care throughout pregnancy and childbirth, as well as the right to be free from violence and discrimination” [7]. In 2016, WHO issued new global guidelines on antenatal care (ANC) during pregnancy [8] as well as standards for improving the quality of maternal and newborn care in health facilities [9] both of which have adopted a human rights–based approach in prioritizing person-centered health and well-being, including the provision and experience of care.

Innovations in the Measurement of Disrespect and Abuse

Increased attention to RMC, coupled with country-level efforts to implement new guidelines for ANC [8], presents a unique opportunity to bolster efforts to measure women’s experiences with facility-based services during pregnancy and childbirth, including disrespect and abuse. To date, efforts to measure disrespect and abuse have largely employed qualitative methods and focused primarily on childbirth at the exclusion of understanding probable linkages with care received during pregnancy. A body of work is emerging, which aims to develop validated quantitative survey tools for the measurement of RMC through direct observation and/or structured face-to-face surveys [10-12]. Findings from a recent systematic review have identified and presented validated instruments for measuring women’s childbirth experiences [11]. Although this study helps to synthesize the state of current tools, including their dimensions, response options, and psychometric properties [13], additional research is needed to refine the optimal content, timing, and location of survey implementation. Furthermore, in light of the intensive resource requirements associated with direct observations and face-to-face surveys, low-cost alternative survey modalities are needed, which could allow for the routine, rapid, and real-time measurement of women’s pregnancy and childbirth experiences, including disrespect and abuse.

Near ubiquitous access to mobile phones globally has catalyzed discourse on the potential of phone surveys for use in the monitoring of population health. Although gender gaps in mobile phone access [14], coupled with uncertain digital literacy, raise important questions about the reliability and validity of phone surveys, they nevertheless may serve as a low-cost, minimally invasive, rapid means of data gathering. In contrast to resource and time-intensive face-to-face surveys, phone surveys offer respondents the option of being interviewed over a personal or shared mobile phone in the privacy of their own home through one of several modalities: Unstructured Supplementary Services Data (USSD), short message service (SMS), interactive voice response (IVR), and computer-assisted telephone interview (CATI) survey modalities [15,16]. In USSD and SMS surveys, respondents answer questions via text message, whereas in IVR surveys, users listen to automated prerecorded voice prompts, which include multiple choice questions and preset answers. The respondent selects the answer by pressing a corresponding number on the keypad or touch-tone phone (eg, “Press 1 for English, 2 for Hindi”). In contrast, CATI surveys employ human interviewers to implement the survey using a script and data capture tool, which could be paper- or software-based [16].

A recent systematic review identified 19 applications of phone surveys in low- and middle-income countries (LMICs) employing varying modalities including 10 CATI, 6 IVR, and 3 SMS surveys [17]. Survey locations have been diverse (South Asia, Latin America, and Africa) and covered a range of topics on health and socioeconomics, including assets, employment, and food security [17]. Participant recruitment has predominately relied on household baseline surveys to collect mobile phone numbers [17]. Less common were alternatives such as Random Digit Dialing (RDD) or phone numbers drawn from mobile network operators [17]. Overall findings from phone surveys conducted to date suggest that the modality of survey implementation is a critical consideration affecting cost, survey metrics (including length and response options), and

quality [17]. CATI surveys, although costlier because of their human resource requirements, resulted in higher response and completion rates [17]. The further implementation through human contact, which permits personalized responses to clarify questions, may additionally translate to improved data quality and lower attrition [17].

In response to calls to improve the standardization of phone survey assessments, research is emerging, which proposes to systematically test the effects of alternative survey modalities on factors influencing cost and key survey metrics, including contact, response, completion, and refusal rates as well as demographic representativeness [18]. Although this body of research is promising, details remain outstanding on the procedures undertaken for validating the survey tools implemented through the phone survey modalities and, in particular, on the assurances that quality criteria are met [13]. Even in instances where validated face-to-face survey tools are utilized as the basis for the phone survey tool, modifications to survey formats, including length and response options and enumerator gender as well as incentives, may be required, which could influence data quality and survey findings. The further influence of the underlying sampling frame from which phone numbers are drawn on data quality and generalizability may also influence findings, particularly in instances where face-to-face population-based surveys are not used to facilitate initial recruitment/participation. Collectively, these factors reiterate the importance of evaluating quality criteria in the development of phone surveys.

In this protocol study, we outline research underway in India to develop validated phone survey tools appropriate for use in the routine measurement of RMC during pregnancy and childbirth in India. Although concurrent efforts are underway as part of the same study to develop phone survey tools for measuring satisfaction and motivation among Accredited Social Health Activists, as well as essential newborn care and infant feeding practices, processes will mirror those proposed for RMC. Study activities will draw from a population-based sample of pregnant and postpartum women with access to mobile phones in 4 districts of Madhya Pradesh (MP). Research activities include substudies on (1) cognitive testing to assess face validity and optimize phone survey tool content; (2) test-retest to determine the reliability of the face-to-face survey modality; and (3) CATI versus face-to-face surveys (intermodal reliability) [13]. To optimize the delivery of phone surveys, we outline plans for analyses exploring the effects of content on survey response, completion, and attrition rates. Research findings are anticipated to result in the development of a valid and reliable phone survey tool for the routine measurement of RMC during pregnancy and childbirth in India.

Methods

Study Setting

Data collection is part of the impact evaluation of Kilkari; an IVR-based maternal messaging program that aims to empower women through improved access to essential health information. Led by the Ministry of Health and Family Welfare (MOHFW) and implemented by BBC Media Action with support from the Bill & Melinda Gates Foundation, United States Agency for International Development, and the Barr Foundation, Kilkari provides weekly stage-based audio messages on topics including birth preparedness, family planning, and maternal and child nutrition directly to the mobile phones of pregnant and postpartum women up to 1 year postpartum. With implementation currently underway in 13 states across India, Kilkari has delivered prerecorded audio content to 8.3 million users in 33 months [19].

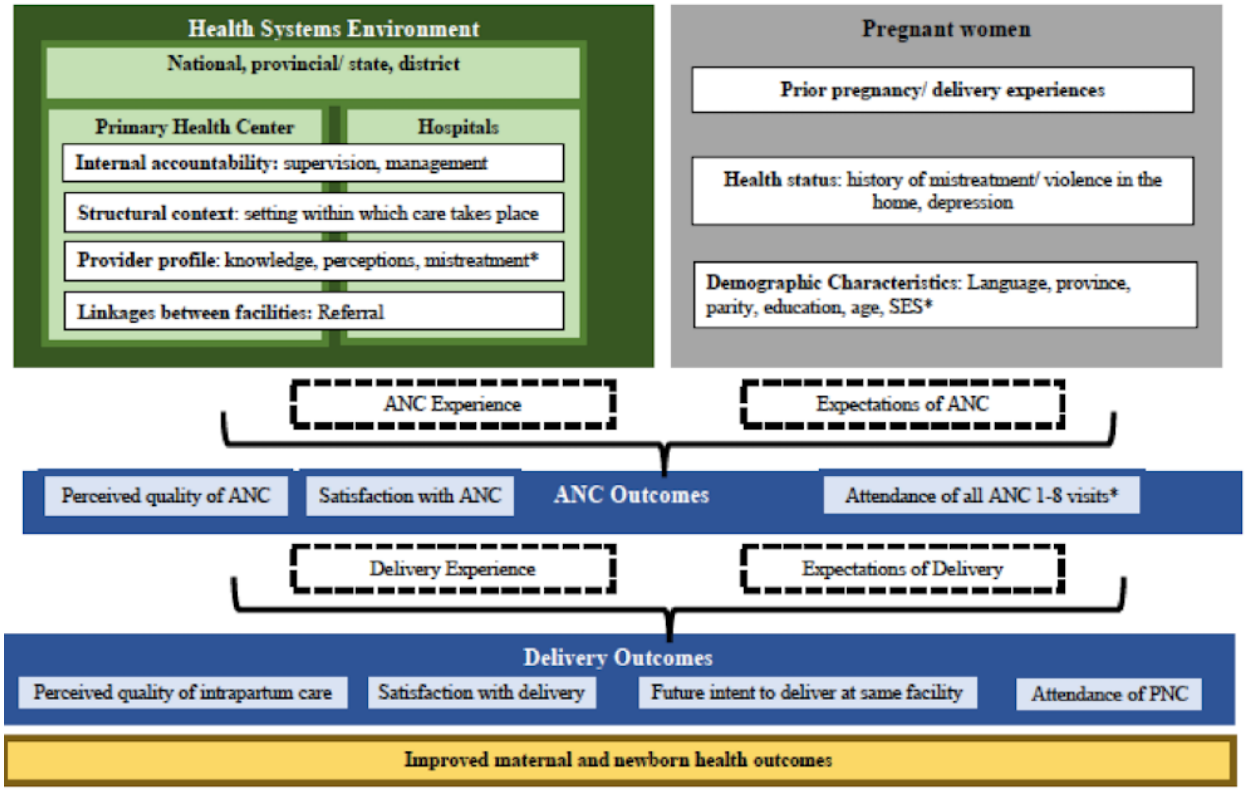
Data collection is occurring in 4 districts (Mandsaur, Hoshangabad, Rewa, and Rajgarh) of MP. MP is located in the geographic heart of India and is home to a population of over 75 million. Among women, an estimated 59% are literate (as compared with 82% of men), 64% have ever attended school, and 29% have access to a mobile phone [3]. In 2015, 53% of pregnant women attended ANC in the first trimester, 36% received the recommended 4 ANC visits, 81% delivered in a health facility, 78% had births attended by a skilled provider, and 18% received a postnatal health check within 2 days following birth [3]. Data on differentials in health outcomes and/or utilization of health services among those with and without access to mobile phones are not available.

Across all 4 districts in MP, data collection is occurring among a subsample of pregnant and postpartum women identified as part of a household listing exercise. During the household listing, all women of reproductive age with access to a mobile phone are identified. Women who are 4 to 7 months pregnant as well as those with a reported pregnancy outcome in preceding 1 to 4 months are then interviewed as part of the pregnant and postpartum women's surveys.

Measuring Respectful Maternity Care

Freedman and Kruk define disrespect and abuse during childbirth as "interactions or facility conditions that local consensus deems to be humiliating or undignified, and those interactions or conditions that are experienced as or intended to be humiliating or undignified" [20]. Building off of this definition and a 2010 landscape analysis by Bowser and Hill [21], Bohren et al outlined 7 categories of disrespectful and abusive care during childbirth: (1) physical abuse; (2) sexual abuse; (3) verbal abuse; (4) stigma and discrimination; (5) failure to meet professional standards of care; (6) poor rapport between women and providers; and (7) health system conditions and constraints [6]. These categories were subsequently conceptualized in 2 dimensions: (1) intentional use of violence, including physical abuse, verbal abuse, and negligent withholding of care and (2) structural disrespect, which stems from "deviations from accepted standards for infrastructure, staffing, equipment availability, and supplies needed to deliver care, as well as in unnecessary interventions, demands for illegal payments, and the detainment of people in facilities until they have paid their bills" [22].

Figure 1. Conceptual framework for measuring respectful maternity care (RMC).



In this protocol study, we focus on the measurement of each of these major typologies of disrespect and abuse along with the underlying contextual factors that underpin them. Figure 1 outlines a conceptual framework for measuring RMC during pregnancy and intrapartum care, which brings together traditional approaches to measuring quality of care [9,23-27] with frameworks for assessing mistreatment of care during childbirth [28]. Viewing mistreatment through the lens of one perspective (eg, intrapartum women) at a single time point (eg, childbirth), although important, may nevertheless provide a limited view of the larger context within which treatment occurs and the risk factors underpinning it. This framework aims to illustrate that maternal health outcomes stem from the interaction of beneficiaries with providers in a complex and evolving community and health systems context through multiple points of contact in different facilities starting with ANC in primary health centers. We posit that women's interactions with the larger health systems' environment help to formulate their care experience and expectations, and ultimately outcomes, including utilization of services and perceptions of quality and satisfaction.

Multimedia Appendix 1 summarizes questions by RMC typology and domain for the proposed measurement of RMC during childbirth. Table 1 summarizes the number of questions by RMC domain for each of the survey planned and compares these against alternatives in the literature. In contrast to approaches in Kenya, Bihar, and Ethiopia, we distinguish questions in MP according to whether they aim to estimate the prevalence of a particular domain or rather users' satisfaction with an aspect of care received. This distinction is important given its implications on the response options required (eg, Likert scales versus binary or categorical) and their associated implications for analyses. Measurement of RMC will occur through 2 modalities: (1) face-to-face survey and (2) phone surveys. Face-to-face surveys will be carried out on 2 populations as part of a larger baseline evaluation of Kilkari: (1) women who are 5 to 7 months pregnant and (2) women with a birth outcome in the preceding 1 to 4 months. In addition to RMC, face-to-face surveys include modules on mobile access and literacy, socioeconomic and demographic characteristics, birth history, and experiences with care during pregnancy or childbirth. Face-to-face surveys will be modified following analyses to yield the following phone survey tools: (1) RMC during pregnancy; (2) RMC during childbirth; and (3) essential newborn care and infant feeding.

Table 1. Comparison and summary of total number of questions by respectful maternity care domain for Madhya Pradesh, India, and other respectful maternity care studies identified in the literature.

Domains	Afulani et ala PCMC in Kenya [12]		Bihar India [29]		Sherferaw et al Ethiopia [10]		Madhya Pradesh India			
							Prevalence module		Satisfaction module	
	No.	Response options	No.	Response options	No.	Response options	No.	Response options	No.	Response options
Physical or sexual abuse										
Use of force	1	Likert scale 1-5	3	Binary; Categorical	2	Likert scale 1-5	2	Binary, Categorical	—	—
Physical restraint	__[a]	—	—	—	—	—	—	—	—	—
Verbal Abuse										
Harsh or rude language	1	Likert scale 1-5	2	Binary; Categorical	3	Likert scale 1-5	2	Binary, Categorical	—	—
Threats and blaming	—	—	—	—	—	—	—	—	—	—
Judgmental or accusatory comments	—	—	1	Categorical	—	—	—	—	—	—
Stigma and discrimination										
Discrimination	1	Likert scale 1-5	1	Categorical	4	Likert scale 1-5	2	Categorical	—	—
Failure to meet professional standards of care										
Refusal to provide pain relief	2	Likert scale 1-5	—	—	1	Likert scale 1-5	—	—	1	Likert scale 1-6
Lack of informed consent process	4	Likert scale 1-5	1	Categorical	3	Likert scale 1-5	3	Binary, Categorical	2	Likert scale 1-6
Breaches of confidentiality	2	Likert scale 1-5	1	Binary	1	Likert scale 1-5	1	Binary		
Neglect, abandonment, or long delays	1	Likert scale 1-5	2	Binary; Categorical	3	Likert scale 1-5	2	Binary, Categorical	—	—
Skilled attendant absent at time of delivery	—	—	—	—	—	—	—	—	—	—
Painful vaginal exams	—	—	—	—	—	—	—	—	—	—
Poor rapport between women and providers										
Poor communication	6	Likert scale 1-5	1 question 9 subcategories	Binary	4	Likert scale 1-5	1	Binary	2	Likert scale 1-6
Language and interpretation issues	1	Likert scale 1-5	—		1	Likert scale 1-5	—	—	—	—
Lack of supportive care from health workers	6	Likert scale 1-5	1	Likert scale 1-5	9	Likert scale 1-5	1	Binary	1	Likert scale 1-6
Trust	2	Likert scale 1-5	—	—	—	—	—	—	—	—
Denial or lack of birth companions during labor and delivery	2	Likert scale 1-5	2	Binary, Categorical	1	Likert scale 1-5	4	Binary, Categorical	—	—
Lack of respect for women's preferred birth positions/ freedom of movement	—	—	3	Binary	1	Likert scale 1-5	2	Binary	—	—

Domains	Afulani et ala PCMC in Kenya [12]		Bihar India [29]		Sherferaw et al Ethiopia [10]		Madhya Pradesh India			
							Prevalence module		Satisfaction module	
	No.	Response options	No.	Response options	No.	Response options	No.	Response options	No.	Response options
Denial of safe traditional practices	—	—	—	—	1	Likert scale 1-5	—	—	—	—
Detainment in facilities	1	Likert scale 1-5	2	Binary, Continuous			2	Binary, Continuous	—	—
Objectification of women	—	—	—	—	—	—	—	—	—	—
Health system conditions and constraints										
Lack of privacy	1	Likert scale 1-5	1	Binary	2	Likert scale 1-5	1	Binary	—	—
Bribery and extortion	1	Likert scale 1-5	—	—	1	Likert scale 1-5	1	Binary	—	—
Safety	1	Likert scale 1-5	—	—	—	—	—	—	—	—
Physical condition of facilities	4	Likert scale 1-5	—	—	—	—	2	Binary	1	Likert scale 1-6
Staffing shortages/constraints	1	Likert scale 1-5	—	—	—	—	—	—	—	—
Supply constraints	—	—	—	—	—	—	—	—	—	—
Lack of redress	—	—	—	—	—	—	—	—	—	—
Unclear fee structures	—	—	—	—	—	—	—	—	—	—
Unreasonable requests of women by health workers	—	—	—	—	—	—	—	—	—	—
Other questions	—	—	2	Likert scale 1-5	—	—	—	—	3	Likert Scale 1-6
Total	38	—	20	—	37	—	26	—	10	—

[a]Question not included.

Phase 1. Scale and Survey Development

Figure 2 outlines proposed processes for validity and reliability testing, whereas Table 2 and Multimedia Appendix 2 summarize survey substudies and validity/reliability tests, respectively. Building off of a strong foundation of existing validated instruments [12], project activities will commence with a literature review from which survey tools will be developed for RMC measurement during pregnancy and childbirth, including scales for measuring satisfaction and prevalence [11]. Item generation for each scale was drawn from concurrent activities underway in Bihar by Rao et al [29] to measure RMC during childbirth through direct observations, exit interviews, and follow-up household interviews during the postpartum period. Indicators from the above listed and other validated survey tools elsewhere in the literature [12] were used in the MP survey tools to allow for cross-site comparison. Once consensus was achieved, items were translated into Hindi and checked by BBC Media Action and MOHFW personnel in Delhi for accessibility, appropriateness of language, tone, and engagingness. Cognitive testing followed in study districts in MP to ensure that survey questions are understandable, appropriate in language and tone, and the words interpreted as intended by varying respondent types.

Figure 2. Processes for reliability testing.

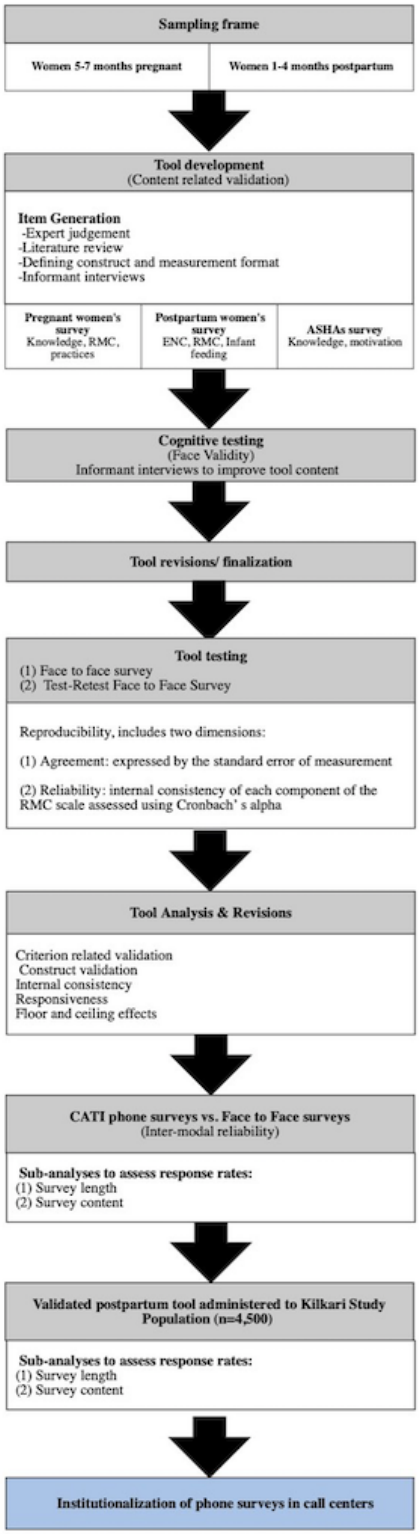


Table 2. Summary description of survey substudies.

Substudy	Objective	Survey activities
Prevalence and scale testing	To determine the prevalence of different typologies of disrespect and abuse	Prevalence surveys in 2 districts of MP, India: RMC[a] during pregnancy and RMC during childbirth
Reproducibility	To determine the degree to which repeated measurements in stable persons (test-retest) provide similar answers	Test-retest: Face-to-face survey repeated within 14 days
Survey modality	To assess intermodal reliability	Face-to-face survey first, CATI[b] survey up to 14 days later
Phone survey length and content	To determine the effect of survey length and content on response, completion, and attrition rates	CATI phone surveys: RMC pregnancy phone survey vs RMC childbirth phone survey; Postpartum phone survey
Interrater reliability	To compare demographic characteristics of respondents in larger sampling frame vs those that complete, partially complete, and do not respond to phone surveys	Characteristics of face-to-face survey respondents versus CATI phone survey respondents

[a]RMC: respectful maternity care.

[b]CATI: computer-assisted telephone interview.

Phase 2. Survey Testing and Refinement

Substudy 1: Respectful Maternity Care Scale Testing

Table 3 summarizes the sample size requirements for each substudy. Face-to-face surveys will be conducted to refine the scale and determine the prevalence of different typologies of disrespect and abuse in 4 districts of rural MP. Among pregnant women, a module on RMC during ANC will be integrated into a planned household survey among 5000 women who are 5 to 7 months pregnant. This is sufficient to measure the RMC indicator of reported verbal abuse (assumed 5% prevalence) during pregnancy with 80% power, alpha of .05, and precision of 1%. To measure RMC during childbirth, a total of 880 women with a birth outcome in the preceding 1 to 4 months will be interviewed. This sample size was designed to accommodate survey mode testing described in Phase 3 and is sufficient to additionally measure the prevalence of the RMC indicator of reported verbal abuse (assumed 10% prevalence) during childbirth with 80% power, alpha of .05, and precision of 2%.

Once data are collected, analyses will principally aim to determine the validity of the scale using psychometric analyses (Figure 2). *Criterion-related validity* will be assessed by testing the hypothesis that scale is correlated to measures of reported satisfaction additionally collected as part of the face-to-face survey tool [12,13]. We propose testing this by regressing the main RMC scale and subscales on women's ratings of their satisfaction with the services and whether they would deliver in the same facility if they were to have another baby [12]. *Construct validity* measures how well the items represent the underlying conceptual structure [13] and will be assessed using factor analysis and the Pearson correlation coefficient between the components. *Reliability analyses* will aim to determine the stability and consistency of results [13]. A Cronbach alpha of .7 or higher is proposed as the cutoff for determining sufficient evidence of reliability [13]. Additional analyses related to the internal consistency of the scale as well as the presence of floor and ceiling effects will be conducted and overall findings on validity and reliability summarized [13].

Substudy 2: Reproducibility

To assess reproducibility, a random subsample of pregnant and postpartum women interviewed as part of substudy 1 will be administered a repeat face-to-face survey between 1 and 2 weeks after the initial survey. This substudy will be conducted to determine the degree to which repeated measurements in women interviewed (test-retest) provide similar answers. Assuming a kappa of 0.80, a margin of error of 0.05, an alpha of .05, and the proportion of positive responses of 0.35 for rater 1 and 0.40 for rater 2, 146 participants who have completed the survey are required. Adjusting for a 15% loss to follow-up/refusal between the first and second women's surveys will require a sample size of 168 women to be interviewed twice. Data will be analyzed for agreement between survey rounds and reliability will be tested using Cohen kappa. The kappa will be adjusted for prevalence and bias, providing Prevalence and Bias Adjusted Kappa.

Phase 3. Phone Survey Reliability and Delivery Optimization

Substudy 3: Survey Mode Testing

Phone survey mode testing will aim to determine the intermodal reliability of face-to-face versus CATI surveys for both the RMC pregnancy and childbirth surveys. Assuming a kappa of 0.80, a margin of error of 0.05, an alpha of .05, and the proportion of positive responses of 0.35 for rater 1 and 0.40 for rater 2, 146 participants who have completed each survey are required. Adjusting for loss to follow-up between the face-to-face women's survey and the following mobile phone survey, 880 women with a birth outcome in the preceding 1 to 4 months will be interviewed face to face. Within 4 weeks of the initial interview, a random sample of those completing the face-to-face interview who consent to be called for the follow-up phone survey will be contacted. Assuming a 20% response rate, 880 women will be contacted as part of the phone survey to yield the 146 completed face-to-face and phone survey interviews. Only women with access to a mobile phone, aged 18 years or older, and who have had a birth outcome in the preceding 1 to 4 months and are identified in the study districts will be interviewed.

Table 3. The number of participants needed by substudy.

Substudy	Study arms	Participants who completed the survey per arm	Total sample size[a]
ANC[b] recipients			
Substudy 1: Face-to-face survey of RMC[c] during ANC	1	400	400
Substudy 2. Reproducibility (test-retest)	1	168	168
Substudy 3: Phone survey (intermodal reliability)	1	146	292
Substudy 4: Interrater reliability	Secondary analysis		
Intrapartum			
Substudy 1: Face-to-face survey of RMC during childbirth	1	400	400
Substudy 2: Reproducibility (test-retest)	1	168	168
Substudy 3: Survey mode testing	2	146	292
Substudy 4: Phone survey length and content	2	294	4500
Substudy 4: Interrater reliability	Secondary analysis		

[a]The total sample size reflects the sum of the sample across all study arms.

[b]ANC: antenatal care.

[c]RMC: respectful maternity care.

Substudy 4: Subanalyses to Optimize Phone Survey Delivery

Phone Survey Content and Length

Survey content refers to 2 components of the phone survey: (1) topical area covered and (2) response options and question framing. We will assess the effects on survey content and length (number of questions) of response, completion, and attrition rates using Kaplan-Meier curves to plot survey attrition by time spent for each survey implemented across key populations. This will include comparisons across RMC surveys administered to pregnant and postpartum women. Assuming a baseline survey completion percentage of 20% to detect an absolute 10% difference in survey completion between 2 study arms at an alpha of .05 and power of 80%, it is calculated that 294 individuals who have completed the survey will be needed per study arm. With a completion percentage of 20%, we estimate that 1470 participants would be required. To attain this sample size, the phone survey tool validated in substudy 3 will be applied to the population of 4500 women enrolled in the Kilkari impact evaluation in 4 districts of MP.

Interrater Reliability

This subanalysis aims to compare the demographic characteristics of respondents in the larger sampling frame versus those who complete, partially complete, and do not respond to phone surveys. Additional data points, including caste, education, and socioeconomic status, collected during the face-to-face household listing and baseline survey will be juxtaposed against CATI phone survey data.

Data Management

All data collected will remain in India and will be managed by the India-based research partner. Tablets used for data collection will be password protected. Any adverse events mentioned to the research team during data collection will be brought to the immediate attention of senior project investigators and Institutional Review Boards at Johns Hopkins School of Public Health and in India at Sigma Research and Consulting in New Delhi. Once collected, all data will be deidentified following the merging of data sets as required reliability analyses.

Ethics Approval

Ethical approval for research activities in India has been obtained from Johns Hopkins School of Public Health's Institutional Review Board in Baltimore, Maryland, United States, and from Sigma Research and Consulting in New Delhi, India.

Results

Data collection in India is anticipated to start in July and span through March 2019. Data analyses and report writing will be completed by mid 2019.

Discussion

Study Implications

Limited evidence exists on the feasibility of utilizing phone surveys in LMICs for the surveillance of population-level health [17], and no studies to date have been conducted that utilize phone surveys to assess the quality of women's experiences with care during pregnancy or childbirth in India. Increasing access to mobile phones, particularly in India where a large proportion of maternal and child deaths occur globally, raises the potential for phone surveys to be used in the routine measurement of key health outcomes. Despite their immense potential, the validity and reliability of phone surveys for RMC as compared with traditional face-to-face or direct observations has yet to be determined.

This protocol study aims to catalyze discourse on quality criteria for phone survey validation, which may in part be driven by the

survey objectives, the available sampling frame, budget for primary data collection, and context within which data collection is occurring. In many contexts, face-to-face surveys are the starting point for participant recruitment in phone surveys. However, examples of large population-level surveys, which rely on RDD, are emerging [18]. In this protocol study, we consider a sampling frame drawn from population-based recruitment through a face-to-face survey. However, in India, a number of mobile health initiatives, including national-level phone surveys conducted through the Maternal Child Tracking Center call center, draw participants from the phone numbers collected as part of routine health information systems. In light of this, potential future applications at scale of the phone survey tools validated in this study may adopt an RDD approach. Although the population-based recruitment is likely to yield greater population-level representativeness, the sample will still be constrained to women with regular access to a mobile phone. In India, the associated likelihood of selection bias is immense because of differentials in mobile phone access, literacy, and numeracy. Separate analyses planned as part of the Kilkari Impact Evaluation on the intersectionality of ethnicity; gender; education; and phone access, ownership, and use may help to shed light on these differences.

Rethinking Approaches to Measuring Respectful Maternity Care

To develop validated survey tools, we first conduct a test-retest analysis drawing from survey data collected face-to-face and then conduct interim analyses to refine the tool before administering it over the phone and assessing intermodal reliability. Elsewhere, RMC tools have been developed through direct observations and follow-up face-to-face interviews [30]. Although the direct observations of delivery led to the identification of additional forms of mistreatment, including privacy violations and the failure to ask for consent during vaginal exams [30], they too are not impervious to observer bias in addition to being resource- and time-intensive. In contexts where face-to-face survey tools have been implemented, differences in the typologies of mistreatment have been reported based on the postpartum timing and locale of survey implementation. Findings from a prevalence survey conducted among 1914 women receiving care from a large referral hospital in Dar es Salaam found that 15% of women reported experiencing at least 1 instance of disrespect and abuse during postpartum interviews—a figure that rose to 70% during community follow-up interviews [31]. In this study, we draw from the scale used by Rao et al [29] with the broader aim of allowing for later comparisons with observations and face-to-face survey data collected in Bihar. Although there are contextual differences between MP and Bihar, this may nevertheless allow for additional comparisons to be made.

As part of efforts to validate the survey mode, we have sought to juxtapose face-to-face survey options against CATI surveys. The implementation of CATI surveys is anticipated to differ based on interviewer cadres and available software. In this study, phone surveys will be administered by graduate students identified and supervised by the National Health Systems Resource Centre using tablets containing CAPI survey tools. Future implementation of these surveys once validated is likely to be carried out through national- and/or state-level call centers that may have enumerators with lower levels of education. Care will thus need to be taken to ensure that the tools developed can be easily adopted and administered by enumerators with differing characteristics.

To improve response rates, we have proposed substudies, which aim to optimize phone survey delivery. Limits in resource constraints and the available sample size have meant that we are not testing the effects of introductory language *calls to action* or the incentives (amount, timing, and structure), all of which have been shown to effect response rates. Similarly, we are limited in our ability to assess the effects of the timing of the RMC survey implementation (eg, receiving the survey call immediately after discharge from facility versus several days or weeks later), a factor that may impact response rates and has been shown to influence the reported typologies of disrespect and abuse [31]. In this study, the measurement of RMC during childbirth will occur 1 to 4 months following delivery and thus outside of the health facility environment. Although comparisons of phone survey data from MP, India, will be made for certain items with face-to-face and direct observation data collected in Bihar, differences in the study contexts and populations will limit scope of and conclusions drawn from these analyses.

Conclusions

This protocol study outlines the proposed strategy for generating validated phone survey tools for the routine, low cost, and rapid measurement of RMC during pregnancy and childbirth in India. Study findings are anticipated to provide a blueprint for the development and validation of phone surveys for the routine measurement of service delivery outcomes in low resource settings.

Acknowledgments

The authors wish to thank Drs Krishna Rao and Nicole Warren for providing access to their data collection tools for RMC measurement in Bihar. These tools provided a strong foundation for our work and were modified both in terms of content and language for application and further testing in MP and over the phone. This work was funded by the Bill and Melinda Gates Foundation.

Authors' Contributions

AEL is the overall project PI, conceived the idea for this stream of research, and wrote the first draft of this manuscript. AEL and SC wrote the first draft of the study tools with inputs from DM, AB, and KS. KS is leading cognitive testing activities and inputted into the content of all questions. DM advised on survey and study design, sampling and proposed analyses. NS, AB, and RV are

overseeing the recruitment and training of enumerators and data collection activities with inputs from ALe and DM. AL inputted into the study design and proposed activities. All authors provided feedback during various iterations of the manuscript draft and approved the final version.

Conflicts of Interest

Sara Chamberlain is employed by BBC Media Action and involved in the implementation of Kilkari. Data from this study were drawn from baseline surveys implemented as part of the external evaluation of Kilkari. Diva Dhar is an employee of the Bill and Melinda Gates Foundation who is providing funding for all data collected as part of this study. No other conflicts of interest are declared. The corresponding author had full access to the data and assumed final responsibility for the decision to publish.

Multimedia Appendix 1

Draft survey questions for measuring respectful maternity care (RMC) during childbirth in India (face-to-face).

[PDF File (Adobe PDF File), 108KB - resprot_v8i4e12173_app1.pdf]

Multimedia Appendix 2

Summary of validity and reliability assessments by survey tool.

[PDF File (Adobe PDF File), 52KB - resprot_v8i4e12173_app2.pdf]

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Abbreviations

ANC: antenatal care
CATI: computer-assisted telephone interview
IVR: interactive voice response
LMIC: low- and middle-income country
MMR: maternal mortality ratio
MOHFW: Ministry of Health and Family Welfare
MP: Madhya Pradesh
RDD: Random Digit Dialing
RMC: respectful maternity care
SMS: short message service
USSD: Unstructured Supplementary Services Data
WHO: World Health Organization

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Protocol

Introducing a New Algorithm for Classification of Etiology in Studies on Pediatric Pneumonia: Protocol for the Trial of Respiratory Infections in Children for Enhanced Diagnostics Study

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Abstract

Background: There is a need to better distinguish viral infections from antibiotic-requiring bacterial infections in children presenting with clinical community-acquired pneumonia (CAP) to assist health care workers in decision making and to improve the rational use of antibiotics.

Objective: The overall aim of the Trial of Respiratory infections in children for ENhanced Diagnostics (TREND) study is to improve the differential diagnosis of bacterial and viral etiologies in children aged below 5 years with clinical CAP, by evaluating myxovirus resistance protein A (MxA) as a biomarker for viral CAP and by evaluating an existing (multianalyte point-of-care antigen detection test system [mariPOC respi] ArcDia International Oy Ltd.) and a potential future point-of-care test for respiratory pathogens.

Methods: Children aged 1 to 59 months with clinical CAP as well as healthy, hospital-based, asymptomatic controls will be included at a pediatric emergency hospital in Stockholm, Sweden. Blood (analyzed for MxA and C-reactive protein) and nasopharyngeal samples (analyzed with real-time polymerase chain reaction as the gold standard and antigen-based mariPOC respi test as well as saved for future analyses of a novel recombinase polymerase amplification–based point-of-care test for respiratory pathogens) will be collected. A newly developed algorithm for the classification of CAP etiology will be used as the reference standard.

Results: A pilot study was performed from June to August 2017. The enrollment of study subjects started in November 2017. Results are expected by the end of 2019.

Conclusions: The findings from the TREND study can be an important step to improve the management of children with clinical CAP.

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KEYWORDS

pneumonia; child, preschool; respiratory tract infections; microbiological techniques; diagnostic tests, routine

Introduction

Biomarkers in Pediatric Respiratory Tract Infections

Respiratory infection is a common reason among children for seeking care [1]. The majority of respiratory infections in children are caused by viruses [2]. Nevertheless, viral and bacterial infections are hard to distinguish clinically, causing many children with viral infections or self-limiting bacterial infections to receive unnecessary antibiotic treatment, which contributes to the development and spread of antibiotic resistance [3,4]. There is a need for new biomarkers that better distinguish viral infections from antibiotic-requiring bacterial infections in children presenting with clinical community-acquired pneumonia (CAP) and that assist health care workers in decision making and improving the rational use of antibiotics [5].

C-reactive protein (CRP), procalcitonin (PCT), and white blood cell (WBC) count are the most commonly used inflammatory markers in clinical practice for the management of children with suspected CAP [6,7]. There is increasing evidence that PCT is superior to CRP as a screening test for serious bacterial infection given the favorable kinetics, including a more rapid response to inflammation [8]. However, neither of the biomarkers have been proven to be reliable in differentiating between mild or moderate bacterial and viral CAP [9,10]. A WBC count of 15,000/µl has been suggested as a cutoff to differentiate between viral and bacterial etiologies. However, critically ill patients with neutropenia will not have an increased WBC count, and certain viruses such as influenza and adenovirus can elicit a strong immune response with a high WBC count greater than 15,000/µl [11]. Neither is a complete blood count reliable in differentiating between bacterial and viral CAP in children [6]. To date, most biomarkers used in clinical practice have been selected for their ability to identify serious bacterial infections, and there is a need for novel biomarkers that can reliably detect *viral* infections [12].

Myxovirus resistance protein A (MxA) is an intracellular protein that is upregulated upon activation of the antiviral defense system. Increased blood MxA has been reported to be specific for viral infection [13-15]. There is a commercially available rapid diagnostic test, FebriDx, that qualitatively detects MxA and CRP at cutoffs of 40 ng/ml and 20 mg/ml, respectively. The test has been reported to have 85% (29/34) sensitivity and 93.4% (183/196) specificity to rule out a bacterial infection in patients (adults and children) with febrile respiratory infection [16]. However, no studies have focused on MxA in children with CAP. It was previously shown that virus-positive asymptomatic children had lower MxA levels as compared with virus-positive symptomatic children with respiratory symptoms [14]. As current viral real-time polymerase chain reaction (PCR) testing of upper respiratory specimens (ie, the routine method for diagnosing respiratory tract infections) is complicated by frequent asymptomatic detection, MxA has the potential to facilitate the interpretation of viral PCR positivity in terms of clinical relevance in children with CAP [17].

Etiology of Childhood Community-Acquired Pneumonia

Defining etiology in childhood CAP is complex [18]. Until recently, our conception of CAP etiology has largely relied on early lung-aspirate studies from the 1970s to 1980s [19]. Vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* type B, the 2 major causative agents in childhood CAP, has been introduced in most parts of the world during the last two decades, coinciding with a global decrease in childhood CAP mortality [20]. This has also contributed to a shift in the etiology of CAP [21,22]. Other important factors include a globally improved socioeconomic and nutritional status, a sharp decrease in the incidence of measles, and the emergence of HIV [5]. Recently, new CAP etiology studies, including the large-scale Pneumonia Etiology Research for Child Health (PERCH) study, have been conducted, mostly with a low-income country focus [21-24]. These have pointed toward an underestimation of viral and mixed viral-bacterial etiologies, which is likely explained by the aforementioned shift in etiology but also by the recent advances in viral diagnostics [25]. Moreover, *Bordetella pertussis* and *Bordetella parapertussis*, the causative agents of whooping cough, have been associated with CAP [21,26]. These bacteria are highly contagious and can cause severe disease, particularly in infants [27]. Recent studies have reported an increasing incidence of *B pertussis*, and there have been several deaths in previously healthy infants associated with whooping cough in Sweden over the last 10 years [28,29]. Consequently, there is a need for new updated studies on CAP etiology in various settings.

A Need for Rapid Microbiological Point-of-Care Tests

Current treatment options with antivirals for respiratory viruses are limited. However, there are several new antivirals that are being developed [30], and furthermore, there is a value in diagnosing viral infections to predict the clinical course and infectivity and to give confidence to withhold the prescription of antibiotics. Real-time PCR is a sensitive molecular-based method that is currently considered gold standard for the detection of respiratory viruses in children with respiratory tract infection [25]. Nevertheless, as PCR usually has to be run in central laboratories and requires complex instrumentation, the

turnaround time can be long and the test results are rarely used for decision making regarding treatment at the point of care. There are currently several new antigen-based point-of-care tests for respiratory infections on the market. One is the multianalyte point-of-care antigen detection test system (mariPOC) respi, ArcDia International Oy Ltd, that uses a 2-photon excitation assay technique to detect 10 different respiratory viruses (influenza A/B, respiratory syncytial virus [RSV], adenovirus, bocavirus, coronavirus, human metapneumovirus [hMPV], and parainfluenza virus [PIV] 1-3) [31]. The advantage of the test is that it gives a preliminary result of strongly positive samples already after 20 min and a final result (including negative results) within 2 hours, which potentially allows for immediate treatment considerations. In children, the mariPOC respi's sensitivity for RSV and influenza virus has been reported to be as high as 90% as compared with PCR, but the sensitivity for less common respiratory viruses, such as hMPV and PIV, and the newly included coronavirus and bocavirus has been insufficiently investigated [32,33].

Recombinase polymerase amplification (RPA) is a nucleic acid amplification technique that does not require thermal cycling. An RPA-based point-of-care test could combine the advantage of high sensitivity with short turnaround time. An RPA-based test using a paper-based vertical flow microarray technique is currently being developed by our partners at the Science for Life Laboratory (SciLifeLab) [34-37]. As the test reaction is carried out at room temperature, it is an interesting method for resource-limited settings where the need for new diagnostic tests is particularly high [38,39].

Long-Term Complications of Community-Acquired Pneumonia

Studies on the long-term outcomes of radiologically confirmed bacterial CAP have indicated that the disease is associated with later development of asthma and decreased lung function [40,41]. However, most of these studies have followed children who were born more than two decades ago, and the risk might therefore not generalize to a modern setting, given the reported shift in etiology of pediatric CAP [42]. Hence, there is a need for new studies of long-term complications from pediatric CAP, such as the development of asthma and the risk for future respiratory infections.

In summary, there is a need for (1) assessing the diagnostic accuracy of MxA as a biomarker for viral childhood CAP; (2) new studies on clinical CAP etiology in children; (3) evaluating the antigen-based point-of-care test mariPOC; (4) evaluating a novel RPA-based point-of-care test developed at SciLifeLab; and (V) assessing long-term complications from CAP, including the risk of developing asthma and the risk for future respiratory infections.

The overarching aim of the Trial of Respiratory infections in children for ENhanced Diagnostics (TREND) study is to improve the differential diagnosis of bacterial and viral etiologies in children aged below 5 years with clinical CAP. The specific objectives of the study are as follows:

- the diagnostic accuracy of MxA for viral CAP in children
- etiology of children with CAP
- sensitivity and specificity for the mariPOC respi test for the detection of respiratory viruses
- sensitivity and specificity for a novel RPA-based point-of-care test for the detection of respiratory viruses
- long-term complications in children with CAP.

Methods

Study Site and Design

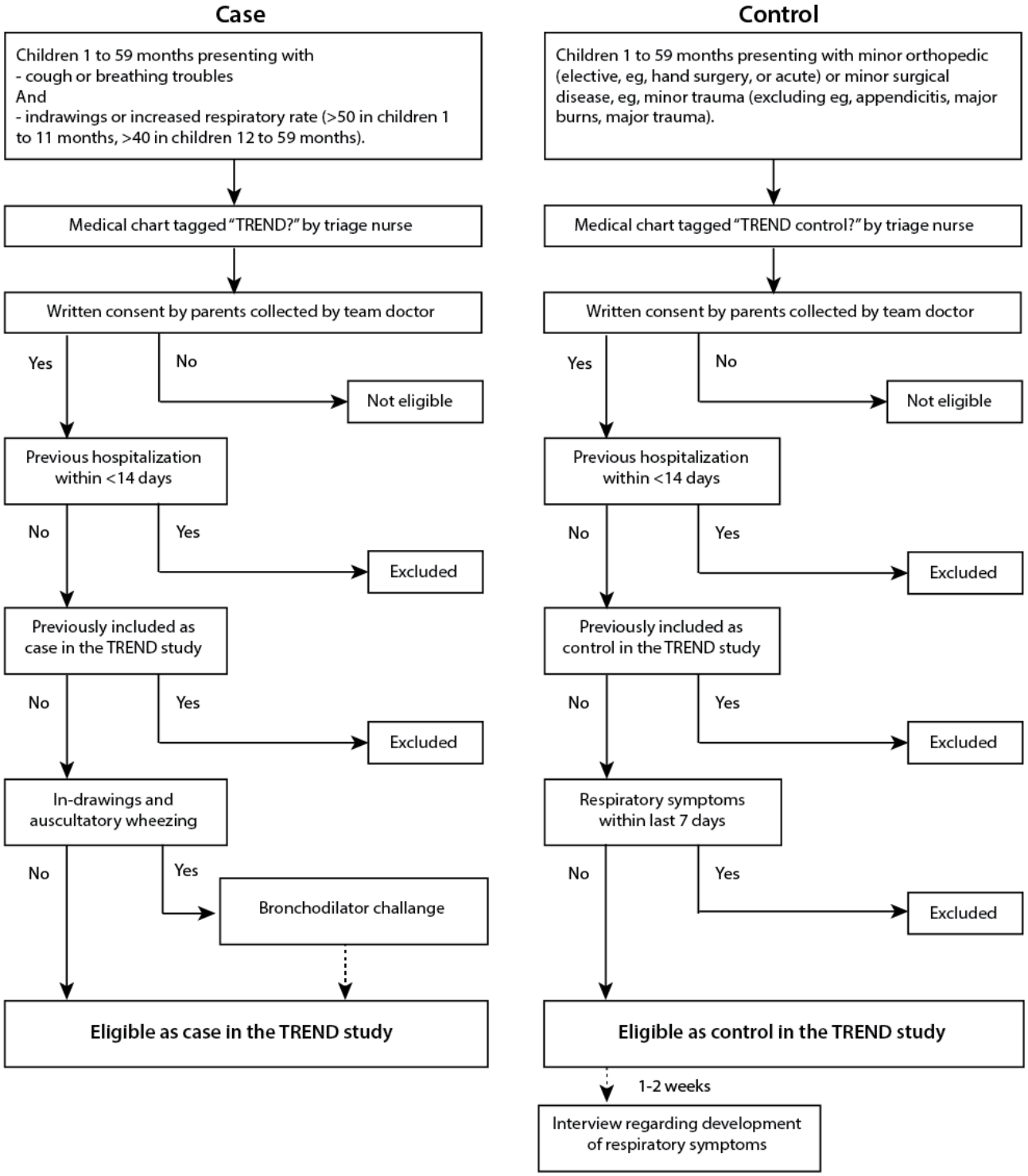
The TREND study is a hospital-based, prospective observational study of children with clinical CAP and asymptomatic controls. The study will take place at Sachs' Children and Youth Hospital, Stockholm, which has one of the largest pediatric emergency departments in Sweden with over 30,000 visits each year. The study is planned to be conducted from November 2017 to December 2019. The study is registered at clinicaltrials.gov (ID: NCT03233516) July 28, 2017.

Study Participants

Case Definition

Children aged 1 to 59 months with clinical CAP (both severe and nonsevere) according to the World Health Organization (WHO) criteria are enrolled as cases (Figure 1). The inclusion criteria (all inclusion criteria to be met to be eligible for participation in the study) are as follows: age 1 to 59 months, reported or observed breathing troubles/coughing, observed age-adjusted tachypnea (≥50 breaths/min in children aged 1-12 months, ≥40/min in children aged >1 year) or chest indrawing, and written informed consent. The exclusion criteria are as follows: previously included as a case in the study or hospitalized during the previous 14 days. Inhalation with a rapid-acting bronchodilator (≥1 dose in children aged <2 years and ≥3 doses in children aged 2-4 years) will be administered to children with wheezing and chest indrawing to improve the specificity of the WHO clinical CAP criteria, as suggested by the PERCH study team [43]. Resolved chest indrawing after bronchodilator challenge will be recorded but not considered as an exclusion criterion to be able to exclude these patients in a subanalysis as well as to analyze these patients separately.

Figure 1. Algorithm for screening and enrollment of study subjects in the Trial of Respiratory infections in children for ENhanced Diagnostics (TREND) study.



Control Definition

Children aged 1 to 59 months treated for a minor orthopedic (elective, eg, hand surgery, or acute) or minor surgical disease, for example, minor trauma (excluding appendicitis, major burns, major trauma, etc) are enrolled as controls. No formal matching will be performed, but age and season will be considered in the analyses. The exclusion criteria are symptoms of respiratory disease 7 days before enrollment, previous inclusion as a control in the study, or hospitalized during the previous 14 days. The guardians of the controls will be contacted by email/telephone 1 to 2 weeks after enrollment to collect information regarding the potential respiratory symptoms developed after discharge. Cases and controls will be included in the emergency unit, and additional controls will also be included in the hand surgery unit of the hospital.

Biological Samples

Capillary blood samples and nasopharyngeal aspirates and swabs will be collected from all study subjects. For the MxA analysis, 20 µl of blood will be collected using a heparinized plastic end-to-end capillary and then immediately diluted in a prefilled

tube containing an in-house buffer [14]. The nasopharyngeal swabs for the mariPOC respi analyses will be diluted in 1.3 ml of a commercial buffer, as advised by the manufacturer ArcDia International Oy Ltd. The nasopharyngeal aspirates for the PCR analyses will be collected in a standardized manner, as has previously been published, but mixed with 1.3 ml of saline to mirror the protocol for the mariPOC respi [17]. All samples will be taken within 24 hours from arrival at the emergency unit, and the time of blood and nasopharynx sampling will be recorded. It will also be noted if antibiotics have been given before sampling. Samples that are not analyzed at the point of care will be stored at −80°C and shipped on dry ice to minimize degradation of the analytes of interest. All samples collected in the study will be stored according to the Swedish act: Biobanks in Medical Care (SFS 2002:297).

Microbiological and Biochemical Analyses

Real-time PCR analysis based on the TaqMan technique will be performed in batches on the nasopharyngeal aspirates at Sahlgrenska University Laboratory, Gothenburg, using previously described methods [44]. The PCR detects the following respiratory agents: influenza A/B, RSV A/B, adenovirus, bocavirus, coronavirus (HKU1, NL63, OC43, and 229E), hMPV, PIV 1-3, rhinovirus, enterovirus, *S pneumoniae*, *H influenzae*, *B pertussis*, and *Mycoplasma pneumoniae*.

mariPOC respi will be performed on the nasopharyngeal swabs directly at the emergency room at Sachs' Children and Youth Hospital at the time of enrollment [32]. The test detects the following respiratory agents: influenza A/B, RSV, adenovirus, bocavirus, coronavirus, hMPV, PIV 1-3, and *S pneumoniae.*

Analyses of MxA will be performed in batches at the Institute of Biomedicine, University of Turku, Finland, using an in-house enzyme immunoassay, as previously described [14].

CRP will be analyzed using the Alere Afinion AS100 Analyzer commercial point-of-care kit at the emergency room at Sachs' Children and Youth Hospital. If multiple CRP tests are performed, the highest value less than 48 hours from arrival at the emergency unit will be recorded [45]. A small amount of blood will be stored to allow future analysis of, for example, PCT if deemed necessary.

Study Variables

Information regarding the study subjects (initials, year and month of birth, sex, date of inclusion, and postal code), number of siblings, days of illness, current symptoms (fever, coughing, runny nose, wheezing, whooping, shortness of breath, hoarseness, sore throat, ear secretion, inability to feed, lethargy, vomiting, and diarrhea), vaccinations, antibiotic treatment, medication, underlying diseases, heredity for asthma, previous hospitalization, recent (last 3 months) trips abroad (if yes, where and for how long), allergies, smoking in the family, recent contact with unwell individuals, breastfeeding, preschool, origin of parents, and socioeconomic status will be collected through a standardized questionnaire based on previous studies [46,47].

Clinical parameters (respiratory rate, consciousness according to the AVPU scale—alert, verbal stimuli, pain stimuli, unresponsive—pulse, peripheral oxygen saturation, weight, body temperature, vomiting, head nodding, central cyanosis, stridor, chest indrawing, nasal flaring, grunting, pedal edema, skin turgor, capillary refill, cool peripheries, and pulmonary auscultatory findings—decreased breath sounds, crackles/crepitations, bronchial breath sounds, and wheezing) and antipyretic medication prescribed within less than 4 hours will be registered by the study doctor responsible for patient screening/enrollment. To avoid overloading the case report form, information about symptoms and danger signs that are rare in a Swedish context (eg, jaundice, bulging fontanelle, rash, gallop rhythm, weak peripheral pulses, and tender liver mass) will be retrospectively collected from the medical records if deemed necessary. Some clinical parameters are routinely recorded multiple times at the emergency unit. In these cases, the most extreme value (highest pulse/respiratory rate/body temperature and lowest peripheral oxygen saturation) during the visit at the emergency unit enrollment will be recorded. Information regarding admission; length of hospital stay; routine clinical examination; radiological, microbiological, and biochemical analyses (eg, bacterial cultures and blood gas tests); treatment; discharge diagnosis; and complications (parapneumonic effusion and sepsis) will be retrospectively collected from the medical records.

Personal identification numbers of all the study subjects will be linked to the national health and population registers to collect information regarding deaths, previous immunization, and discharge diagnoses according to the International Statistical Classification of Diseases and Related Health Problems 10 (ICD-10) as well as Anatomic Therapeutic Chemical classification system codes for prescribed drugs.

Classification of Etiology in the Trial of Respiratory Infections in Children for Enhanced Diagnostics Study

The algorithm for classifying etiology in the TREND study is based on the current literature and will classify children into viral, bacterial, atypical bacterial, mixed viral-bacterial, and undetermined infections based on clinical, microbiological, radiographic, and biochemical findings (Figure 2). A second, stricter algorithm only considering microbiologically confirmed diagnoses will be used in a complementary subanalysis (Figure 3).

Figure 2. Classification of community-acquired pneumonia etiology in the Trial of Respiratory infections in children for ENhanced Diagnostics (TREND) study. CAP: community-acquired pneumonia; CRP: C-reactive protein; hMPV: human metapneumovirus; PCR: polymerase chain reaction; PIV: parainfluenza virus; RSV: respiratory syncytial virus.

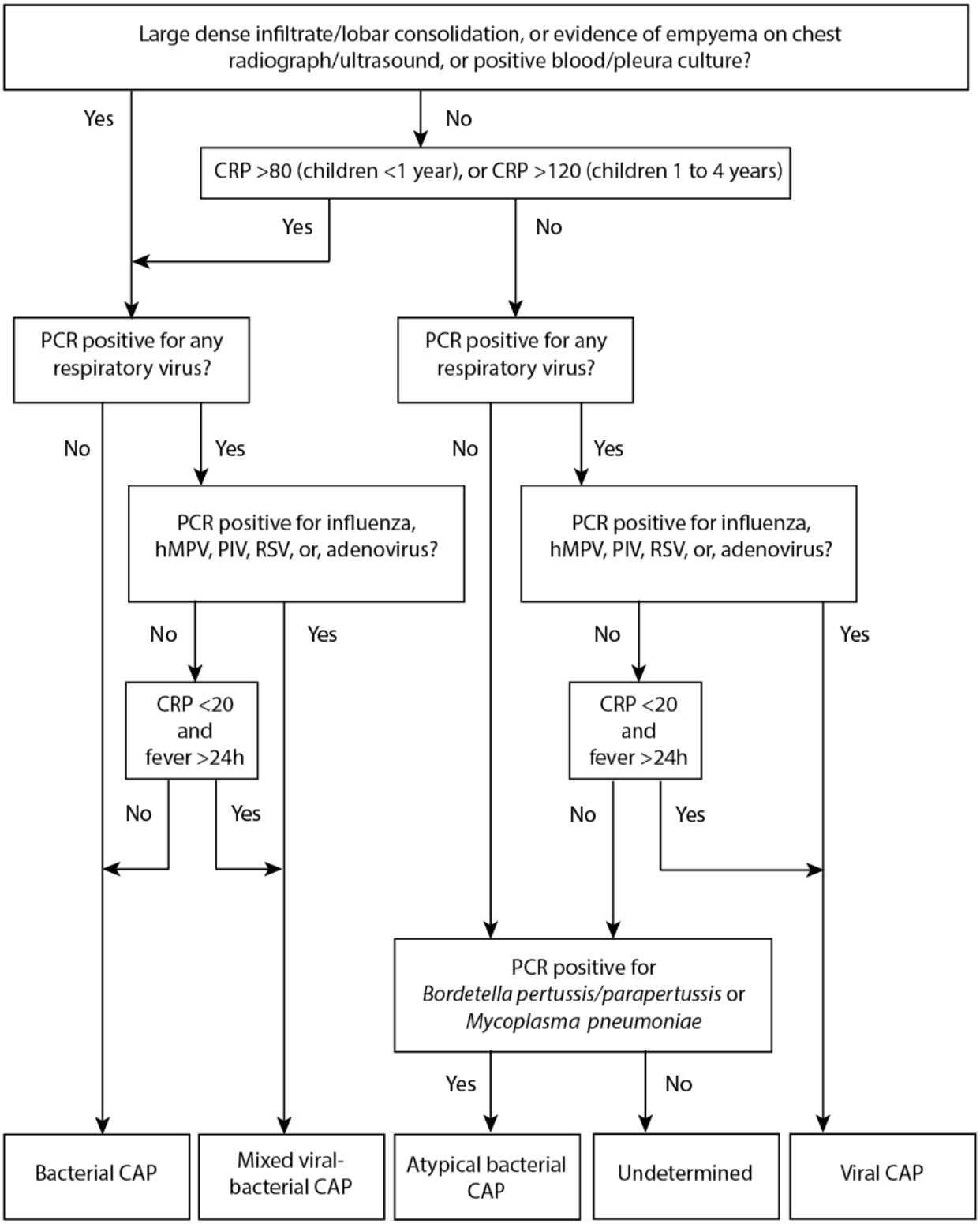
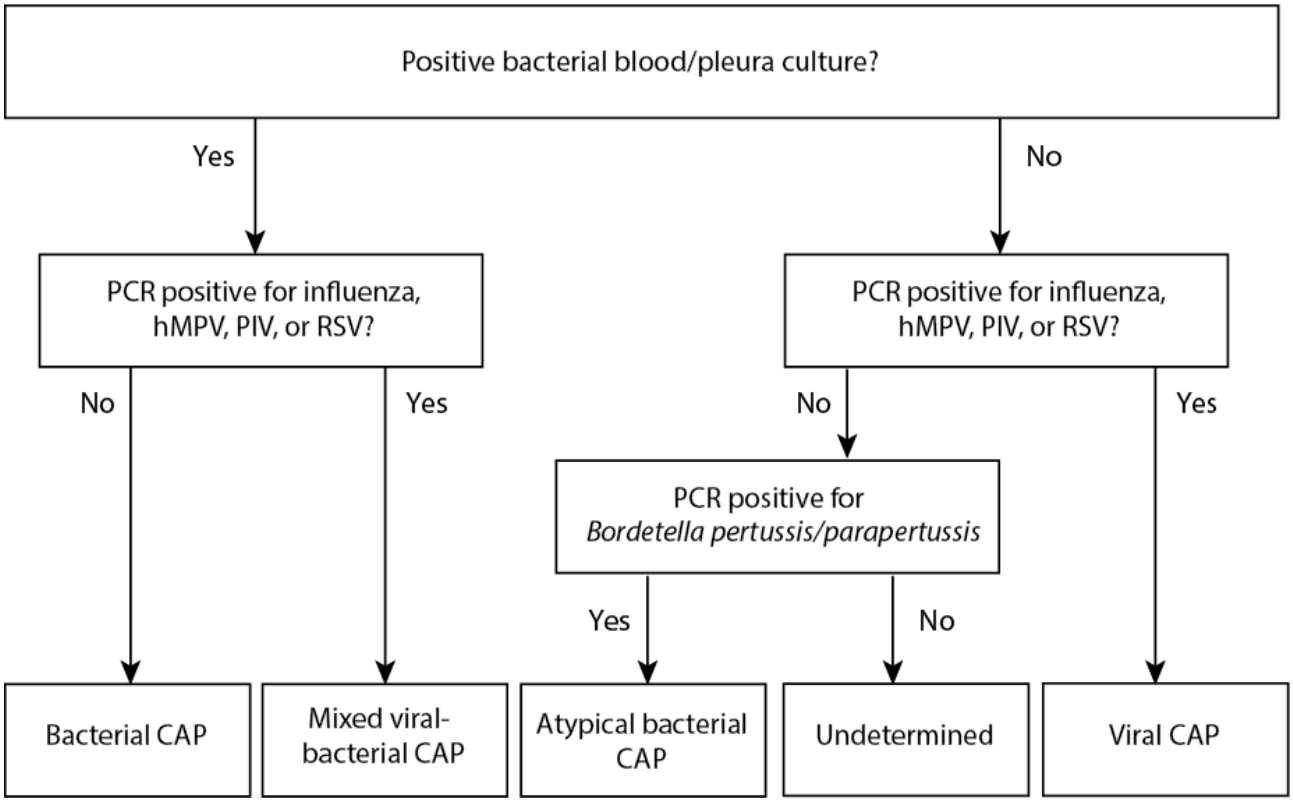


Figure 3. Classification of community-acquired pneumonia (CAP) etiology in the Trial of Respiratory infections in children for ENhanced Diagnostics study—strict definition. CRP: C-reactive protein; hMPV: human metapneumovirus; PCR: polymerase chain reaction; PIV: parainfluenza virus; RSV: respiratory syncytial virus.



Long-Term Complications

Long-term complications (asthma and number of hospital-requiring respiratory infections) will be assessed by linking to the National Patient Register. Asthma will be classified according to the ICD-10 diagnosis and/or prescriptions of asthma medication in the Swedish Prescribed Drug Register using a previously validated algorithm [48].

Study Size and Power Calculation

A total of 300 cases and 120 controls are estimated to be included in the TREND study. For the sample size calculation, we focused on the assessment of MxA levels in cases with viral CAP as compared with cases with bacterial CAP/controls (study I). Overall, 2 power calculations were made, 1 for viral CAP versus bacterial CAP and 1 for viral CAP versus controls. The following assumptions were made: (1) A difference in MxA level of 500 µg/l between the groups was considered clinically relevant. (2) A standard deviation of 1000 and 300 was assumed in cases with viral CAP and bacterial CAP/controls, respectively, based on previous studies on MxA [13,14]. Using an alpha level of .05 (2 sided) at an 80% power, with an additional 20% to account for nonparametric testing and multivariate analyses, 42 children in each group (viral CAP, bacterial CAP, and controls) would be needed. To ensure that enough of the included cases would fulfill the study definitions for viral and bacterial CAP, the proportion of children with viral and bacterial CAP (TREND definition) was calculated in our previous study that assessed Swedish children with x-ray–verified CAP [47]. By doing this, the prevalence of viral and bacterial CAP was estimated at 45% and 14%, respectively. Hence, 300 cases and 42 controls would be needed to ensure sufficient collection of cases with viral and bacterial CAP, respectively. We also would like to compare viral CAP cases with controls testing positive for 1 or more viruses by PCR. In our previous study, 35.4% of asymptomatic children tested positive for 1 or more viruses. Hence, to include a sufficient number of virus-positive controls, we aim at including 300 cases and 120 controls in the TREND study.

Statistical Methods

A clinically relevant difference in MxA levels will be compared between cases with viral and bacterial clinical CAP as well as between cases with viral clinical CAP and controls using appropriate statistical methods according to the number and distribution of data points. Sensitivity and specificity for different respiratory viruses with mariPOC respi and the novel RPA-based test will be calculated as compared with real-time PCR. The difference in asthma prevalence and the difference in the number of hospital-requiring respiratory infections between cases and controls as well as between cases and the general child population will be assessed after 3, 7, and (if deemed necessary) 10 years. Data will be presented with 95% CI, and a *P* value of <.05 will be considered significant.

Ethics Approval and Consent to Participate

The study will be conducted in accordance with the latest version of The Declaration of Helsinki and the fundamental principles of respect for the individual's (Article 8) right to self-determination and to make informed decisions (Articles 20, 21, and 22) regarding participation in research, both initially and during the course of the research.

We estimate that the benefit of knowing more about viral respiratory infections with the aim of improving diagnostics of CAP overweighs the discomfort for the individual study participant in terms of extra sampling. For all the participating children, a minimal, reduced amount of blood will be collected, and accordingly, the analysis of PCT and CRP will not routinely be performed in control children for the following reasons: (1) data on these biomarkers in the controls are not necessary for the study objectives; (2) to get a sufficient amount of blood for running these analyses, it would require a larger lancet and/or additional punctures; and (3) these children would likely not have been subject to capillary puncture, were they not enrolled in the study. Results from point-of-care tests will be provided to guardians and treating physicians. Other test results will not be provided as they will be analyzed in batches and thus not influence management. Written informed consents will be collected from the guardian(s) by the study nurse/physician before sampling. To ensure confidentiality for the participants, samples will be given a study ID and results will only be presented at a group level. Data of personal identities will be stored in a password-protected data file at Sachs' Children and Youth Hospital and will only be available to the study researchers. Good clinical practice and good laboratory practice will be followed. The study was approved by the Regional Ethical Review Board in Stockholm (ref 2017/958-31).

Results

The study was approved by the Regional Ethical Review Board in Stockholm in June 2017 (ref 2017/958-31). A pilot study was performed from June to August 2017 to evaluate the study protocol from a logistical and methodological point of view. Overall, 6 out of 9 invited cases and 1 out of 3 invited controls were included. Valuable information was retrieved during the pilot study, which has led to alterations and improvements in the recruitment process, the questionnaire, and other study documents as well in the logistics and handling process of the samples. Enrollment of study subjects started in November 2017. Results are expected by the end of 2019.

Discussion

Principal Findings

The TREND study aims to improve the differential diagnosis of bacterial and viral etiology in children aged below 5 years with clinical CAP presenting at an emergency unit in a tertiary pediatric hospital in Sweden. This is the first study of children with clinical CAP that evaluates the diagnostic accuracy of MxA as a biomarker for viral CAP. Previous studies on MxA have shown promising results on the role of MxA as a biomarker for viral infection but have been smaller in size [14] or have included more heterogeneous groups of study subjects [13,15,16]. The TREND study aims to add further information on the role of MxA as a marker to improve the interpretation of viral PCR positivity and to differentiate between viral and bacterial infections with a specific focus on children with CAP. Further aims are to validate the findings from recent pediatric CAP etiology studies, including the EPIC and PERCH studies, as well as to assess the long-term complications of pediatric CAP [21-24].

A New Algorithm for Classification of Etiology in Pediatric Community-Acquired Pneumonia Studies

One major weakness in the studies of diagnostic biomarkers in pediatric infectious diseases is the lack of a reliable gold standard for the microbiological diagnosis [5,49]. The gold standard for assigning bacterial etiology has traditionally been the detection of bacteria in cultures from normally sterile sites (lung, blood, and pleura). However, as sampling from the lung/pleura is infeasible in most cases and blood cultures have limited sensitivity, this approach is of little use in clinical studies of CAP [5]. Previous studies assessing the performance of diagnostic tests in terms of distinguishing bacterial infections from viral infections have used either an independent expert panel or a laboratory-/radiological-based approach to classify disease etiology [12-15]. Both approaches have their advantages and limitations. Using a strict microbiologically confirmed diagnosis as the reference has the advantage of high specificity, but the generalizability of the findings is hampered as the majority of children in clinical practice will not have a clear microbiologically confirmed diagnosis. In addition, for a diagnostic test to be useful, it is more important to distinguish between etiologically less clear cases of respiratory infections rather than to identify the school book examples of bacterial and viral infections. In the TREND study, we chose a more pragmatic approach favoring generalizability for microbiological accuracy. However, given that doctors in expert panels rely on microbiological and biochemical findings, we reasoned that it still would be more stringent to create an algorithm for the classification of etiology. In the TREND study, a diagnostic algorithm has been created a priori to serve as the reference based on the current evidence for the classification of CAP etiology. Detection of RSV, hMPV, influenza virus, and PIV has, in previous case-control studies, been highly associated with CAP. Furthermore, these viruses appear to be rarely detected in asymptomatic individuals, and hence, detection will be considered to be a definitive indicator of etiology [21,22,47,50,51]. For other respiratory viruses as well as for the atypical bacteria *M pneumoniae*, the clinical significance of PCR positivity is less clear owing to frequent detections in asymptomatic children [17,52-55]. For that reason, PCR positivity will not be considered enough for establishing etiology. Virkki et al reported that a CRP level of more than 80 in children aged less than or equal to 2 years and more than 120 in children aged 2 to 5 years was specific (>85%) for bacterial etiology, whereas a CRP level of less than 20 was specific for viral etiology (78%) [56]. These cutoffs will be used to aid in the definition of probable bacterial and viral infections in less clear cases. Hence, detection of viruses other than influenza, RSV, hMPV, and PIV will be considered as viral infections only if the CRP value is less than 20. Given that adenovirus has been associated with high CRP, this rule will not be applicable for adenovirus [11]. However, adenovirus detections will not be considered in the strict algorithm, as asymptomatic detection of the virus is common [17]. Finally, given that CRP levels depend on the disease duration and to avoid false-negative test results (ie, low but rising CRP values), an additional criterion

of reported fever duration of more than 24 hours will be applied in the TREND study when considering CRP levels [45]. As discussed above, there is no optimal reference standard for the classification of CAP etiology, neither clinically nor in research. However, we believe that much is to be gained if we use an algorithm instead of an expert panel. The decisions taken by expert panels differ between different studies, over time, and between different settings. When using an algorithm, this can be controlled for. We look forward to comments and inputs on our algorithm so that together we can develop it further.

Difficulties in Pediatric Community-Acquired Pneumonia Etiology Studies

The WHO criteria for clinical CAP lack specificity and will result in the inclusion of a significant proportion of children who will not have true CAP, including children with bronchiolitis and asthma [57]. To improve the specificity of the WHO criteria for clinical CAP, a rapid-acting bronchodilator will be administered to children with wheezing and chest indrawing, as suggested by the PERCH study team [43]. Other clinical parameters from the PERCH study will also be included and used for further subanalyses [43].

Conducting research in the pediatric emergency department is difficult [58]. High patient flows and long waiting times create a stressful environment for all personnel categories. Motivating nurses/doctors to spend the extra time and effort it takes to recruit patients is, therefore, challenging. Continuous education/information about the research project, interpersonnel teamwork (nurse and doctor), and incentives are all key success factors. Recruitment of healthy controls in this age group is an obvious challenge as the sampling (blood and nasopharyngeal sampling) causes discomfort to the child. Therefore, attempts have been made to include patients who will undergo elective hand surgery (and thereby be sedated during the sampling). Certain clinical parameters can be deceptive if not recorded correctly, which is a potential source of bias. In children where peripheral oxygen saturation and heart rate are measured continuously, data will still only be recorded at certain time points when the children are at rest.

Requirements of Future Rapid Diagnostic Tests

Transcriptomic studies have shown promise in differentiation between different infectious agents but currently require advanced instrumentation with a long turnaround time and are hence more suitable for an intensive care unit setting than for routine testing at pediatric emergency units [59]. However, given the complexity of the host immune response elicited by respiratory pathogens, it is possible that a single biomarker will not be sufficient to accurately differentiate between viral and bacterial CAP. However, MxA could be valuable in a rapid combination test of biomarkers and selected microbiological testing if it proves to be specific for viral CAP. Such commercial combination point-of-care tests of inflammatory biomarkers are already being developed and some, such as FebriDx and MeMed BV, have shown promise [15,60].

Improved near-patient differential diagnosis is a prerequisite for rational antibiotic use and decreasing unnecessary antibiotic treatment. Furthermore, easier identification of the pathogens causing acute respiratory infections makes it easier to advise guardians to care for their sick children and for better disease surveillance in the society. Hence, the findings from the TREND project can be an important step toward the improved care of children with clinical CAP. At this stage, the methods are developed and evaluated in a Swedish context but might have wider implications, for example, to resource-limited settings where the need for similar tests is even higher than in a high-income context such as Sweden.

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Authors' Contributions

SAR and TA conceptualized the study, had a leading role in the study design, and drafted the manuscript. PN and MRR conceptualized the study, participated in the study design, and contributed to the development of the algorithm for the classification of etiology. RR and AM participated in the study design from an early stage and contributed to the development of the algorithm for classification of etiology. AE and IZ participated in the study design, supervised the pilot study, and optimized the enrollment procedure. JG, HAS, and SN participated in the study design with a focus on the collection and handling of the nasopharyngeal samples. VP actively took part in the study design from an early stage and contributed to the development of the algorithm for the classification of etiology. MW optimized the protocol for blood sampling of the study subjects and performed/supervised the MxA analyses. ML and MR took part in the study design, with a focus on the sampling procedure for the respiratory specimens, as well as performed/supervised the PCR analyses. All authors critically revised, commented on, and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CAP: community-acquired pneumonia
CRP: C-reactive protein
hMPV: human metapneumovirus
ICD-10: International Statistical Classification of Diseases and Related Health Problems 10
mariPOC: multianalyte point-of-care antigen detection test system
MxA: myxovirus resistance protein A
PIV: parainfluenza virus
PCR: polymerase chain reaction
PCT: procalcitonin
PERCH: Pneumonia Etiology Research for Child Health
RPA: recombinase polymerase amplification
RSV: respiratory syncytial virus
TREND: Trial of Respiratory infections in children for ENhanced Diagnostics
WBC: white blood cell
WHO: World Health Organization

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Original Paper

Socioeconomic Status and Racial or Ethnic Differences in Participation: Web-Based Survey

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Abstract

Background: Web-based survey data collection has been widely used because of its advantages, although attaining and retaining participants can be challenging. There are several factors associated with successful Web-based survey participation; yet little is known regarding racial or ethnic and socioeconomic differences in the progress of a Web-based survey.

Objective: This study aimed to examine racial or ethnic and socioeconomic status (SES) differences in participation in a Web-based survey.

Methods: We conducted a secondary data analysis of a study dataset containing information on parents of preschool children. We used 2 phases of Web-based surveys: (1) screening questions including race or ethnicity information and (2) full survey with a consent form. Once potential participants submitted the screening questions, including their racial or ethnic information, the team sent the full survey link to potential participants who met study eligibility criteria. We calculated the proportion of racial or ethnic groups in each of the following areas: consent, partial survey completion, and total survey completion.

Results: A total of 487 participants (236 non-Hispanic white, 44 Hispanic, 137 black, and 70 Asian) completed initial screening questions, and a total of 458 participants met study eligibility criteria. Compared with black participants, non-Hispanic white and Asian participants were more likely to consent to participate in the study (odds ratio [OR] 1.73, 95% CI 1.08-2.78, *P*=.02; OR 2.07, 95% CI 1.04-4.13, *P*=.04, respectively). There was no racial or ethnic difference with respect to the completion of demographic questions or completion of a partial survey. Finally, compared with black participants, non-Hispanic white participants were more likely to complete the entire survey (OR 3.36, 95% CI 1.51-7.06, *P*<.001). With respect to SES, less educated non-Hispanic white participants were less likely to complete the survey compared with their counterparts with more education (OR 0.15, 95% CI 0.50-1.48, *P*<.001).

Conclusions: We found a significant difference among racial or ethnic groups as well as different education levels in Web-based survey participation. Survey researchers need to consider the SES and racial or ethnic differences in Web-based survey participation and develop strategies to address this bias in participation and completion in their research.

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KEYWORDS

survey; technology; race; socioeconomic status

Introduction

Self-report surveys are often a main data collection or measurement strategy in quantitative research. The self-report data collection method is used not only for major nationally representative datasets such as National Health and Nutrition Examination Survey and the US Census [1,2] but also by researchers conducting individual research [3]. Due to numerous

advantages such as convenience and cost-effectiveness, self-report surveys are frequently used to collect data from individuals [4].

There are challenges to promoting reliable and credible data collection by a self-report survey. A primary challenge for researchers employing self-report surveys is to encourage the target population to initiate and complete the survey as the method heavily relies on self-selection. Self-selection bias refers to when survey participants are allowed to decide whether or not they want to participate in a survey [5] and is often mentioned as a limitation on the generalizability of the results of survey studies [6]. Random sampling from the general population for survey research is a key method for enhancing the generalizability of the study outcomes. However, the convenience sampling method instead of random sampling is widely used despite the known weaknesses because of the ease of researchers' access to the target population [7]. Even after researchers have accessed the target population, there are some challenges for both researchers and participants in completing the survey, which could influence the data collection procedures. The issues of a low completion rate and a low return rate even for nationally representative epidemiological studies are well documented in survey research [8]. For instance, the traditional method of administering surveys using paper and pencil could make the processes of data collection time-consuming, including survey preparation, survey distribution, survey turnaround or return, data entry, and data preparation [9].

More recently, Web-based survey methods with advantages over traditional paper surveys have been widely used. The identified advantages compared with the traditional paper survey method include more flexible design options, lower delivery cost, and less data entry time [10]. However, there are also several challenges that researchers often face when implementing a Web-based survey method for data collection. Similar to traditional survey methods, initiating and completing the survey can be still challenging. Participants who respond to survey research are often more motivated, more technologically savvy, and more actively engaged in their health as well as the topic being studied, which could result in self-selection bias [11]. There have been mixed reports in the literature regarding the differences in response rate between a Web-based survey and a traditional paper survey. Zuidgeest et al reported comparable response rates for a mixed-mode survey, which included a Web-based survey and a mailed questionnaire [12]. However, Aitken et al obtained a return rate from a Web-based survey that was much lower than the equivalent paper-based survey [13]. Thus, Web-based survey methods might be in a transitional phase as an alternative method to collect data; as such, their use, which can be conducted with several advantages such as a lower cost, might yield varying response rates [14].

For further advancement of Web-based survey, researchers need to understand that there are many factors that influence Web-based survey participation. First, a principal factor influencing an initiation of the Web-based survey includes survey target population characteristics such as age, gender, socioeconomic status (SES), and race or ethnicity. These characteristics might influence the potential respondent's accessibility to the internet as well as their motivation to participate in a Web-based survey. Age might influence the response to a Web-based survey because of different rates of internet usage by age group; for example, according to the Pew Research Center, about 97% to 98% of adults aged 18-49 years use the internet, whereas only about 66% of adults aged 65 years and above use the internet [15]. Thus, younger potential participants might more frequently participate in a Web-based survey and be more familiar with the features of a Web-based survey method. Although gender, family income, and race or ethnicity are not known to be directly related to internet usage, those who have not completed high school are less likely to access the internet than college graduates (65% vs 97%) [15]. McDonald et al [16] targeted young college students to investigate tobacco use and assessed the response rate during the second phase of the data collection. They found that individuals who were male, black, or seeking a bachelor's degree were less likely to complete the survey compared with those who were female, white, or seeking an advanced degree.

The methods by which a survey is presented and delivered as well as its features comprise another principal factor influencing completion of the survey. The presentation of a Web survey might be more flexible than a traditional paper version survey, including the proper implementation of skip patterns or branching items that could filter responses to questions within or subsequent to the trigger question [10]. Web-based survey instruments also include features such as a progress bar to help participants to track their progress in the survey, which might improve the likelihood that they will complete the survey by reducing the perception of task burden [17]. In terms of survey delivery, Sauermann et al [18] found that personalized survey contact (eg, using the first name of the participant when sending a reminder email), a lottery incentive for survey completion, and changing contact wording (ie, change the wording of each contact message to maintain respondent attention) were positively associated with response rate. Thus, factors related to the transition of a survey from a paper format to a Web-based version with more flexible approaches might influence the completion rate [10].

It has been emphasized to include socioeconomically disadvantaged populations and under-represented racial or ethnic minorities to health research to diminish health disparities and improve health equity. As internet and other technologies are ubiquitous in today's society, researchers might anticipate that such technologies can diminish SES and racial or ethnic participation differences in participation in a Web-based survey. However, with the exception of specific studies of response rates, such as that of McDonald et al [16], there is limited information regarding SES and racial or ethnic differences in Web-based survey participation. Due to a paucity of information, it is important to understand whether the progress of participation in Web-based surveys is similar across socioeconomic and racial or ethnic groups.

This study aimed to examine the SES and racial or ethnic differences of participation progress in a publicly available Web-based survey.

Methods

Study Setting and Recruitment

We conducted a secondary analysis of data from a cross-sectional study that enrolled racially or ethnically diverse parents of preschool children to examine the relationship between parental psychological distress and parental feeding practices in families of preschool children and to understand parents' practices in child feeding and food preparation [19]. Inclusion criteria were as follows: a participant was a parent or guardian of a child aged 2-5 years (1) who spoke and read English and (2) whose child did not have any chronic disease diagnosed by a health care provider that could affect his or her diet or body mass index.

We started our recruitment for the parent study at local community settings (including preschools, churches, and libraries) as well as community activity facilities (eg, Young Men's Christian Associations) in the southeast area of the United States using convenience sampling methods. With permission from school authorities, several local preschool administrators and teachers informed families about the study using the study flyer (eg, sending the flyer home with each child). A research staff member visited the preschool as needed to introduce the study to potential participants when they dropped off or picked up their children. We identified ethnicity-specific churches (eg, Korean churches, black churches, and Hispanic churches) and asked them to post study flyers on their church bulletin boards. The research staff also visited ethnic grocery stores (ie, Hispanic and Asian stores) to post flyers with the permission of the owners. We asked each enrolled participant to mention our study to their friends, relatives, or other potentially eligible families. We also targeted local pediatric clinics to post the flyer in the waiting room. The research staff visited the clinics as needed to introduce the study and to give a flyer to potential participants when they visited their health care providers.

In addition, we posted the study flyer in online communities or other social media such as Facebook to enhance our reach to potential participants. To accelerate the recruitment, we also posted the flyer on Craigslist, which is a nationwide advertisement website for community residents. We selected at least one city from each state (excluding Hawaii and Alaska) and targeted major metropolitan cities to have a more socioeconomically and racially or ethnically diverse sample.

Data Collection

Our initial goal was to recruit comparable participants across racial or ethnic groups to compare subgroup differences in the relationship between parental psychological distress and parental practices in feeding. Thus, we used a 2-phase Web-based survey developed in Research Electronic Data Capture (REDCap) hosted at Duke University [20], which included (1) screening questions, including race or ethnicity information, and (2) the survey, with a consent form preceding the survey. This strategy allowed us to identify the race or ethnicity of potential study participants before the initiation of the survey. Once potential participants accessed and completed the screening questions (using a publicly available survey link), including their race or ethnicity, we sent the full survey link to eligible participants within 12 hours of confirming their eligibility.

Once they consented, they could freely access the Web survey for up to a month to encourage their completion of the survey. We sent each participant at least one reminder email if they did not finish the survey within a week, using the individual's first name and different wording for each reminder email. We sent up to 2 weekly reminder emails. The survey required approximately 30-40 min to complete. In brief, the main survey consisted of demographic questions including SES indicators (ie, annual family income and level of education) and other validated questionnaires to assess perceived stress (Perceived Stress Scale, 10 items) [21], parenting stress (Parental Stress Scale, 18 items) [22], sleep quality (Pittsburgh Sleep Quality Index, 19 items) [23], perceived depression (The Center for Epidemiological Studies Depression Scale, 20 items) [24], social support (Social Support Questionnaire-Shortened version, 12 items) [25], home food availability (Home Food Inventory, 13 major food categories) [26], feeding practices (subscales from Child Feeding Questionnaire, 12 items) [27], and child eating behaviors (Harvard Service Food Frequency Questionnaire) [28]. We provided a thank-you gift by mail (eg, water bottle or divided plate for children) to each participant who completed the survey.

Data Analysis

We exported all data from REDCap and conducted data analysis using SPSS (version 24, IBM). First, we conducted descriptive data analyses of sample distributions and characteristics (ie, race or ethnicity, age, and gender) of those who at least completed the demographic questions, which were on the initial page of the main survey after they consented. We categorized the participants based on their eligibility, consent response, whether they completed demographic questions (initial section of the main survey), whether they completed at least half of the survey (partial survey), and whether they completed the entire survey. We used annual family income and the education level as proxy indices of SES. We calculated the proportions for each group by participants' demographic characteristics (mainly SES and race or ethnicity). We then used logistic regression to test for any significant differences in terms of completing the survey across racial or ethnic and education groups. On the basis of different progress and completion rates, we treated black participants (for race or ethnicity) and those participants who had completed graduate school (for education level) as reference groups for the regression model. We then conducted a 3-factor Chi-square (χ^2) analysis to explore survey participation by SES within each racial or ethnic group.

Results

Sample Characteristics

A total of 459 participants (223 non-Hispanic white [NHW], 42 Hispanic, 132 black, and 62 Asian) completed screening questions identifying their race or ethnicity and met study eligibility criteria (Table 1). Of these, a total of 310 participants consented to participate in the study, and 259 participants completed the demographic questions. Table 1 shows the

demographic characteristics of those who consented and completed demographic information. Of those who completed demographic questions (n=259), 84.4% (221/259) were female; we had asked the primary caregiver, who tended to be the child's mother, to participate in the survey. A majority of participants (81.3% [213/259]) were at least college graduates, and 33.4% (87/259) of the participants had an annual family income of US $80,000 or more.

Proportion of Participation Among Different Racial or Ethnic Groups and Socioeconomic Status Groups

Table 2 shows the patterns of study participation by race or ethnicity and education.

There was a racial or ethnic difference in obtaining informed consent for participation. Among those who completed screening questions and were eligible, NHWs were 1.7 times more likely to consent to participate in the study than blacks (odds ratio [OR] 1.73, 95% CI 1.08-2.78, *P*=.02) and Asians were twice as likely to consent to participate in the study as black participants (OR 2.07, 95% CI 1.04-4.13, *P*=.04). However, there was no racial or ethnic difference in the rates of completion of both the demographic questions and of partial surveys. Finally, there was a significant difference among racial or ethnic groups for total survey completion rate. Compared with black participants, NHW participants were more likely to complete the entire survey (OR 3.26, 95% CI 1.51-7.06, *P*<.001).

Table 1. Sample characteristics (N=259).

Characteristics	n (%)[a]
Sex	
Male	38 (15.6)
Female	221 (84.4)
Age group (years)	
≤30	61 (23.6)
30-40	148 (57.1)
40-50	47 (18.1)
≥50	3 (1.2)
Race or ethnicity	
Non-Hispanic white	134 (53.4)
Hispanic or Latino	22 (8.8)
Black	48 (19.1)
Asian	35 (13.9)
Education	
Less than or equal to high school graduate	48 (18.4)
College graduate	143 (54.8)
Graduate school graduate	70 (26.8)
Annual family income	
≤US $19,999	25 (9.6)
US $20,000-US $39,999	39 (15.0)
US $40,000-US $59,999	53 (20.4)
US $60,000-US $79,999	48 (18.5)
US $80,000-US $99,999	31 (11.9)
≥US $100,000	56 (21.5)

[a]Total numbers might vary because of missing values.

Table 2. Logistic regression for the relationships of race or ethnicity and education with Web-based survey participation.

Predictor	Beta	SE	Wald chi-square (*df*)	*P* value	OR[a] (95% CI)
Consent signed to participate					
Race or ethnicity (black as a reference group)					
NHW[b]	0.55	0.24	5.17 (1)	.02	1.73 (1.08-2.78)
Hispanic	0.24	0.38	0.42 (1)	.52	1.28 (0.61-2.69)
Asian	0.73	0.35	4.32 (1)	.04	2.07 (1.04-4.13)
Demographic data completion					
Race or ethnicity (black as a reference group)					
NHW	0.42	0.35	1.44 (1)	.23	1.52 (0.77-3.01)
Hispanic	−0.01	0.51	0 (1)	.98	0.99 (0.36-2.69)
Asian	−0.03	0.44	0.01 (1)	.94	0.97 (0.41-2.30)
Half of the survey completion					
Race or ethnicity (black as a reference group)					
NHW	0.69	0.44	2.44 (1)	.12	1.99 (0.84-4.69)
Hispanic	0.58	0.72	0.64 (1)	.42	1.78 (0.44-7.26)
Asian	0.46	0.72	0.41 (1)	.52	1.58 (0.38-6.44)
Education (graduate school graduate as a reference group)					
High school graduate or less	−2.53	0.81	9.86 (1)	.001	0.08 (0.02-0.39)
College education	−1.51	0.77	3.86 (1)	.05	0.22 (0.49-1.00)
Total survey completion					
Race or ethnicity (black as a reference group)					
NHW	1.18	0.39	9.02 (1)	<.001	3.26 (1.51-7.06)
Hispanic	0.91	0.64	2.04 (1)	.15	2.48 (0.71-8.67)
Asian	1.24	0.69	3.24 (1)	.01	3.44 (0.90-13.20)
Education (graduate school graduate as a reference group)					
High school graduate or less	−1.87	0.58	10.55 (1)	<.001	0.15 (0.50-0.48)
College education	−0.68	0.53	1.63 (1)	.2	0.51 (0.18-1.44)

[a]OR: odds ratio. Models adjusted for age for both race or ethnicity and education of study participants.

[b]NHW: non-Hispanic white.

Table 3. Web-based survey participation by education level within each racial or ethnic group (N=259).

Categories and subcategories	Demographics completion, n (%)	Partial survey completion, n (%)	Total survey completion, n (%)	Chi-square (*df*)	P value
Non-Hispanic white (n=143)					
High school or less (N=28)	27 (96)	20 (71)	19 (68)	1.59 (2)	.12
College graduate (N=74)	71 (96)	68 (92)	66 (89)	12.65 (2)	<.001
Graduate school graduate (N=39)	39 (100)	38 (97)	38 (97)	13.34 (2)	<.001
Hispanic (n=24)					
High school or less (N=5)	5 (100)	4 (80)	3 (60)	3.97 (2)	.21
College graduate (N=14)	14 (100)	13 (93)	13 (93)	0.88 (2)	.17
Graduate school graduate (N=5)	4 (80)	4 (80)	4 (80)	2.91 (2)	.07
Black (n=59)					
High school or less (N=13)	13 (100)	9 (69)	7 (54)	2.15 (2)	.20
College graduate (N=37)	36 (97)	29 (78)	26 (70)	1.21 (2)	.06
Graduate school graduate (N=9)	8 (89)	8 (89)	6 (67)	1.16 (2)	.04
Asian (n=35)					
High school or less (N=1)	0	1 (100)	1 (100)	—[a]	—
College graduate (N=18)	15 (83)	15 (83)	15 (83)	3.1 (2)	.12
Graduate school graduate (N=16)	0	16 (100)	16 (100)	3.09 (2)	.13

[a]Unavailable chi-square.

Among indices of SES, we found that there was a significant difference by education levels with respect to the completion of a partial survey and the entire survey. Although there was no significant difference between college graduates and graduate school graduates, participants with a high school diploma or less were less likely to complete the partial survey or the entire survey (OR 0.08, 95% CI 0.02-0.39, *P*=.001; OR 0.15, 95% CI 0.50-1.48, *P*<.001, respectively). There was no significant relationship between annual family income and the rate of proportionate completion.

We then explored survey participation by education level within each racial or ethnic group (Table 3). Among NHW participants, we found a significant difference by education level, that is, higher education was associated with more completion of a partial survey as well as the entire survey (χ^2_2=12.7, *P*<.001; χ^2_2=13.3, *P*<.001, respectively). Among black participants, there was a significant difference by education levels in total survey completion (χ^2_2=1.2, *P*=.04). There were no significant differences by education level in the Hispanic or Asian groups.

Discussion

Summary of Findings

We examined the rate of participation in a Web-based survey using convenience sampling strategies by different SES and racial or ethnic groups. We found that there were significant differences in the progress of Web-based survey participation among different groups in terms of race or ethnicity and education level. This is an important finding as the issue of health disparities is a major challenge in our health care system. It has been suggested that survey research results based on disproportionate participation by different portions of the population limit the applicability or generalizability of those results to the general population. Our results confirm reports from the literature that disproportional study attrition levels by different groups of race or ethnicity and education still exist for a Web-based survey.

We identified some trends in study participation of black participants. Of our different racial or ethnic groups, black participants were the least likely to consent compared with NHWs. Once they consented, they initiated the survey (there was no significant difference for initiation and partial survey completion); yet they were less likely to complete the entire survey. Furthermore, with publicly available study recruitment materials (flyer and online ads), black participants were likely to access the link to the screening questions, but they were less likely to consent to participate. However, once other minorities including Hispanic and Asian populations completed the screening questions and consented, they were likely to complete the survey. Even if internet accessibility has been increased across populations, our findings indicate a disproportionate distribution in the response rate.

Comparison With Prior Work

There has been discussion of the historical barriers to participating in health research among black communities. Mistrust of health research is rooted in the mistreatment of black people by medical researchers [29], and this built mistrust still hinders the participation of blacks in health research [30]. In our study population, black participants were less likely to consent even if they completed the screening survey (which

indicated that they were able to be reached by internet), and they were less likely to complete the entire survey. Although a Web-based survey has the potential to decrease health disparities in health research through its reach to a different proportion of the population, black populations might still be less likely to complete a survey even after they initiate it. Thus, we need to consider several factors (in addition to internet access) that influence the rate of study participation among black populations, including more limited access to resources, lower literacy levels, and a fear of disclosure [31]. These factors might continue to influence their perception of researcher disrespect and thus their decision as to whether to participate in Web-based survey research.

Biased findings based on limited representative sampling might lead to biased health recommendations, further deepening health disparities. Prior research has been focused on how to improve recruitment of underrepresented populations by addressing facilitators (eg, benefits to participants and cultural congruence) and barriers (eg, mistrust, stigma, and competing demands) [32]. Some researchers have posited that the use of a Web-based survey might diminish the issue of the disproportionate participants from different population [33]. Current research initiatives have been focused on improving health equity by involving underrepresented and disadvantaged members of the population in health research. Historically, racial or ethnic minorities are less likely to participate in any type of health research, and the health equity issue originates from unequal participation in health research, which forms the basis of health care [34]. Thus, research data are usually generated from the racial or ethnic majority, and the research findings are generally applied across racial or ethnic groups. The discrepancy in racial or ethnic different participation in health research has been a critical issue for the current health care system in the United States.

Moreover, health literacy is a significant issue in recruiting community residents to participate in health research. The different attrition rate we found based on the education indicator of SES is not surprising. In our findings, the level of education was related to the degree of survey completion, whereas annual family income was not. Moreover, this result is not just an issue of access to the internet because our study participants had internet access, but the attrition rate differed by the level of education. An interesting finding was the significant differences in survey completion by the level of education within the NHW and black subpopulations. Within the same racial or ethnic groups, disadvantaged individuals' circumstances might hinder them from completing a Web-based survey. Health literacy in those with less education across race or ethnicity population might be overlooked if we focus only on racial or ethnic disparities. These differences in Web-based survey participation might be related to health literacy. Thus, we need to consider that disproportional survey participation is not only an issue of race or ethnicity. The difference by education level that we found is consistent with previous reports, which stated that individuals with lower education level were less likely to complete a Web-based survey [35]. We suggest that it would be related to electronic health (eHealth) literacy, which is defined as an ability to work with technology such as thinking of media-related issues, searching for numerous information, and making decisions based on the information [36]. Individuals with lower education levels might possess lower levels of both health literacy and eHealth literacy [37]. As health research methodology has been improved using more advanced technologies, we might need to consider eHealth literacy as a principal factor in the successful transition to the technology-based health research and health care outcomes.

Implications

For further enhancement of participation by underrepresented populations in Web-based survey research, researchers need to consider enrichment as a strategy to build a relationship with the subpopulation of interest. On the basis of an awareness of the disproportionate distribution of the educational and racial or ethnic composition of study populations, researchers must develop strategies to improve their relationship with their participants. Technological barriers have been discussed in technology-based research [38], but such research has been focused on how to reach those subpopulations to improve their enrollment. We noted the different attrition levels of the subsample of our study participants. Survey researchers need to consider the racial or ethnic and educational level differences within their target population and the impact of these factors on Web-based survey participation.

Moreover, we cannot assume that it is easy for anyone from different demographic groups to complete a Web-based survey simply because they have a computer or a mobile phone and access to the internet. We need to promote the motivation to join a survey and support their completion of the survey. Web-based surveys might possess some advantages such as ease of distribution of the survey, utilization of images, and improvement of confidentially or anonymity. A clear description of the survey (including the study goals and example questions) and some features to encourage the completion of the survey such as images for low literacy groups, friendly reminders, secure access to the survey, and a progress bar might enhance survey completion. Community-based participatory research is considered a principal method for increasing the trust of and partnership with the community [39]. Building trust with communities is a strategy often used to encourage potential participants to engage in Web-based survey research [40]. Researchers might need to work with stakeholders in target communities to understand their needs and goals and to incorporate those items into the research [41]. As one of the main purposes of any research study is to be able to generalize the study results to the overall population through the use of a representative sample, we need to consider targeting underrepresented populations to encourage and promote their participation in a Web-based survey. Finally, we continuously need to make effort to improve eHealth literacy through understanding the users' interaction with health technologies [42]. Thus, we can help the study participants complete the research tasks, use the health information, and therefore participate in making an impact on health care.

Limitations

There are several limitations. As this was a secondary data analysis, we did not obtain demographic information (including

gender, age, and SES) for those potential participants who only completed screening questions. These demographic factors could influence their motivation and decision to consent to participate and to complete the survey. We did not consider our survey content as a factor influencing the completion rate of the survey; however, some stress and depression measures, which were presented in the early portion of the survey, might have influenced the rate of continuation and completion of the survey. Moreover, most participants were female with young children (84.4%, 221/259), which is a group more likely to participate in a Web-based survey, thus our findings might not apply to males. We could not evaluate literacy level or other community-level characteristics to determine how those characteristics might influence the motivation for survey completion.

Conclusions

Researchers need to understand that there is a significant difference between racial or ethnic groups as well as educational levels in terms of progress in Web-based survey participation. Public health research, especially community-based research, heavily relies on self-report and self-selection based on voluntary participation. Future researchers will need to make the effort to target underrepresented racial or ethnic groups and less educated populations to encourage their participation in Web-based survey research.

Conflicts of Interest

None declared.

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Abbreviations

eHealth: electronic health
NHW: non-Hispanic white
OR: odds ratio
REDCap: Research Electronic Data Capture
SES: socioeconomic status

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Corrigenda and Addenda

Correction: A Multidisciplinary Model to Guide Employment Outcomes Among People Living With Spinal Cord Injuries in South Africa: A Mixed Methods Study Protocol

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The authors of "A Multidisciplinary Model to Guide Employment Outcomes Among People Living With Spinal Cord Injuries in South Africa: A Mixed Methods Study Protocol" (JMIR Res Protoc 2016;5(4):e238) made a small copyediting error wherein the word "exploratory" should have read "explanatory".

In the Methods subsection of the Abstract, the sentence:

> *This study will utilize exploratory mixed methods during 3 phases.*

Has been revised to read:

> *This study will utilize explanatory mixed methods during 3 phases.*

Additionally, in the first paragraph of the main Methods section, the sentence:

> *This exploratory mixed methods study will entail the collection and analysis of both quantitative and qualitative data [29-31]. An exploratory sequential approach will be used as described by Cresswell [30]. This study is divided into 3 phases, each of which consists of a number of stages to address the study objectives (see Figure 1).*

Has been revised to read:

> *This explanatory mixed methods study will entail the collection and analysis of both quantitative and qualitative data [29-31]. An explanatory sequential approach will be used as described by Cresswell [30]. This study is divided into 3 phases, each of which consists of a number of stages to address the study objectives (see Figure 1).*

The correction will appear in the online version of the paper on the JMIR website on April 3, 2019, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article also has been resubmitted to those repositories.

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Original Paper

Developing a Sexual Health Promotion Intervention With Young Men in Prisons: A Rights-Based Participatory Approach

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Abstract

Background: The sexual health of young men in prisons is often among the poorest in any given country. They may have developed sexual behaviors that, from a public health perspective, are considered problematic and burdensome. These include poorer use of condoms and engaging in more frequent casual sex, resulting in higher rates of sexually transmitted infections, including HIV and viral hepatitis. Thus, young incarcerated men are a highly marginalized and socially excluded high-risk group, in greater need of sexual health education and services.

Objective: The aim of this study was to create an innovative sexual health promotion intervention, made for and with young men in prisons, to encourage them to avail of regular sexual health checkups. This included developing a Web-based animated-style sexual health promotion intervention (1.42 min) coupled with upskilling the prison nurses to offer a partnership approach to prison health care. This paper focuses on the development of the intervention and the importance of the underpinning rights-based (RB) participatory intervention design.

Methods: We employed an RB participatory approach and recruited 14 participants who attended 3 coproduction workshops held within a prison site in Northern Ireland, United Kingdom. A bespoke 3-day training for nurses beforehand, ensured they gained a deeper understanding of the determinants of poor sexual health. The coproduction team comprised young men, prison nurses, nurse sexual health consultant, media company representatives, and facilitator. Workshops focused on content, design, tone and medium of communication for a Web-based intervention that would be appealing and engaging for young incarcerated men.

Results: A 1.42-min animation *Dick loves Doot* was created to promote a positive attitude toward sexual health checkups. The RB approach enabled the young men to participate, have their voices heard and see their stories reflected through the animation. The nurses' capacities to protect, fulfill, and respect the young men's rights to appropriate sexual health services and education was also enhanced. Evaluations confirmed that we successfully provided accurate sexual health information in a way that was engaging and accessible and that encouraged the young men to avail of the new prison sexual health services that were set up in the prison and now provided by nurses.

Conclusions: The RB participatory approach to health advanced in this study provided a means to (1) gain invaluable insider knowledge to understand the impact of structural determinants on health and health inequalities and strategies by which to target young incarcerated men (2) create inclusive opportunities for developing bespoke targeted interventions, and (3) galvanize collaborative partnerships to disrupt the structures and processes that lead to and encourage health inequities. To reduce future risk, effective treatment, coupled with coproduced interventions that transmit relevant health messages in a relevant and meaningful way, is key to success.

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KEYWORDS

sexual health; male; prison; health promotion; rights-based participation

Introduction

Background

Globally, the health and well-being of young men who enter prison are often among the poorest in any given country [1,2]. Moreover, men involved in the criminal justice system have some of the poorest sexual health with especially high rates of sexually transmitted infections (STIs), including HIV and viral hepatitis [3-9]. Most of these young men will have experienced circumstances of structural and political adversity and many will have been exposed to the *toxic trio* in relation to their risk of harm, that is, parental mental ill health, substance misuse, and domestic violence [10-13]. Due to their circumstances, lower socioeconomic status, and lower levels of education, they may have experienced chaotic lifestyles and developed risky sexual behaviors that are grounded in a particular form of hegemonic masculinity, which exhibits patriarchal attitudes toward women, sex, and contraception [14-16]. Such behaviors may include poorer use of condoms and engaging in more frequent casual sex with partners whose sexual behaviors also place themselves and others at increased risk of STI and HIV, etc, (eg, commercial sex workers and intravenous drug users) both during incarceration as well as before and after. In many ways, the prison population is reflective of marginalized disadvantaged men more broadly, but incarceration may further compound these young men's marginalization, future economic prospects, as well as their potential to form safe and secure relationships [5,17]. Importantly, sexual health issues greatly affect not only economically and socially marginalized young men's lives but also that of their partners and communities [15,18-21]. The public health issues in prison are one part of the risk and the public health issue once they leave is another [2,5,22]. Hence, to address sex-related and other communicable diseases effectively, prisoners are identified in national and international sexual health strategies and guidelines as a key population in greater need of targeted sexual health promotion, education, and services [2,23-30].

However, the challenge is how to engage and communicate about sexual health with marginalized incarcerated young men in a way that is informative and effective, while not reifying hegemonic representations of masculinity that underpin " *high risk-low concern* behaviors, and in a way that respects, protects, and fulfills their human rights [18,19,29,31]. Equally important is the representation of partners who for the most part will be external to prison. To be meaningful, sexual health promotion must address partnering-up scenarios relevant to the young men's lived experience both within and beyond prison walls. Men's sexual behaviors and practices do not occur in a vacuum but intersect with the gender and power, emotions, wants, needs, and rights of another person. Therefore, there is also a need for a more gender-relational approach [21] to sexual health promotion that seeks to empower marginalized young men to engage better with their partners to look after each other's sexual health together.

According to recent reviews [32-36], engaging men and boys in developing sexual health and well-being interventions is crucial to enable positive change for all. Tailored interventions that empower them by using male-friendly language, speaking to men's potential, and ensuring young men's active participation are effective [33,34,36-38]. The use of videos, dramas, and digital media has also been shown to be more successful for men than some cognitive behavioral change models [32,34,35,38-40]. In addition, providing men with opportunities to critique stereotypical gender ideologies and explore the sexual rights of women may encourage partner and peer support and communication, which are enablers to positive sexual health [28,29,37,40]. In relation to the prison environment, the creation of a nurturing and safe space within the prison setting is crucial for encouraging the relationship building between the facilitators and the young men; it is also critically crucial for the relationship building between the facilitators and the prison management [41]. Some research suggests that men in prison might have greater opportunities to engage with health services and in activities and therapies to improve their well-being [2,5,12,42]. The potential for them to regress in prison and develop poorer health behaviors, arguably greater access to drugs, is also a concern [43].

This paper describes the development of a pioneering Web-based sexual health promotion intervention made for and with young men in prisons from inception to production, alongside the development of a partnership approach to sexual health care between the primary care providers (prison nurses) and the young men they serve. We begin by describing the human rights-based (RB) approach employed, which resulted in a Web-based animated-style sexual health promotion intervention entitled *Dick loves Doot* (1.42 min). An RB approach was chosen as our preferred way of working with young incarcerated men, as in this approach, they are viewed as *rights-holders*, and mechanisms can be put in place to create an environment in which their voices can be heard, to enable them to participate in developing services that are relevant for them, as opposed to *duty-bearers* providing support or services on an assumed needs basis and the young men typically having no say in what action is taken.

Mechanisms for assisting *rights-holders* to claim their rights include the following:

- A *designated-listener*, who is aware of the situation of the rights-holders and duty-bearers, seeks to build the capacity of, and help, both.
- Framing the issues in relation to national and international law, legislation, and jurisprudence, by considering the accountability of duty-bearers and their obligations.
- Advocacy to duty-bearers on behalf of rights-holders with limited *voice*.
- Participation and empowerment of rights-holders to help themselves.

Theoretical Approach

A Rights-Based Approach

There are many conceptual frameworks and guidance available for public health intervention development [44-50] that describe key implementation stages and their components, as critical links for the translation of sciences into public health services. However, we opted to employ an *RB* approach to accentuate

the link among human rights (violations), health outcomes, and the development of contextually relevant and sustainable interventions. The human RB legal discourse was also a strong argument that helped to mobilize the state actors and get them on board to secure the inclusion, engagement, and participation of young men within the prison setting, and create an enabling environment whereby their voices could influence the end product [28,51]. For our project to conform to the standards of an RB project, we needed to fulfill the following 3 key principles:

1. The goal must further the realization of human rights.
2. The process must be guided by human rights standards and principles.
3. The outcome should strengthen the capacity of (1) state agents (duty-bearers) to meet their obligations, (2) rights-holders to claim their rights, via the processes of empowerment and accountability (United Nations, Statement of Common Understanding, 2003) [52].

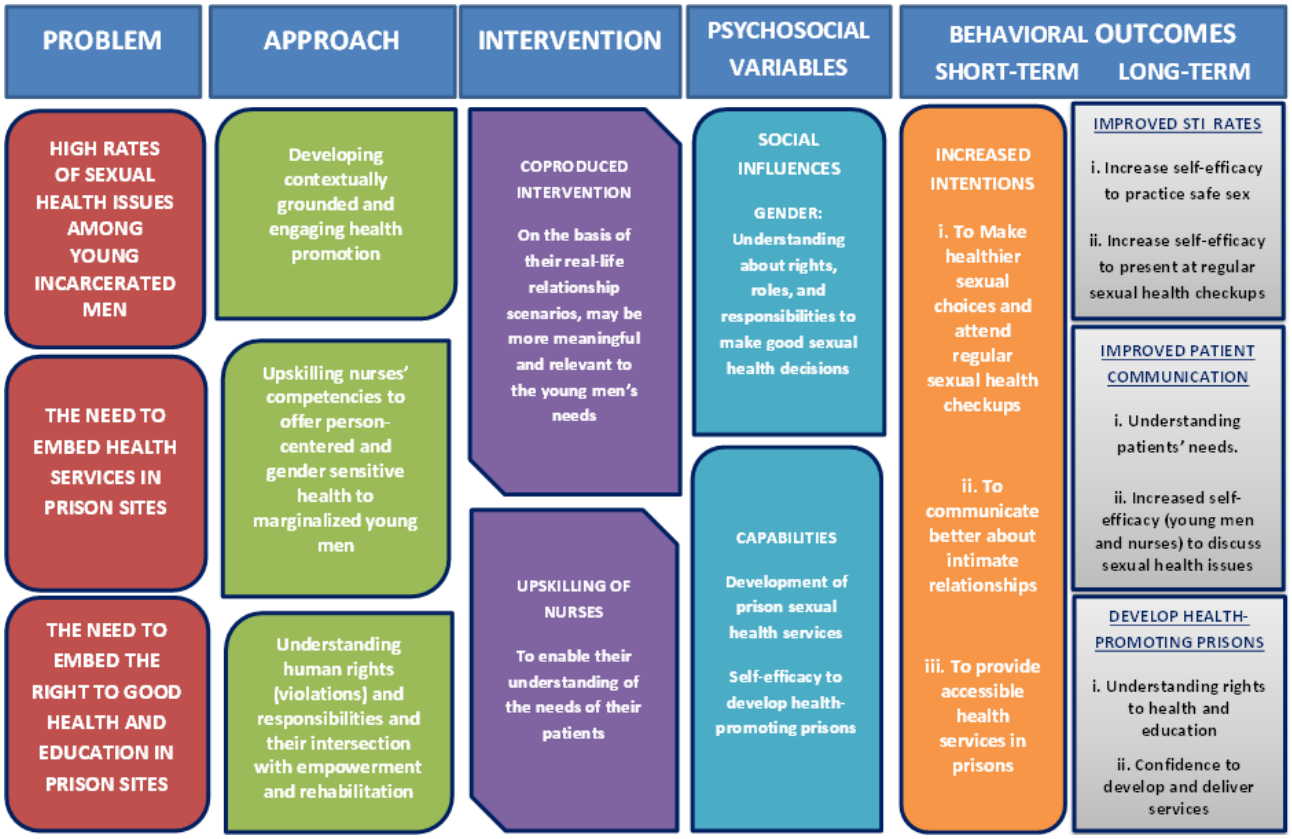
There are a number of human rights standards relevant for prisoners that guide the process that are included in major international treaties [53,54]. These standards consistently emphasize that prisoners' incarceration should not interfere with their human rights to health and education [2,23,26-29].

The ultimate goal in this project is to empower marginalized young men to further their right to health, which not only includes access to health services but also appropriate health-related education and information (information that is understandable and relevant to the target population). Applying human rights discourse in this study helps us to understand that poor sexual health outcomes for these young men are not simply issues of *public health* but are also the consequence of many structural and institutional rights violations, which marginalize them and their communities [51,53,55]. That is, they have *not* had adequate access to health services and *not* received appropriate education and information to enable them to make positive healthy decisions in relation to their sexual lives. Focusing on the young men's right to good sexual health and related sexual health education and information rather than viewing their sexual practices as problematic highlights the inextricable link among individuals' risk taking, human rights violations, and social and governmental responsibility and accountability, and this particular group's poor sexual health outcomes [31].

The coproduction occurred alongside the development of a partnership approach to sexual health care between the primary care providers (prison nurses) and the young men they serve. The latter involved upskilling of the nurses to gain a deeper understanding of the lives and sexual health needs of incarcerated young men and develop the nurses' ability to engage in more health promoting sexuality-related communication during both one-to-one and educational-style group consultations with their patients. The specific aim of the intervention then is to promote positive sexual health and sexual health checkups leading to a reduction of STIs. More broadly, our aim was to improve the health and well-being of marginalized groups of men by fostering a human rights and gender-relational focused approach, essentially to empower disadvantaged men to take responsibility for their own and their partner's sexual health. In the remainder of the paper, we describe the development processes, and include the logic model, to demonstrate the decision making during the creation of the intervention, from design stage through to production and dissemination strategies.

It was this understanding that underpinned the logic model of the project (Figure 1), which demonstrates how we framed the problem, the ultimate goals, and the mechanisms to achieve these goals.

Figure 1. Project logic model.



Methods

Research Design

Drawing from this RB axiom, outlined in Figure 1, the young men have the right to take part in educational activities to enhance their rehabilitation and their reintegration back into society. On the basis of the principles of inclusion, empowerment, capacity building, and accountability, the RB approach ensures that concepts such as respect, voice, and equality converge with participation rights [56-59]. In this way, the young men are viewed as experts on their situation and are invited to participate as consultants on the project to offer guidance and advice. The young men are identified as the rights-holders, whose rights to appropriate health and education may have been violated. The duty-bearers (agents of state—state employees) currently involved in the young men's lives are (1) the prison nurses, who are obligated by law to uphold the young men's rights by providing relevant sexual health information and treatment and (2) the prison staff, who are obligated to provide access to appropriate health and education for these young men.

We discussed our RB approach with the nursing and prison management staff who agreed to become involved in the project, and we also discussed that the young men had the right, the skills, aspirations, and expertise required to be included in the project also as consultants. This was important as for a participatory process to be successful and the end product to be relevant, we needed the right people around the table and all collaborators to share a mutual understanding of the expertise each brought to the team [60]. However, some ways of working may create distance with affected populations, which can impede the building of relationships on the basis of mutual respect [60,61]. Reflecting on the imbalances of power between the young men and prison officers, it was agreed that the prison officers, in this case, would be excluded from the working group. However, every effort was made to convey information about the study to keep them informed and invested, and their support was critical in allowing the young men to participate and providing the team with access, space, and technology to engage with the young men during our participatory meetings.

Consequently, the young men and the prison nurses were deemed the two significant parties to bring together in a collaborative partnership to create a useable solution. We sought to build their capacity around developing a mutual understanding of the determinants that cause poor sexual health outcomes and a lack of individual agency and autonomy for these young men, in the context of broader social structures [62,63]. In the collaborative partnership, key health messages that the young men need to know are shared by the health professionals and the young men share information on their experience of the issues and the reality of their lives. Both parties collaborate to decide how best to share positive sexual health messages with their peers in a way they will hear, listen to, and act upon. The coproduction approach to knowledge realizes the human rights of the young men by empowering them to share their relevant expertise, alongside *duty-bearers*, who are also empowered to fulfill their obligations to provide appropriate health-related education and information [61].

The products of this type of coproduction can lead to the creation of tailored and targeted interventions that are relevant and

meaningful to the young men's lives. This empowering approach can increase knowledge and awareness of gendered norms that intersect with intergenerational poverty and lack of social and economic opportunity for the young men. Developing health promotion messages together in this way can also increase both the nurses' and young men's sense of efficacy and control and it can create a greater sense of community and social support and thus ensure that the nurses protect, fulfill, respect, and deliver the young men's rights to appropriate sexual health and education, which may lead to positive behavior change around sexual health communication and services, for both the health care professionals and their patients [62,63]. This paper focuses on the development of the intervention and the importance of the participatory intervention design with a preliminary evaluation of the young men's participatory experience. Please see Figure 2 for an overview of the RB process.

Research Setting

Hydebank Wood College (HBW) is one of 3 prison sites in Northern Ireland, United Kingdom. The college accommodates young men between the ages of 18 and 21 years and all female prisoners who are separately housed, 172 prisoners in total as of May 24, 2018. HBW college has a focus on education, learning, and employment, and it was the first young offenders' institution in the United Kingdom to transition to *secure school* status (April 2015), which has required a major rethink about the role of punishment and the remit of prisons in young people's lives. Notable changes have included the introduction of universal vocational training and employability skills and a new educational curriculum provided in-house, placed firmly at the heart of rehabilitation. Importantly, the inclusion of health behaviors, particularly relationships and sexuality education (RSE), is now being recognized as a critical element of the rehabilitation process within this prison context too [64]. The health promotion intervention is developed with the men's prison section only. However, the development of the clinical sexual health service within the prison is made available to both the women and men.

Ethical approval was awarded by the Office for Research Ethics Committees Northern Ireland (reference: 17/NI/0082) and Governance permissions and security clearance from the Northern Ireland Prison Service and South Eastern Health and Social Care Trust. Verbal approval was given by the voiceover actors to use their image as part of the study.

Participants and Procedures

There were 2 stages to the study, Stage 1 involved upskilling the prison nurses, and Stage 2 involved upskilling the young men by coproducing the sexual health promotion animation. The project ran over 1 year from January 2017 to December 2017.

Stage 1: Upskilling Nurses

Target Population

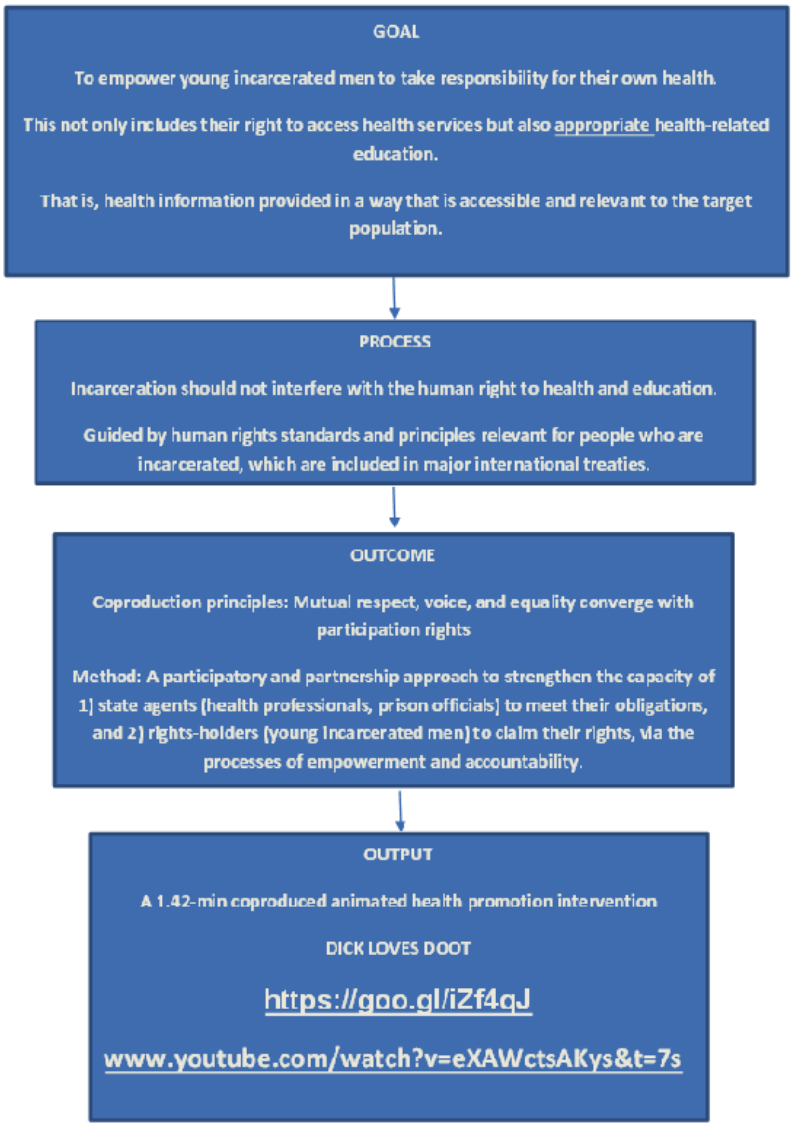
An important element in the RB approach is to build the capacity of all those identified to become involved to understand the issues of rights violations. The duty-bearer identified in this instance was the prison nursing team.

Sampling and Recruitment

Prison nurses (n=8) who work in the Northern Ireland prison service were selected because of their interest in further developing sexual health services within the prison context. The nurses received a 3-day in-depth training course, where they learned more about sexual health behaviors, education, and group facilitation skills with young men. This course was developed in collaboration with sexual health education specialists specifically for this project, and it had 2 strands. The first sought to improve the nurses' knowledge and understanding of the young men's lives and how the development of their sexual behaviors and practices may be linked to human rights violations in relation to their personal circumstances and lack of quality health and educational information. The second strand aimed at improving the nurses' skills and personal competencies to deliver sexuality-related communication [29] and health promotion during sexual health consultations with young men in prisons. This could be one-to-one clinically-focused consultations, which was their typical way of working and also promoted their competency to move toward educational group style consultations within prisons.

Topics over the 3 days included up-to-date research on young people's sexual behaviors and practices in general, and they included the results of recent research interviews conducted with the young men in their care, in relation to their understanding, wants, and needs around RSE. We also focused on sexual language and communication during sexual history taking, exploring personal sexual values and prejudices, legal issues, gender relations, sexual consent and exploitation, trauma and adverse childhood experiences, and the benefits of coproduction and participation. This helped the nurses develop a more psychosocial-oriented and deeper understanding of the needs of their patients' and also helped to breakdown barriers between their personal values and their professional health provider role and address their levels of embarrassment and discomfort when discussing the expression of sexuality and sexual practices that they may not agree with or may find immoral. In an additional strand of the project, the nurses completed Web-based sexual health modules and received training and support in STI assessment, treatment, and management, to develop their competencies in these areas and also to set up sexual health clinics in the prisons. The clinical development strand of the project is reported elsewhere.

Figure 2. Overview of rights-based approach.



Stage 2: Coproduction Workshops With Young Men and Whole Group

Target Population

The participatory coproduction team comprised 14 members who met on 3 occasions during 2-hour workshops in HBW. The group comprised members of the research and nursing teams, and we required a sample of young incarcerated men to complete the group.

Sampling and Recruitment

The young men were recruited via the health care team within the prison site and chosen on the basis of their interest in the project and their ability to work together in a group situation. They were provided with information leaflets 1 week before a face-to-face meeting with the researcher who ran through all the information with them and reiterated what was expected of them. Their consent was then taken to become involved, and a meeting of the whole group was arranged for the following week. The group was constructed as follows:

- Young Men×6
- Consultant Nurse in Sexual Health×1 (CK)
- HBW Nurses×4
- Participation Facilitator×1 (MT)
- Media Company Representatives×2

Data Collection and Analysis

Data were collected during each workshop and the team would take this information away and report back their interpretation of this at the following workshop. The young men refined this interpretation as we went along checking that they were able to identify with the scenarios, language, and tone of the interpretation and see their lived experience reflected in the final scripts and images.

Workshop 1

After introductions, of all 14 members of the group as described above, workshop 1 focused on developing the purpose of the Web-based sexual health promotion intervention and developing the content for the intervention, that is, giving and receiving information among individuals to understand cultures, values, beliefs, and skills. Facilitated discussions centered on the following key issues around getting a sexual health check:

- Why is it important?
- How would you approach it?
- What can happen?
- What would you have to do?
- How can it be fixed?
- Partner notification

At times, the personality and behavior of the young men as they shared their experiences during our discussions made some members of the workshop, who may have less experience working with the young men, uncomfortable. It was the role of the facilitator to encourage the team to pay attention to the project's central ideas and values and to listen to, understand, and reflect the concerns of the affected population. This realization helped bring everyone together around our common goal. Both parties exchanged views on the key issues and a picture emerged around the reality of the young men's lives on the basis of their narrative that would shape the end product. The media company representatives took this information away to develop a creative storyline around the young men's narratives and liaised with the research team to ensure the accuracy of the sexual health information.

Workshop 2

Workshop 2 focused on refining the storyline and discussing how to transmit our messages in an engaging medium of communication. An important consideration was the restrictions placed on the young men by being in prison and the technology to which they are denied access. For example, we ruled out mobile phone and digital apps as they would have no access to these technologies. Our preferred delivery method was to host our intervention on television screens throughout the prison site, such as visiting, and recreation areas. We decided to additionally host it on our research institution's YouTube channel to freely share with other interested parties and allow greater accessibility to the general public. We focused on script and storyboard development, which was the backbone to the content of the intervention.

The media experts came to this workshop with a creative brief that comprised 2 scenarios. One was based on 2 characters meeting in a nightclub for the first time and the other was centered on a *sexpert* in a Physician's office talking to a young couple about sexual health. They read both scripts aloud for the team and we all discussed the pros and cons of each. The young men decided that both scenarios were not overly relatable as nightclubs are not the only place they meet a sexual partner and they would never present at a *sexpert's* office for relationships and sexual health advice with a new partner. Instead, they suggested keeping the scenario to a regular male and female character discussing between themselves about initiating a sexual relationship. This was very pleasing to the team who appreciated the importance of getting a sexual health check in the context of communicating with a new partner.

During this workshop, the young men told us that to be effective, an intervention for them would need to be pitched at the right language level including accent, it had to be realistic, easy to understand in terms of style and tone, and they added that the length should be *short and snappy*. The young men explained that a short video was the preferred medium to fulfill this brief. The media experts then showed numerous examples of this to the group on computer. After much deliberation, the young men decided on an animated explainer style, narrated video with eye-catching visuals. They reiterated that the tone of this was to be simple, short, snappy, and fun, for use on social and Web-based media, and they also commented that humor was essential.

Workshop 3

Workshop 3 focused on refining the language and visuals that would be truly representative of the young men's lived experience. The media experts in collaboration with the research team developed a new script and storyboard (Figure 3) on the basis of the young men's suggestion of 2 characters discussing their sexual health and negotiating having sex for the first time together. Again, we refined the script together on the basis of language the young men would actually use and agreed that humor was used effectively. We discussed the relatability of the characters and names were chosen *Dick and Doot*.

We also sought input from a group of 4 young women when refining the female character (Figure 4). The group unanimously agreed that caricature number 2 was representative of most young girls today, with long straight hair, eyelashes, and eyebrows. The team also agreed on the number and characteristics required of the voiceovers for the animation. A young male and a young female about 17 to 18 years of age with a Northern Ireland accent were deemed to be required to voice the characters of Dick and Doot. An adult female with a smooth, clear, upbeat voice was to be the third voice over. Participants prescribed that she would read an encouraging message at the end of the animation in an upbeat and positive way in an effort to normalize going for a regular sexual health checkup.

The media team hired 3 actors, a young male, a young female, and an older female, on the basis of the young men's suggestions, to record the voiceovers to embed into the animation (Figure 5).

Final Sign-Off Workshop

A final sign-off workshop was organized in Hydebank with the facilitator in which the penultimate storyboard was showcased to the young men who gave it a final seal of approval. Please see Figure 6 and Figure 7 for a screenshot from the intervention.

Figure 3. Example from the storyboard.

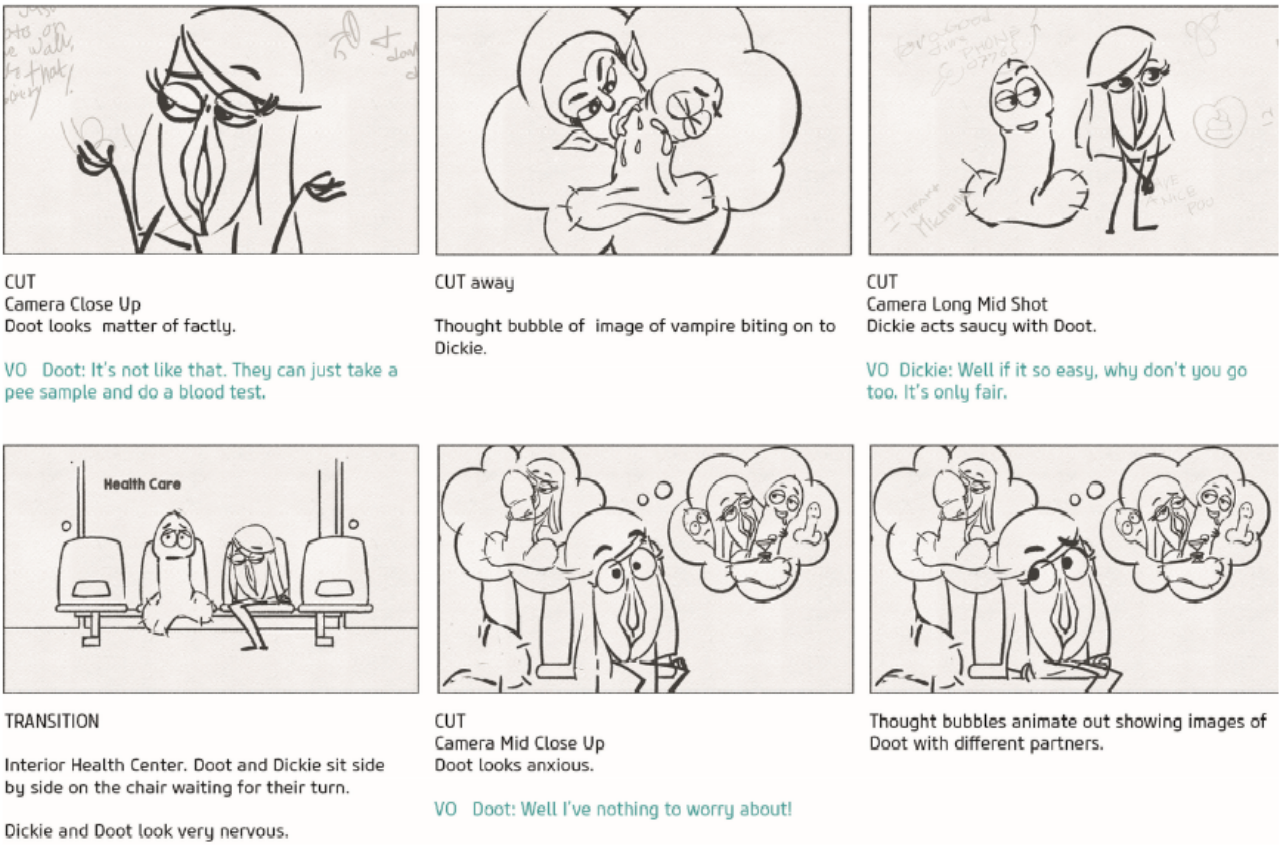


Figure 4. Refining the Female Character.

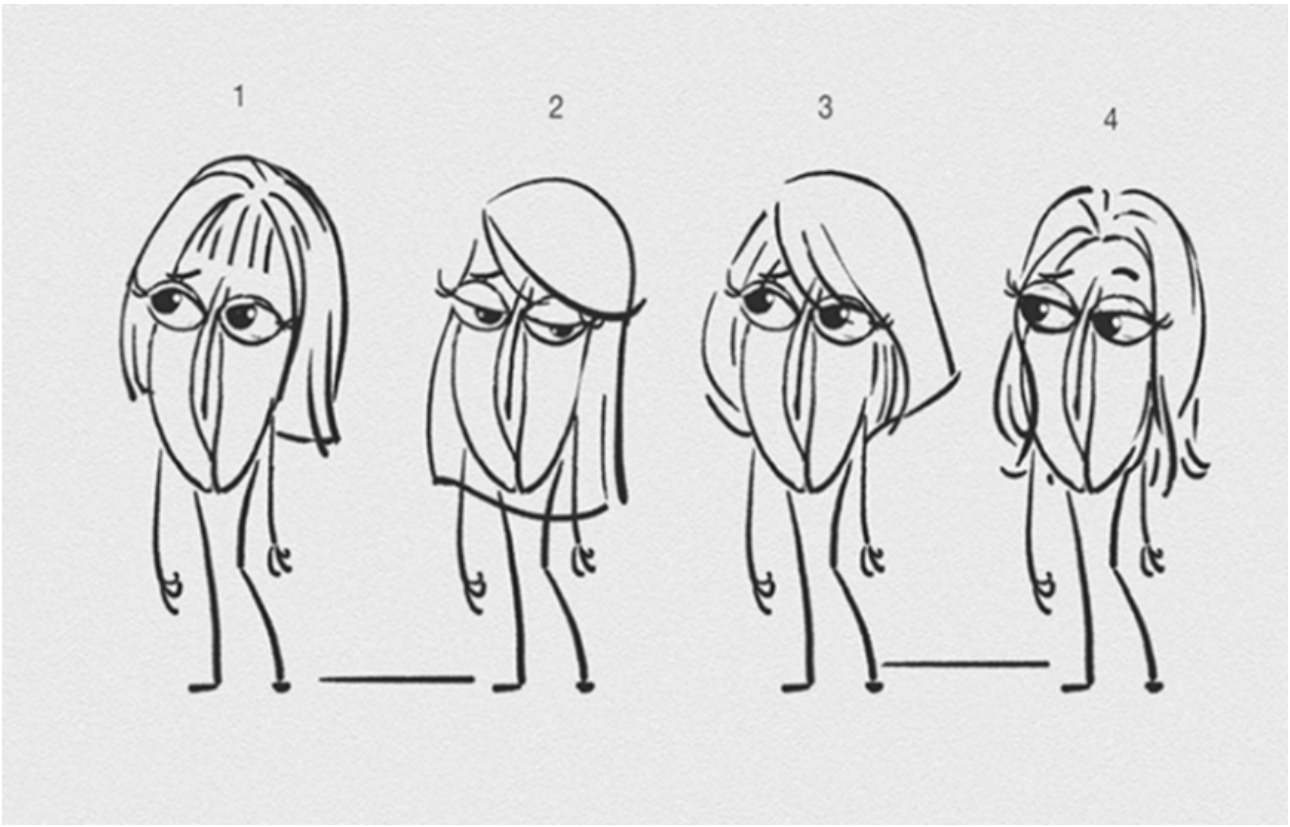
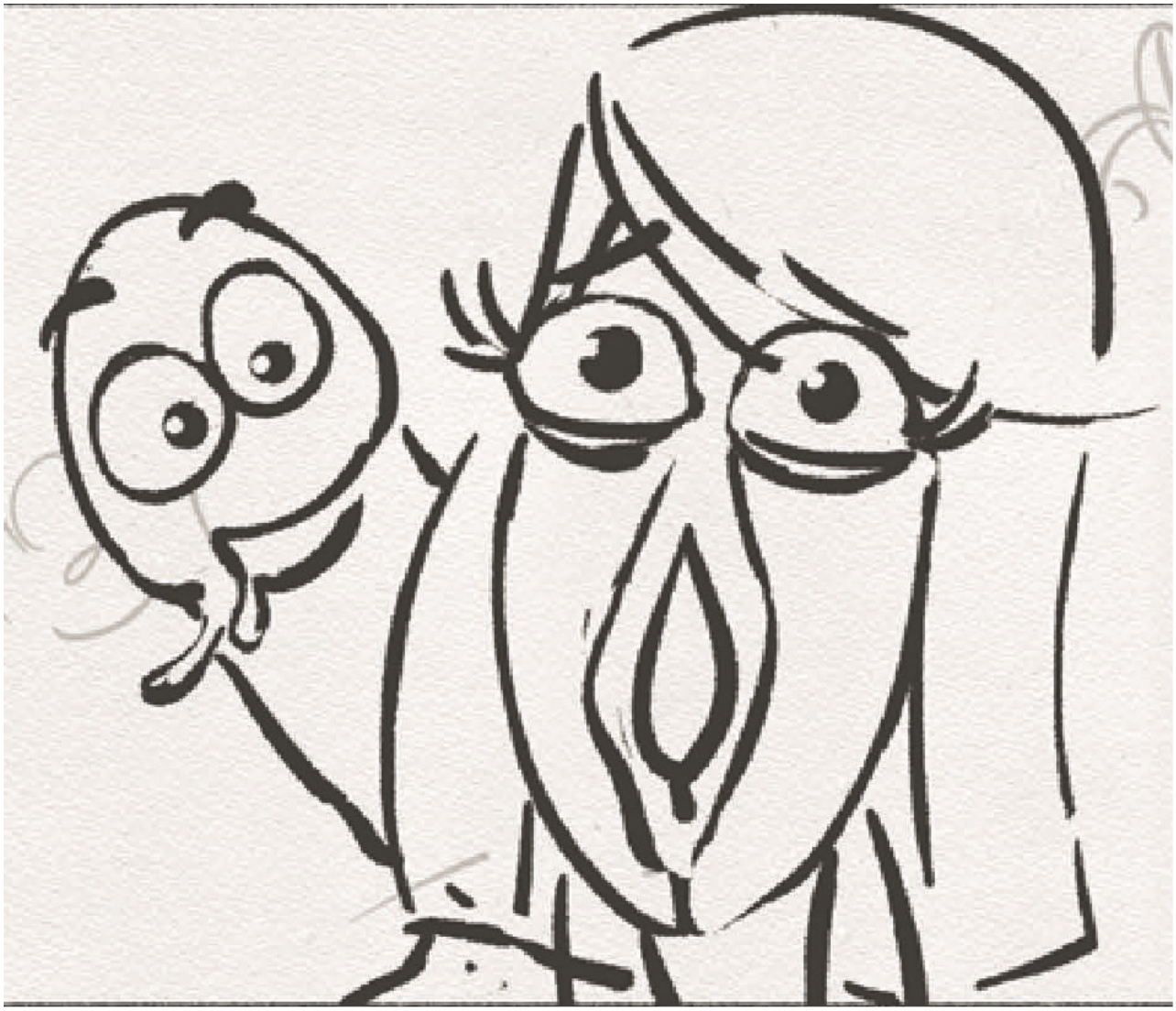


Figure 5. Voice over actors in the sound booth.

Figure 6. Screenshot from the intervention.

Figure 7. Screenshot from the intervention.



Results

Participation

In conversations during the workshops, the 6 young men in the group claimed they had gained a better understanding of the impact of their behaviors, and all self-referred to the nurses to have their first sexual health checkup. Having reviewed the final storyboard, they were excited for the launch of the animation, *Dick loves Doot*, which was launched at HBW on March 15, 2018. It is hosted on the Queen's University Belfast, School of Nursing and Midwifery, YouTube channel [65]. (Please contact the authors if you are having trouble accessing the animation). It has been agreed to play this on television screens throughout all 3 Northern Ireland prisons, and we are also exploring useful contexts to use this with other young men via the university and with community health promotion colleagues. This promotion tool will also be included in the sexual health module of a broader program of work we are developing in the prison—a *Relationships and Future Fatherhood* intervention for young incarcerated men.

Preliminary Evaluation

A focus group was arranged at the end of the project to explore issues around the experience of participation and the final product. Unfortunately, because of the transient nature of the prison population, only 2 members of the young men's group were available to attend. Overall, they said they enjoyed their participation in the project, found it interesting, and fun:

> *everybody was all good, the work was all good, and everyone was 100%.* [Male 1]

> *oh aye we had good craic (fun) with them-ins aye, it was funny.* [Male 2]

> *whenever I was out there I went with someone but it did make me think…so I got checked anyway and tested when I came back in.* [Male 2]

They also regarded it as useful learning and made speaking up and asking questions about their bodies and their health easier:

> *its opened my eyes.* [Male 1]

> *it was great to get out (of their cell) and come over here and get a bit of craic, there's certain questions that you'd be afraid to, reach out like, its mad, but it*

> *was easier to ask because you's were already there.* [Male 1]
>
> *knowing that other people think about things the same way and have done similar things it's easier to talk about what you've done cause sometimes you don't wanna talk about things that you've done just in case you embarrass yourself.* [Male 2]

The young men agreed that their voices had been listened to and that the intervention reflected their real-life issues and concerns, while also portraying a clear message that would be useful to other young men.

> *it's just spot on like everything was there.* [Male 1]
>
> *It's gonna be good like its short and its funny as well, that's the way you need it.* [Male 2]

They also felt grateful to, and valued by, the prison authorities for providing the opportunity for them to participate in something that was relevant to them and other young men:

> *fair play to them (prison officials) for letting you's in to do this…the more you put in the more you get back.* [Male 1]

In relation to accessing the sexual health services that had been set up inside the prison, the young men had made full use of this, which is reflected in the number of tests being carried out in the clinics, and were encouraging others to do so as well:

> *before I went out I got checked and then whenever I came back in after going with her I got checked again, so I know.* [Male 2]
>
> *I got my bloods and urine and all done like, we all did.* [Male 1]

The nurses' evaluations of the 3-day training course, which prepared them to better understand and engage with their patients on sexual health matters, described how much they enjoyed and greatly benefitted from this knowledge; they highly recommended the course to their colleagues who work in other prison sites:

> *The course was delivered by a great team who made it very interesting and funny at times. A lot was learned and I am glad that I got the chance to participate in this.* [Nurse 1]
>
> *I feel perhaps more nurses who work with patients doing sexual health checks on sites should go on this course. Currently I am the only nurse from my prison to attend this 3-day course.* [Nurse 2]

Importantly, the nurses described developing a completely fresh attitude on becoming upskilled to assess asymptomatic sexual health concerns, particularly in the manner in which they approached sexual health communication with their male patients. This also included, for the first time, delivering health promotion in a group setting with their patients within prison sites, and this experience exceeded their expectations. The following quote illustrates a common reaction from all the nurses on completing the course:

> *I have had a complete U-turn on previous view that 1-to-1 sexual health education was better than group work. Now a convert to the idea of group work!* [Nurse 3]

Discussion

Principal Findings

This study adds to the scant literature on conducting sexual health promotion research with hard-to-reach young men within prison and describes an empowering RB method on how to engage them in developing health interventions that are relevant to their particular needs, that is, *made by them, for them*. These young men tend to have multiple and complex problems and often lack the personal assets and opportunities on which to draw on to build healthy lifestyles [1,10,12]. This example describes how health care professionals can come together with a target audience to share information and communicate health messages in a way that is relevant and engaging [29].

This RB process used is designed to empower both the service-user (young men in prison) to take responsibility to improve their own health and *agents of state* (duty-bearers—nurses) to fulfill their obligations under human rights legislation to provide appropriate and accessible health and education [12]. Such an inclusive approach can reduce the young men's risk behaviors upon release and assist with their reintegration back into the community [66]. Working within the prison environment and employing an RB approach provided an opportunity to work with a group of marginalized young men and support and advance the concept of *healthy prisons* [20,28,41], that is, to reinforce the idea that *prison health is public health* and that prisoners should benefit from rehabilitation strategies that empower them to be released back into the community in better health than they entered, for the good of themselves, their families, and communities [2,23,25,26,28].

This study also adds to our understanding of how health promotion can be cocreated in the prison context. According to our methodology, the responsibility is on *agents of state* to provide health and education information that is accurate, accessible, and useable. Our approach to developing fun and engaging sexual health promotion materials within prisons can help normalize sexual health among a high-risk population in an accurate yet accessible and meaningful way. Consequently, incarceration can provide an opportunity for health researchers to reach this high-need and typically hard-to-reach group. Although this situation can enable access to participants, an effort was still required on their part to continue to attend and engage at each meeting. Factors that fed into their engagement centered on the focus on their rights, and the amount of decision-making power and autonomy they were given to input into the content, design, and mode of communication of the Web-based intervention, which also added legitimacy to the end product [57,61]. The young men found the meetings fun and informative, which impelled them to attend. They learned lots, felt valued and listened to, and seeing their ideas reflected in the products created in them a sense of ownership and pride over the intervention.

Focusing on the needs of society's most marginalized young men by helping them to maintain good sexual health is a

powerful way of addressing health inequalities overall [15,16]. Situating their sexual health in the wider context of human rights is a strong argument for the inclusion of their voices, which have largely been missing in the sexual and reproductive health research and education agenda to date. The findings support the contention that a human RB approach to coproduction, particularly for marginalized groups, can add insider value to interventions that can empower incarcerated young men to make positive healthier decisions about their lives and their partner's lives, and thus support their rehabilitation. The experience at Hydebank has shown that strong collaborations among academics, health and social care, prison management, and the young men themselves can be forged to support learning and skills development and enhance the overall rehabilitation experience of young men in prisons.

The support we received for our RB participatory work from the Northern Ireland Prison Service and the Department of Justice in Northern Ireland has been crucial to allow us to provide the space for prisoner voice to be heard, which was key to the success of this project. As such, Northern Ireland is leading the way in promoting innovative approaches to developing education and health behaviors as part of the rehabilitation of young men. This project demonstrates what can be achieved when agencies work together around a common goal of reforming and rehabilitating these young men to encourage good health behaviors within, and on leaving, their incarceration. Future steps of this research will be evaluation of the intervention.

Limitations

Participants in this study were restricted to 1 prison site in Northern Ireland (United Kingdom), which could mean that the issues and priorities they presented may not be representative or generalizable. However, the literature suggests that their experiences are consistent with young men residing in other marginalized areas and contexts. The evaluation of the animation and participatory process discussed during the 1 focus group at the end of the project included only 2 participants who shared similar positive views. However, the broader generalization we advance in this study is the approach and not the product.

Conclusions

The RB participatory approach to prison health advanced in this study can provide invaluable insider knowledge and strategies by which to target the health inequities that affect young incarcerated men. It provides a means to (1) understand the impact of structural determinants on health and health inequalities, (2) create inclusive opportunities for developing bespoke targeted interventions, and (3) galvanize collaborative teams to work together to disrupt the structures and processes that lead to, and encourage, health inequities. To reduce future risk, effective treatment, coupled with coproduced interventions that transmit relevant health messages in a way that is meaningful, is key to success.

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Conflicts of Interest

None declared.

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Abbreviations

HBW: Hydebank Wood College
RB: rights-based
RSE: relationships and sexuality education
STI: sexually transmitted infection

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Protocol

Mobility and Participation of People With Disabilities Using Mobility Assistive Technologies: Protocol for a Mixed-Methods Study

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Abstract

Background: Many community-dwelling individuals living with a disability use mobility assistive technologies (MATs). MAT devices are generally beneficial for individuals with mobility impairments. However, less is known about the specific factors that may foster or deter mobility and community participation.

Objective: The purpose of this protocol is to describe the methodology for a study including three main objectives: (1) to understand the places people using MAT go and the things they do, (2) to identify perceived barriers and facilitators as well as users' desired environmental modifications, and (3) to understand subjective and objective issues related to environmental accessibility.

Methods: A mixed-methods study was conducted in Vancouver and in Quebec City. Qualitative interviews were conducted to address all three objectives. In addition, Objective 1 was achieved through collection of global positioning system (GPS) data and activity diaries with 36 participants per site who represented six types of MAT users (ie, cane, walker, crutches, manual wheelchair, power wheelchair, and scooter). All participants were invited to take part in all aspects of data collection. PhotoVoice was used to address Objectives 2 and 3. Two environmental audits were used to address Objective 2. The Stakeholders' Walkability/Wheelability Audit in Neighbourhood (SWAN) measured perceptions related to a variety of community environmental features associated with mobility and participation. A total of 24 participants were recruited to each study site for SWAN data collection. The Measure of Environmental Accessibility (MEA) was also used to objectively measure access to exterior and interior environments selected earlier in the project by the participants that could benefit from improvements.

Results: Funding for this study was obtained from the Social Sciences and Humanities Research Council of Canada. Approval was obtained from the University of British Columbia Research Ethics Board and the *Centre intégré universitaire de santé et de services sociaux de la Capitale-Nationale* Research Ethics Board. Regarding the MEA evaluations, 19 locations (ie, buildings and exterior spaces) where obstacles have been identified by the participants of the PhotoVoice focus groups have been evaluated

in Quebec City and 20 locations have been identified in the Vancouver region by the participants of the community forums. Data collection for this project was completed in December 2018. Analysis and writing of manuscripts are underway.

Conclusions: The use of a variety of methods to gather data on participation and mobility will allow a more holistic consideration of factors influencing mobility with a MAT device. This study will provide objective information about the mobility of participants and identify barriers and facilitators that impact their mobility and community participation. Through the mixed-methods approach employed in this study, we will gain a subjective evaluation of the participants' neighborhoods, including personally meaningful information on environmental features that influence participants' everyday mobility and participation. We will also gain an objective evaluation of particular obstacles that community users of MAT identify as significant barriers to their ability to access public environments. We anticipate that these findings will help to identify a broad spectrum of solutions to improve the mobility and community participation of MAT users.

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KEYWORDS

mobility limitation; physical barriers; social participation; assistive technology

Introduction

In 2012, over 7% of Canadians aged 15 years or older (ie, approximately 1,971,800 individuals) reported having a mobility-related disability [1]. According to Charette et al, approximately 1,125,000 community-dwelling individuals aged 15 years or older used walking aids, representing 3.2% of the Canadian population [2]. Of these individuals, 962,290 used canes, walking sticks, or crutches and 465,340 used a walker [2]. Approximately 1% of Canadians (ie, approximately 288,800 individuals) used wheeled mobility devices (eg, scooters and manual or powered wheelchairs) for their daily activities [3]. Mobility assistive technologies (MATs) have been associated with increased mobility [4-7], defined as all movements leading to a change in position or location of an individual by his or her own means [8]. Moreover, some research has indicated that MAT use increases independence [4,5,9] and community participation [9-11].

Unfortunately, there are a variety of issues related to the use of MAT, such as accessibility to buildings via doors, accessibility to restrooms [12-14], and absence of sidewalks or of curb cuts [15-17], inducing physical strain on individuals who have to overcome these barriers. These issues reduce MATs' potential impact on mobility, independence, and community participation. Although access to MAT is recommended by the World Health Organization to improve the lives of people with disabilities [18], many users do not receive the devices they need and fewer users receive the MAT training they require to effectively use the devices [19-21]. For example, it is estimated that half of all manual wheelchair users in Canada need assistance for propulsion [10], which likely affects their independence. Moreover, social stigma may represent a barrier for some MAT users [22-25]. In Canada and many other contries, there is a wide variety in how MAT are funded. In 2006, out of the entire Canadian adult population with mobility disabilities who used MAT, 15.2% needed more aids (ie, some needs met) and 10.5% had none of the required equipment (ie, no needs met) [26]. Furthermore, despite several legislative changes, individuals using MAT still frequently encounter accessibility problems [5,11,27-33]. Laws regarding the built environment are intended to foster social participation and equal access rights for people with disabilities, however, they do not address all potential barriers and, thus, many environmental barriers persist [34,35].

There is a general understanding of the characteristics of MAT users' mobility (ie, distances travelled and encountered obstacles); however, we know little about how MAT influences users' community participation, here defined as "the involvement of people in a geographic community that includes mobility, daily activities, work, and social engagement" [36]. Different methods of documenting travel habits and environments should be explored with MAT users to find a combination of measures that allows a thorough assessment of their community participation and daily activities. Although many authors have discussed the potential for objective measures using global positioning systems (GPS) and data loggers to capture real-time mobility [37-41], few studies have reported such data [39-41]. Furthermore, these data alone do not provide a complete picture of MAT [39-41], as they do not take into account the individuals' lived experience. Although some authors have measured the frequency of participation and perceived limitations among wheelchair users [42,43], there is scarce information about their day-to-day participation.

It is therefore critical to study MAT users' mobility in a more comprehensive and in-depth manner in relation to their community participation. By identifying barriers to MAT users' mobility, this study aims to create a more inclusive society for all. With this overarching goal, we present a mixed-methods study with the following objectives:

1. To understand the places MAT users go and the things they do.
2. To identify perceived barriers and facilitators as well as the users' desired environmental modifications.
3. To understand subjective and objective issues related to environmental accessibility.

Methods

Overview

This project used a participatory approach [44-47] that involved collaborators from municipalities and the community who were concerned with the daily lives of citizens with disabilities. The

aim was to create a partnership that enabled the implementation of concrete actions and modifications that facilitated community participation among individuals with disabilities. A participatory approach was used to encourage the identification of solutions to overcome barriers to community participation, including improvements to MAT design; provision and training in MAT use; or the development of policies, regulations, actions, or services to improve the mobility of individuals with disabilities.

Participants

To qualify for the study, participants must have lived in Metro Vancouver, New Westminster, or North Vancouver, British Columbia, or in Quebec City, Quebec, and the surrounding area. Participants were required to use a MAT as their primary means of mobility, which could have been a cane, walker, crutches, manual wheelchair, power wheelchair, or scooter. Participant demographics (ie, age, type of disability, job, gender, or technological affinity) were not considered as eligibility criteria to facilitate the recruitment procedure. Individuals were excluded from the study if they were unable to communicate in French or English or if they could not provide informed consent. People who lived in nursing homes or residential care facilities were also excluded from the study.

Study Design

To address the above-mentioned objectives, a mixed-methods approach was proposed. All participants took part in a semistructured interview, provided demographic information, and completed the standardized measures. Participants also had the option to participate in three additional methods: (1) GPS tracking of participants' movement in the community combined with an activity diary, (2) PhotoVoice, and (3) physical environmental audits (see Table 1 for a detailed description of the relationship between the methods and the study objectives).

Procedure and Data Collection for Global Positioning System Tracking, Activity Diary, and Qualitative Interview

Participants' mobility was recorded using a portable GPS (Travel Recorder XT, model BT-Q1000XT, Qstarz International Co). These data were supplemented with an Apple iPad mini (model ME280C/A, Apple Inc)-based activity diary app (ie, the customized Filemaker Go app) that allowed participants to describe the places they visited, their activities, the modes of transportation they used, and whether they were accompanied by others (see Multimedia Appendix 1 for details). The participants took part in a training session on how to use the app and the GPS. Participants were given a troubleshooting document for the devices and contact information for the research assistants in case of any difficulty with the devices and app or for emergencies. Research assistants were also available during the data collection process to answer any questions regarding the equipment and process. The participants used the GPS and app for a 1-week period. Upon completion of the data collection process, the participants returned the devices to the research assistants who reviewed the data (ie, tracks from GPS data and the diaries) with them. The research assistants then conducted a 20-minute, qualitative, semistructured interview with the participants regarding their main MAT and other MATs used.

Table 1. Research questions and methods.

Methods	Study objectives	Subresearch questions
GPS[a] mobility data + activity diary + qualitative interview	1. Understand the places people go and the things they do	Where do people who use different types of MAT[b] go?
		Where do people who use different types of MAT not go?
		What activities do they recall doing and what device were they using?
		When do they do these activities?
		Where do they do these activities?
PhotoVoice (includes qualitative interviews and focus groups)	2. Identify perceived barriers and facilitators as well as the users' desired environmental modifications	What barriers to mobility and social participation do people who use different types of MAT encounter?
		What facilitators to mobility and social participation do they encounter?
	3. Understand subjective and objective issues related to environmental accessibility	What changes would they like to see happen to improve their mobility and social participation?
		How would they like to see these changes facilitated?
Adapted SWAN[c] tool (subjective audit) + MEA[d] (objective audit)	2. Identify perceived barriers and facilitators as well as the users' desired environmental modifications	How walkable or wheelable is the selected block? What positive or negative elements are identified?
		How accessible is public infrastructure when visited by device users? What positive or negative elements are identified?

[a]GPS: global positioning system.

[b]MAT: mobility assistive technology.

[c]SWAN: Stakeholders' Walkability/Wheelability Audit in Neighbourhood.

[d]MEA: Measure of Environmental Accessibility.

To describe the sample, the research assistants also gathered quantitative data, including demographic information and the following outcome measures:

1. Hospital Anxiety and Depression Scale (HADS) [48]: auto-administered measure evaluating and screening of potential anxiety and depression cases; measure is divided into two scales of seven items; rating is on a scale of 0-3; a score is generated for each subscale and for all items.
2. Self-report Late-Life Function and Disability Instrument [49]: assessment of meaningful change in function and disability; frequency and capability of performing life tasks are measured.
3. Life-Space Assessment (LSA) [50]: 20-item questionnaire measuring mobility areas (ie, home, around the home, neighborhood, city, and outside the city) while considering interactions between the person and the environment.
4. Mobility Device Use Confidence [51,52]: 65-item self-report questionnaire designed to measure confidence with mobility device.
5. Social capital measure [53]: measure examining social and behavioral determinants of health and well-being.

The data will also be combined with anxiety and depression data in predictive analyses and will be included in analyses to determine the influence of personal, MAT, and environmental factors on the activity spaces of people who use MAT using the GPS and trip diary data. Each method reported in this protocol requires separate analyses. To avoid bias, the interview guide (see Multimedia Appendix 2) was developed by team members prior to the data collection and all interviewers received training. The interview guide allowed participants to describe their own perception of barriers and facilitators to their mobility. The interview guide was developed to help participants provide their personal experience. According to participants' addresses, a walking score was calculated using the website Walk Score [54], which is available for every address in the United States, Canada, and Australia. The tool ranks cities and neighborhoods according to the level of walkability, taking into account public transit, better commutes, and proximity to people and places. Our objective was to recruit 36 participants per site (n=72 total), representing 6 users from both sites per type of MAT (ie, cane, walker, crutches, manual wheelchair, power wheelchair, and scooter). Participants were invited to take part in other data collection methods.

Procedure and Data Collection for PhotoVoice

PhotoVoice is a community-based participatory research method through which participants are asked to record visual images that capture their lived experiences [55,56]. It facilitates participant empowerment by considering investigators and participants as equal partners in the research process, such that participants are recognized as experts of their own experiences. Through a four-step PhotoVoice process, participants completed training, individual interviews, GPS data collection, and focus groups.

First, each participant took part in a training session on how to operate the camera feature of the app discussed in the previous method used. The training session allowed exchanges on ethical photo etiquette, specifically the importance of using a photo and video release form when taking pictures of other individuals. During the training session, participants worked with the researchers to identify potential images that they might purposefully set out to capture. Participants received a troubleshooting document for the provided device as well as the research assistants' contact information in case of a problem with the devices and apps or an emergency. They were also provided with a folder containing a summary of the project and photo and video release forms for obtaining consent from individuals in their pictures.

Second, over a 2-week period, which could have been concurrent with the GPS data collection method, participants were asked to take pictures or videos of the mobility- and participation-related barriers and facilitators they encountered. They were encouraged to take the tablet with them at all times during this period. It was suggested that they use the app to record notes about each image, describing their reasons for taking it. At the end of the first week, the research assistants contacted the participants to check in and ask about any problems or difficulties the participants may have been experiencing.

Third, upon completion of the above-mentioned 2-week period, participants took part in an individual PhotoVoice interview to discuss their most significant photos (ie, a personal selection of a maximum of 10 images). The interviewer looked for common themes among the pictures, and discussed suggestions for improvements and how to facilitate them (see Multimedia Appendix 3). This interview lasted approximately 20-30 minutes, depending on the number of photos selected by the participant.

Finally, PhotoVoice focus groups were held until a total of 24 participants per site were recruited for this method of data collection. However, 36 participants per site completed the PhotoVoice procedure excluding the focus group, as they could have also participated in the GPS tracking, activity diary, and qualitative interview phase or they could have been different participants. After 5-7 participants who used various types of MATs finished taking pictures, they were asked to take part in a group discussion about the photos they had taken and a PhotoVoice focus group was planned (ie, approximately three focus groups per site). Participants were not required to participate in the focus groups. Participants who completed focus groups took turns sharing the most important images they had previously selected during their individual PhotoVoice interview. Participants were asked the following questions about their images and videos: "Please describe the photo/video you have chosen." "Why did you select this photo/video for the interview?" and "Where was the photo/video taken?" Then, the entire group was asked, "Do members of the group have questions or comments about this picture?" After the photos were shared, the group was asked the following questions:

1. "What common themes do you see among your photos/videos and which photos can be grouped in those themes?" (Group photo selection)
2. "If you wanted to see any improvements made based on the images/videos that you selected, what would those be?"

3. "How would you suggest these improvements should be made?"
4. "How could the images or videos you took be used to facilitate those improvements?"

Participants that were unable to attend the focus groups were able to access the results if they were interested. The themes identified by the groups were shared among participants to gain a sense of how the findings resonated. The PhotoVoice focus groups were audio-recorded and transcribed verbatim. Images were numbered and referenced in transcripts. Each focus group lasted 2-2.5 hours.

The transcribed interviews will be analyzed using thematic analysis [57] through an inductive approach to coding. This process requires identification of relevant text in order to categorize data into emerging themes. The visual data collected from participants will be used to supplement the thematic analysis.

At the end of the study, a photo exhibition will be held to celebrate the participants' work and raise public awareness of relevant issues. Family, friends, relevant stakeholders, and the general public will be able to view the pictures and listen to the stories behind them. The exhibition will be held in local libraries, community centers, or other public venues. Participants interested in taking part in the photo exhibition will be asked to select photos from the previous focus groups and write captions to accompany them. If the participants prefer, captions can be written by the researchers and approved by email to ensure the captions match their interpretations. The participants' photos and captions will be presented in full consultation with them. Participants will also be integrated in the planning process of the exhibition regarding the type of presentation and the date(s) and place at which the exhibition will take place.

Procedure and Data Collection for SWAN and Measure of Environmental Accessibility

Two instruments were used as environmental audits. The first, a modified version of the Seniors' Walkability Audit in Neighbourhood, renamed the Stakeholders' Walkability/Wheelability Audit in Neighbourhood (SWAN) [58-60], was developed to collect objective data across five domains of the built environment: functionality, safety, destinations, aesthetics, and social aspects. The 98-item tool was designed to conduct microscale audits of street segments or blocks between two intersections. In addition to the checklist, participants were asked to take photographs to document barriers or facilitators to walkability and wheelability found in their neighborhood. The SWAN tool also included a secondary form to record additional contextual information that was not taken into account in the audit tool, such as general land use of the area. The original measure was pilot-tested with 24 older adults in three neighborhoods in Frankfurt, Germany, to assess its acceptability and utility and to collect pilot data on microenvironmental features (eg, sidewalk quality and street lighting) [61]. In this study, one research team member was paired with a MAT user to audit four segments in his or her neighborhood. Segments consisted of street sections between two intersections that were purposefully chosen by the participant to highlight barriers and facilitators to their daily mobility. In this way, the SWAN tool helped participants identify areas and elements of the built environment that could be improved for mobility and participation outcomes among MAT users. In our study, 24 participants per site were targeted for this method of data collection.

The SWAN data collection procedure was divided into three parts. The first part consisted of training the participants in how to use the SWAN tool. During the training sessions for the SWAN, participants received a Google Maps image of their own neighborhood. They were asked to identify four segments that they wanted to assess using the tool. The participants chose their own segments according to the following criteria: (1) segments that represented their neighborhood and had environmental features that had barriers or facilitators to maneuvering around with their MATs and/or (2) segments on streets that they frequently traveled.

The research assistants ensured that selected segments were auditable within a 2-hour period (ie, the chosen segments were not too far from one another). The four segments did not necessarily have to be in close proximity to the participant's house nor were they required to have automobile traffic. The selected segments could be *incomplete* (ie, due to temporary maintenance work of one sidewalk or crosswalk).

The second part of data collection with the SWAN consisted of user-led data collection for each of the selected segments. Each participant was accompanied by a research assistant during data collection who helped take pictures of environmental factors, while conducting simultaneous audits of the segments. If participants wanted to change a previously selected segment on the day of data collection, they were permitted to do so as long as the new segment was not located at a distance too far from the other three.

The third and last part of data collection with the SWAN was a community forum. Community forums were held to share preliminary findings with the SWAN study participants and stakeholders. Although, it was not mandatory for each participant to attend the community forum, they were encouraged to do so. Invited stakeholders were selected from citizen committees, advocacy groups, city planners, or other community organizations working in the fields of disability, accessibility, and mobility. Members of the advisory committee who serve in the study sites were also invited. These forums fostered dialogue and discussion around methods for facilitating knowledge translation of SWAN findings and identifying potential intervention sites and strategies in each city.

The second audit tool was the Measure of Environmental Accessibility (MEA) [62], which required the research assistants to rate the indicators of the environments identified for improvement by the participants. The MEA was briefly presented to the participants during the PhotoVoice focus groups in Quebec City and during community forums in Vancouver. It included observable and measurable features of the built environment that were considered valuable indicators of accessibility to urban infrastructure for adults with disabilities. The MEA assessed exterior and interior urban built environments, including seven types of urban infrastructures: parking lots, pedestrian facilities, building access from the

exterior, access to equipment, interior maneuvering areas, places for learning and leisure, and public restrooms [62]. The MEA labels were deconstructed to create three categories of information: (1) elements (ie, what was going to be evaluated), (2) components (ie, subcategories refining the description), and (3) criteria (ie, what needed to be measured) [62]. The rating scales included the following: (1) actual measures (ie, observable measures in the environment), (2) compliance (ie, regarding an observed measure with the criterion provided for each item—absent, compliant, or not compliant), and (3) observations and modifications (ie, explanations of the observations made and information on possible modifications to be made to improve accessibility) [62]. Most items had good-to-excellent interrater reliability indicators (626/882, 71.0%, using Gwet's agreement coefficient) [62]. Participants who took part in the PhotoVoice focus groups in Quebec City and the community forums in Vancouver were asked whether certain pictures presented environments to be evaluated with this measure or if other environments that were not included in the pictures should be evaluated. The gathered data from the MEA evaluations will be analyzed by identifying the most recurrent obstacles and by comparing those found in Quebec City and in Vancouver.

Ethics

The protocol for this study was approved by the Research Ethics Boards at the University of British Columbia (approval number H15-01340), the *Centre intégré universitaire de santé et de services sociaux de la Capitale-Nationale* (approval number 2015-424), and the regional health authorities of each site. All study participants provided informed consent.

Results

Funding for this study was obtained from the Social Sciences and Humanities Research Council of Canada. A summary of recruitment and completion of the different steps of the project can be found in Table 2. As for the MEA evaluations, 19 locations (ie, buildings and exterior spaces) where obstacles have been identified by the participants of the PhotoVoice focus groups have been evaluated in Quebec City and 20 locations have been identified in the Vancouver region by the participants of the community forums. Data collection for this project was completed in December 2018. Analysis and writing of manuscripts are underway.

Table 2. Recruitment and completion status of the study.

Study site	Participants recruited (N)	Participants, n (%)			
		Completed GPS[a] tracking, activity diary, and qualitative interview	Completed PhotoVoice	Completed SWAN[b]	Withdrew
Metro Vancouver	63	35 (56)	32 (51)	24 (38)	3 (5)
Quebec	41	39 (95)	40 (98)	25 (61)	1 (2)
Total (both sites)	104	74 (71.2)	72 (69.2)	49 (47.1)	4 (3.8)

[a]GPS: global positioning system.

[b]SWAN: Stakeholders' Walkability/Wheelability Audit in Neighbourhood.

Discussion

The purpose of this protocol is to describe the methodology for a study that includes three main objectives: (1) to understand the places people go and the things they do, (2) to identify perceived barriers and facilitators as well as the users' desired environmental modifications, and (3) to understand subjective and objective issues related to environmental accessibility. Thus, this study should allow us to discover information regarding the following elements:

1. Describe how environmental factors influence the mobility and participation of people with disabilities using a variety of MATs.
2. Identify environmental and personal factors that influence mobility and participation among adults with mobility impairments.
3. Identify the changes these people would like implemented to improve their mobility and participation.

The use of a variety of methods to gather data on participation and mobility allows for a more holistic consideration of the factors influencing these outcomes. The GPS tracking, activity diaries, and qualitative interviews provide objective information on the whereabouts of the participants as well as their subjective reports about the activities they are participating in and the means of mobility and transportation they are using.

Second, the identification of barriers and facilitators to mobility and participation through PhotoVoice focuses on the participants' preoccupations. An objective evaluation of the encountered obstacles judged as priorities of improvement when accessing public environments are performed from the results obtained though the PhotoVoice focus groups in Quebec City and the community forums in Vancouver via the MEA [62]. This will provide input into the most recurring obstacles in an objective and measurable fashion (ie, proposing a design ideal) and, thus, on the practical targets that could be proposed to improve access. To support the analysis and interpretation of the data collected with the SWAN tool, a scoring system was developed. Two different types of scores were produced from each evaluation of a segment: a participant score and a total score. The participant score was based on the subjective evaluation of each domain using a 5-point Likert scale. The total score was based on objective data noting the absence or presence of the barriers and facilitators in each segment. The presence of features supporting mobility obtained the highest scores, and segments with absent or mobility-impeding features obtaining the lowest scores in the total score category. Using this combination of objective and subjective evaluation of the

participants' neighborhood via the SWAN, the MAT users provided meaningful information on what is truly important to them within the built environment that influences their everyday mobility and participation.

Finally, the photo exposition and the community forum will allow participants to be heard by referring to the collected data and the sharing of their daily reality with stakeholders, the general public, and other researchers to heighten awareness on the barriers and facilitators they commonly encounter. The participants will also be encouraged to contribute to the discussions to find solutions to the most common problems.

Foreseeable limitations of this study include challenges in recruiting users with different MAT devices. During the recruitment process, two MAT devices had to be integrated into the same group since too few participants using these MAT devices participated (ie, canes and crutches). More participants had to be recruited in Vancouver to attain the same number of overall participants as in Quebec City. This is due to the fact that fewer participants in Vancouver participated in more than one method (11/63, 17%, participants completed all three methods of data collection in Vancouver versus 25/41, 61%, in Quebec City). Also, the sample of convenience may influence generalizability of the findings. The cross-sectional nature of the data only allows the consideration of one moment in time, whereas mobility likely fluctuates due to a variety of factors.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Activity monitoring questions.

[PDF File (Adobe PDF File), 17KB - resprot_v8i4e12089_app1.pdf]

Multimedia Appendix 2

Interview guide for all participants.

[PDF File (Adobe PDF File), 60KB - resprot_v8i4e12089_app2.pdf]

Multimedia Appendix 3

PhotoVoice interview guide.

[PDF File (Adobe PDF File), 59KB - resprot_v8i4e12089_app3.pdf]

Multimedia Appendix 4

Peer-reviewer report from SSHRC.

[PDF File (Adobe PDF File), 3MB - resprot_v8i4e12089_app4.pdf]

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Abbreviations

GPS: global positioning system
HADS: Hospital Anxiety and Depression Scale
LSA: Life-Space Assessment
MAT: mobility assistive technology
MEA: Measure of Environmental Accessibility
SWAN: Stakeholders' Walkability/Wheelability Audit in Neighbourhood

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Protocol

Model-Based Methods to Translate Adolescent Medicine Trials Network for HIV/AIDS Interventions Findings Into Policy Recommendations: Rationale and Protocol for a Modeling Core (ATN 161)

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Abstract

Background: The United States Centers for Disease Control and Prevention estimates that approximately 60,000 US youth are living with HIV. US youth living with HIV (YLWH) have poorer outcomes compared with adults, including lower rates of diagnosis, engagement, retention, and virologic suppression. With Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) support, new trials of youth-centered interventions to improve retention in care and medication adherence among YLWH are underway.

Objective: This study aimed to use a computer simulation model, the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)-Adolescent Model, to evaluate selected ongoing and forthcoming ATN interventions to improve viral load suppression among YLWH and to define the benchmarks for uptake, effectiveness, durability of effect, and cost that will make these interventions clinically beneficial and cost-effective.

Methods: This protocol, ATN 161, establishes the ATN Modeling Core. The Modeling Core leverages extensive data—already collected by successfully completed National Institutes of Health–supported studies—to develop novel approaches for modeling critical components of HIV disease and care in YLWH. As new data emerge from ongoing ATN trials during the award period about the effectiveness of novel interventions, the CEPAC-Adolescent simulation model will serve as a flexible tool to project their long-term clinical impact and cost-effectiveness. The Modeling Core will derive model input parameters and create a model structure that reflects key aspects of HIV acquisition, progression, and treatment in YLWH. The ATN Modeling Core Steering Committee, with guidance from ATN leadership and scientific experts, will select and prioritize specific model-based analyses as well as provide feedback on derivation of model input parameters and model assumptions. Project-specific teams will help frame research questions for model-based analyses as well as provide feedback regarding project-specific inputs, results, sensitivity analyses, and policy conclusions.

Results: This project was funded as of September 2017.

Conclusions: The ATN Modeling Core will provide critical information to guide the scale-up of ATN interventions and the translation of ATN data into policy recommendations for YLWH in the United States.

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KEYWORDS

adolescent; costs and cost analysis; health policy; HIV; medication adherence; modeling; retention in care; youth

Introduction

Background

Approximately 60,000 youth are living with HIV in the United States. Youth living with HIV (YLWH) have poorer outcomes than adults living with HIV, including lower rates of diagnosis, engagement, retention, and virologic suppression [1,2]. Established in 2001 by the Maternal and Pediatric Infectious Disease Branch of the Eunice Kennedy Shriver National Institutes of Child Health and Development, the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) has conducted rigorous evaluations of interventions to improve medication adherence, retention in care, and viral load (VL) suppression among YLWH [3]. ATN is the only national clinical research network that specifically studies adolescents aged 12 to 24 years living with HIV and at risk for acquiring HIV. ATN collaborations have included the United States Centers for Disease Control and Prevention; the Health Resources and Services Administration; the AIDS Clinical Trials Group; the HIV Vaccine Trials Network; the HIV Prevention Trials Network; the International Maternal, Pediatric, and Adolescent AIDS Clinical Trial (IMPAACT) Network; and the Microbicide Trials Network. This ATN began with new National Institutes of Health (NIH) support in 2016 to fund youth-focused projects that aim to reduce risk factors for adolescents at risk of acquiring HIV and to promote behaviors related to adherence and engagement with care for those living with HIV. ATN currently supports 22 protocols [3].

By projecting outcomes beyond the time horizon of traditional studies and thereby permitting estimates of long-term clinical outcomes and cost-effectiveness, computer-based health policy models can add substantial value to clinical trials and observational studies [4]. Projecting such long-term estimates is particularly important for studies among YLWH, for whom the health effects of poor virologic control may not manifest for years or decades [5]. Models can also combine data from multiple sources and compare a wide range of possible interventions, leveraging the extensive data collected within ATN and other studies into timely guideline and policy recommendations [6]. The Cost-effectiveness of Preventing AIDS Complications (CEPAC)-computer simulation models [7] of HIV infection in infants, children, and adults have been used to inform health policy related to HIV prevention [8,9], testing [10-12], and care [13-18], both in the United States and internationally. CEPAC model-based work has been cited in national HIV care guidelines for the United States, Brazil, Chile, Mexico, France, and Colombia, among others, as well as in the World Health Organization (WHO) guidelines [19-23]. For example, a CEPAC-Pediatrics model-based analysis projected that use of lopinavir/ritonavir in children younger than 3 years as first-line antiretroviral therapy (ART) led to longer life-expectancy and was cost-saving compared with first-line use of nevirapine; this analysis helped inform the WHO's recommendation in 2013 of a lopinavir/ritonavir-based regimen for first-line ART in that age group [16,24]. To date, few HIV modeling or cost-effectiveness studies have been conducted among youth; most have focused on HIV screening and prevention [25-32]. Previous work has not incorporated age- and time-varying changes in adolescent and young adult health-related behavior among YLWH.

Table 1. National Institutes of Health–supported studies from the Adolescent Medicine Trials Network for HIV/AIDS Interventions and the International Maternal, Pediatric, and Adolescent AIDS Clinical Trials Network included in the proposed analysis.

Study; time[a,b]	Title	Years	Age at enrollment	N (13-24)[c]	Population[d]
ATN[e] 061 [33-36]; 2.9 years	T-cells in ART[f] deintensification	2007-2010	18-24 years	130 (all)	NPHIVY[g]
ATN 106/086 [37-40]; 1 year	Health status and behavioral risk factors	2011-2012	12-24 years	2196 (all)	NPHIVY and PHIVY[h]
ATN 125 [41,42]; 1.5 years	Treatment at ATN sites	2015-2017	13-24 years	922 (all)	NPHIVY
P[i]1055 [41,43,44]; 1.8 years	Psychiatric conditions in PHIVY	2005-2006	6-17 years	294 (199)	PHIVY
P1066 [45-48]; 1 year	RAL[j] safety, PK[k], effectiveness	2007-2013	1 month to 19 years	126 (71)	PHIVY
P1074 [49-51]; 5.3 years	Long-term outcomes	2009-2014	0-24 years	1236 (all)	NPHIVY and PHIVY
P1093 [52,53]; 2 years	Dolutegravir-based ART	2011-2018	1 month to 18 years	160 (23)	PHIVY

[a]Mean or median follow-up time.

[b]Minimum key data for all studies: viral loads, cluster of differentiation 4 (CD4) cell count, ART regimens, opportunistic infections, sexually transmitted infections, pregnancy, and other clinical diagnoses.

[c]Total N (n aged 13-24 years): 4904 (4777).

[d]Population: primarily NPHIVY or PHIVY.

[e]ATN: Adolescent Medicine Trials Network for HIV/AIDS Interventions.

[f]ART: antiretroviral therapy.

[g]NPHIVY: nonperinatally HIV-infected youth.

[h]PHIVY: perinatally HIV-infected youth.

[i]P: pediatric.

[j]RAL: raltegravir.

[k]PK: pharmacokinetic.

Objectives

This protocol will leverage existing data from successfully completed NIH-supported studies (Table 1) to inform the development of novel approaches for modeling critical components of HIV disease and care in YLWH. As ATN investigators study new interventions to improve VL suppression among YLWH, the CEPAC-Adolescent computer simulation model will be developed to define the benchmarks for uptake, effectiveness, durability of effect, and cost that will make these interventions clinically beneficial and cost-effective. In addition, as new data emerge from ongoing ATN trials about the effectiveness of these interventions, the computer simulation model will serve as a flexible tool to project the long-term clinical impact and cost-effectiveness of these interventions. This project will, therefore, provide critical information to guide the scale-up of ATN interventions and the translation of ATN data into policy recommendations for YLWH in the United States.

Methods

Adolescent Medicine Trials Network for HIV/AIDS Interventions Structure and Establishment of the Modeling Core

The ATN structure consists of 3 ATN research program projects (U19s) and a Coordinating Center (U24; Figure 1). Each of the 3 ATN research program projects (U19) has a well-defined research focus supported by core infrastructures as well as participant recruitment and enrollment capacity. These research program projects are as follows:

- Comprehensive Adolescent Research and Engagement Studies [54], a comprehensive community-based project that aims to optimize the HIV prevention and treatment continuum for at-risk and acutely infected youth as well as youth with established HIV infection.
- iTech [55], a research program that aims to impact the HIV epidemic by conducting innovative, interdisciplinary research using technology-based interventions across the HIV prevention and care continuum for adolescents and young adults.
- Scale it Up [56], a research program that aims to assess and enhance the real-world effectiveness, implementation, and scalability of theoretically based and developmentally tailored interventions focused on improving HIV treatment and prevention self-management for youth.

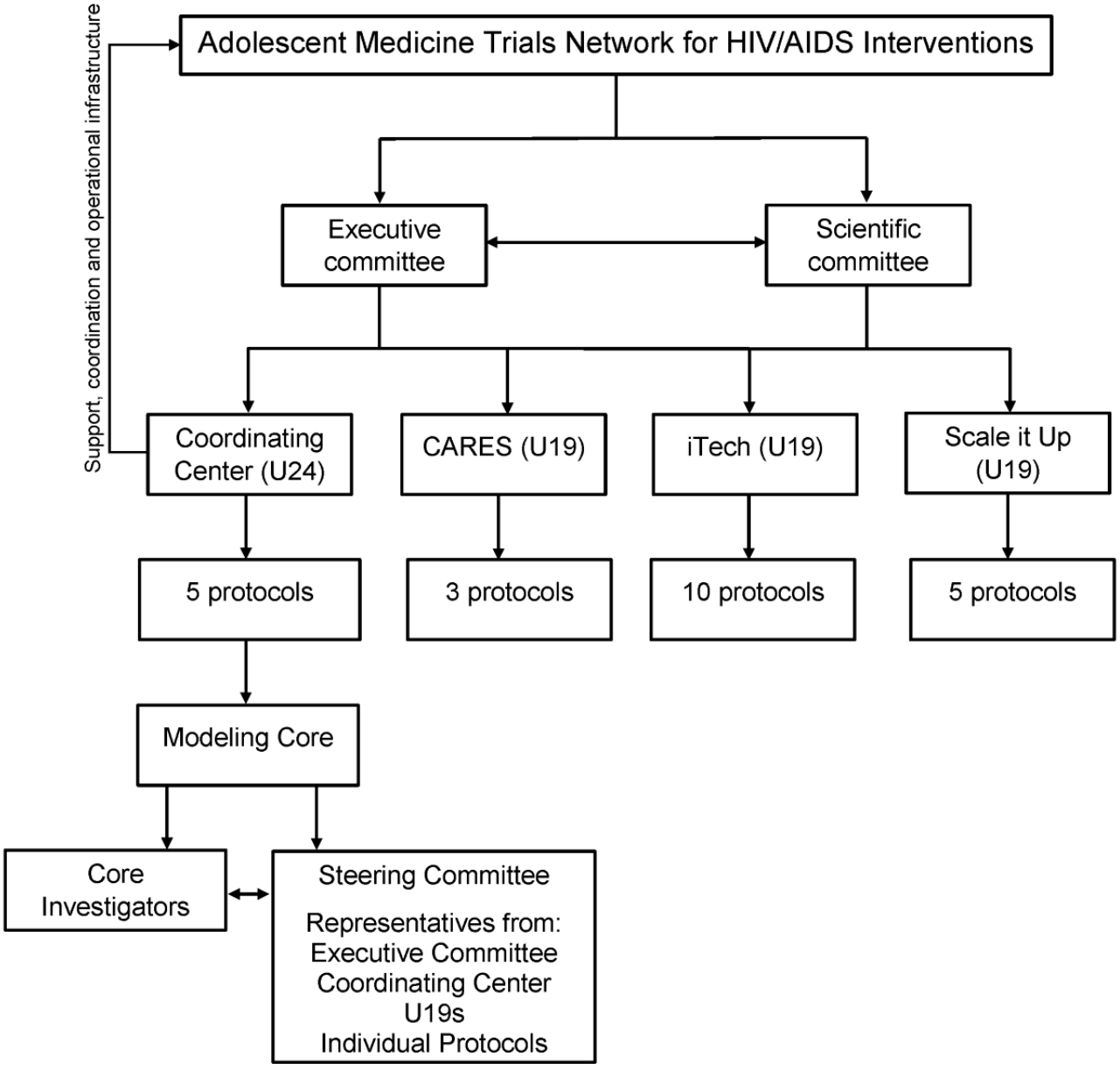
Each research program project (U19) supports several individual protocols [54-56]. The ATN Coordinating Center (U24) is located at the University of North Carolina at Chapel Hill. The Coordinating Center provides support, coordination, and operational infrastructure to ATN. The Coordinating Center also supports several stand-alone protocols such as "A Triggered, Escalating, Real-Time Adherence Intervention," which uses electronic-dose monitoring to inform an adherence intervention for youth without virologic suppression. The Coordinating Center also supports the Modeling Core.

The Modeling Core has established a Modeling Core Steering Committee that will meet regularly and include Modeling Core investigators, at least 1 principal investigator or liaison from each of the 3 ATN research program projects (U19s) and the ATN Coordinating Center, protocol chairs or representatives from stand-alone trials for which modeling is planned, and additional interested ATN investigators.

ATN investigators in the Modeling Core Steering Committee will provide feedback on the derivation of data inputs, design of new model structure within the CEPAC-Adolescent model, and selection of policy analyses to perform. Once specific ATN studies are identified as potential candidates for modeling analyses, the Modeling Core investigators will work with relevant protocol teams to ensure that data likely to be useful for later modeling are collected prospectively in each study.

After the Modeling Core Steering Committee has determined which policy analyses will be performed, project teams will be assembled for each analysis. Each project team will include Modeling Core investigators and the protocol chair or a representative from the trial being analyzed. Project team members have expertise in multiple relevant areas including epidemiology, health services research, economics, intervention science, implementation science, behavioral science, clinical trials development, and the clinical care of YLWH. Project teams will help develop the research question, identify any additional structural simulation model modifications, provide input on needed data parameters (eg, help identify potential issues of population mismatch for parameters derived from different sources), and review preliminary model results (eg, for face validity and identifying key sensitivity analyses). Abstracts, presentations, and manuscripts presenting model results will be reviewed in accordance with the ATN publications policy.

Figure 1. Organizational structure of the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN).



Textbox 1. Categories of key outcomes (specific events within each listed category will also be analyzed separately).

Categories of key outcomes:

- Centers for Disease Control and Prevention (CDC) HIV clinical diagnoses (CDC-A, B, and C)
- Severe or life-threatening, non-HIV–related diagnoses (eg, pneumococcal events)
- Chronic non-HIV-related diagnoses (eg, cardiac and renal disease and malignancy)
- Medication toxicity (division of AIDS ≥Grade 2)
- Psychiatric events
- Sexually transmitted infections
- Pregnancy or pregnancy outcomes
- Death

Scientific Objectives' Overview

Objective 1

Objective 1 was to determine rates of key clinical events for YLWH engaged in care stratified by age, CD4 cell count, and antiretroviral (ARV) and VL status in completed and ongoing NIH-supported studies. Using ClinicalTrials.gov [57], studies were reviewed that included YLWH aged 13 to 24 years at the US sites, and collected data related to CD4 cell count, VL, and ART regimens as well as clinical event data during the era of modern ART. Selected studies were conducted within the 2 largest NIH-sponsored national networks supporting clinical trials and observational studies in youth affected by HIV—the ATN and the IMPAACT Network. Incidence rates of opportunistic infections; HIV and non-HIV events (Textbox 1); and mortality based on age, sex, patterns of CD4 count and VL, and ARV use among YLWH will be evaluated in completed and ongoing NIH-sponsored studies (Table 1) in accordance with individual data use agreements.

Objective 2

Objective 2 was to develop the CEPAC-Adolescent model—a simulation model to reflect unique characteristics of YLWH.

The CEPAC-Adolescent simulation model will be developed to reflect the unique characteristics of YLWH. The foundational inputs of the expanded model will be populated with estimates from completed and ongoing NIH-supported studies (Table 1) derived in Objective 1 as well as other published sources. As new data emerge from the ATN or other sources related to clinical events, resource utilization, and specific interventions, model inputs will be updated.

Objective 3

Objective 3 was to use the simulation model to project the clinical impact, cost, and cost-effectiveness of selected interventions evaluated in ATN.

The Modeling Core Steering Committee will work with the ATN Executive Committee and the ATN External Scientific Panel to prioritize ATN studies for model-based analyses, based on data availability and the most relevant questions in health care policy for YLWH each year. The Modeling Core Steering Committee functions will include activities such as providing feedback on the costing perspectives to be used, the primary outcome to be modeled, secondary outcome measures to be included, and the types of economic estimates to be derived from the model.

Design for Objective 1

The design for Objective 1 was to determine rates of key clinical events for YLWH engaged in care stratified by age, CD4 cell count, and ARV and VL status in completed and ongoing NIH-supported studies.

Incidence rates of key clinical events (Textbox 1) will be described based on current age, sex, current CD4, current ARV use, and VL as well as mode of HIV acquisition (perinatally HIV-infected youth [PHIVY] or nonperinatally HIV-infected youth [NPHIVY]) [58]. These data will permit assigning risks of clinical events to simulated patients in the simulation model developed in Objective 2.

Population and Data Sources

Formal requests were approved to analyze data from 4800 YLWH in completed NIH-supported studies after appropriate data use agreement and network approvals were secured (Table 1). These studies include observational studies, nonrandomized interventions, and a randomized trial. All include youth aged 13 to 24 years at study entry. The primary focus of each study ranged widely, from determining the safety and efficacy of ARV medications to evaluating clinical, immunological, and psychiatric outcomes. All included a minimum set of key outcomes needed for this analysis, and all clinical events were recorded using comparable diagnostic codes. Protocols and data collection forms from all studies will be reviewed to understand how data can be harmonized among studies, as has been done in previous analyses [58]. Resource use input parameters will be derived from adolescent intervention or trial-specific data where available, as in previous work [29,59]. New data emerging from ongoing studies will be integrated into the model.

Data Management

Data analysis concept sheets and data use agreements have been approved for these analyses by individual networks as well as through the Eunice Kennedy Shriver National Institute of Child Health and Development Data and Specimen Hub repository [60]. Data will be cleaned (when applicable), harmonized, and safely stored at the Center for Biostatistics in AIDS Research at the Harvard TH Chan School of Public Health, which is

compliant with federal regulations governing information security.

Outcomes

Clinical events that impact short- and long-term (lifetime) outcomes and health care costs, such as the occurrence of specific opportunistic infections, non-AIDS-defining illnesses, sexually transmitted infections, pregnancy, and psychiatric events, within the categories listed in Textbox 1 will be analyzed.

Statistical Analysis

Incidence rates of each outcome will be estimated, stratified by mode of HIV acquisition and the combination of time-varying age (7-12, 13-17, 18-24, and 25-30 years), CD4 cell count (<200, 200-499, and ≥500/μL), and VL and ARV status, as in previous work [58]. The VL or ARV status will be categorized as follows: (1) suppressive ARVs—VL less than 400 copies/mL and any prescribed ARVs, (2) nonsuppressive ARVs—VL 400 copies/mL or more and prescribed ARVs expected to be suppressive, and (3) no ARVs—VL 400 copies/mL or more and no prescribed ARVs [58]. Linear interpolation between CD4 cell counts and $\log_{10}$-transformed VL will be used to estimate dates when strata thresholds are crossed. These estimated dates will allow us to determine baseline strata and calculate total person-time contributed to each stratum.

As in previous work, trends in incidence rates of outcomes across ordinal age, CD4 cell count, and VL/ARV categories, stratified by mode of HIV acquisition, will be assessed using Poisson regression models, accounting for within-subject correlation with robust SEs [61]. The hypothesis that higher rates of clinical events will be associated with person-time spent with lower CD4 counts, older age, and at higher VL will be examined [58]. VL of 400 copies/mL or more was selected based on historic lower levels of detection for assays used during the study period [58].

We will also advance approaches to describe and predict the trajectories of CD4, VL, and care engagement over time. Locally weighted smoothing plots will be used to obtain a graphical summary of CD4 and VL trajectories over time by mode of HIV acquisition and baseline age [62]. On the basis of visual inspection, linear regression or piecewise linear regression models will be fitted to obtain slope parameters for CD4 and VL over follow-up time among subjects with at least 2 available measures. Baseline covariates such as mode of HIV acquisition, age, CD4 count, VL, and ART regimen will be added to these regression models to assess association with observed CD4 and VL trajectories. To determine whether there are any important differences between subjects with longitudinal CD4 and VL data and those missing such data, baseline characteristics will be compared between these 2 populations.

If there are sufficient numbers of YLWH who miss visits or are lost to follow-up, these will also be used to identify patterns of care followed by distinct subgroups such as those who are in care, those who are care interrupters, and those who are not in care. Latent trajectory groups will be identified from the study data with group-based trajectory modeling [63,64]. After we identify groups of participants following similar trajectories, in a secondary analysis, we will assess associations between baseline characteristics of study participants and membership in particular trajectory groups. In the CEPAC-Adolescent model, these attributes will be used to account for heterogeneity in care engagement.

Design for Objective 2

The design for Objective 2 was to develop a simulation model to reflect the unique characteristics of YLWH.

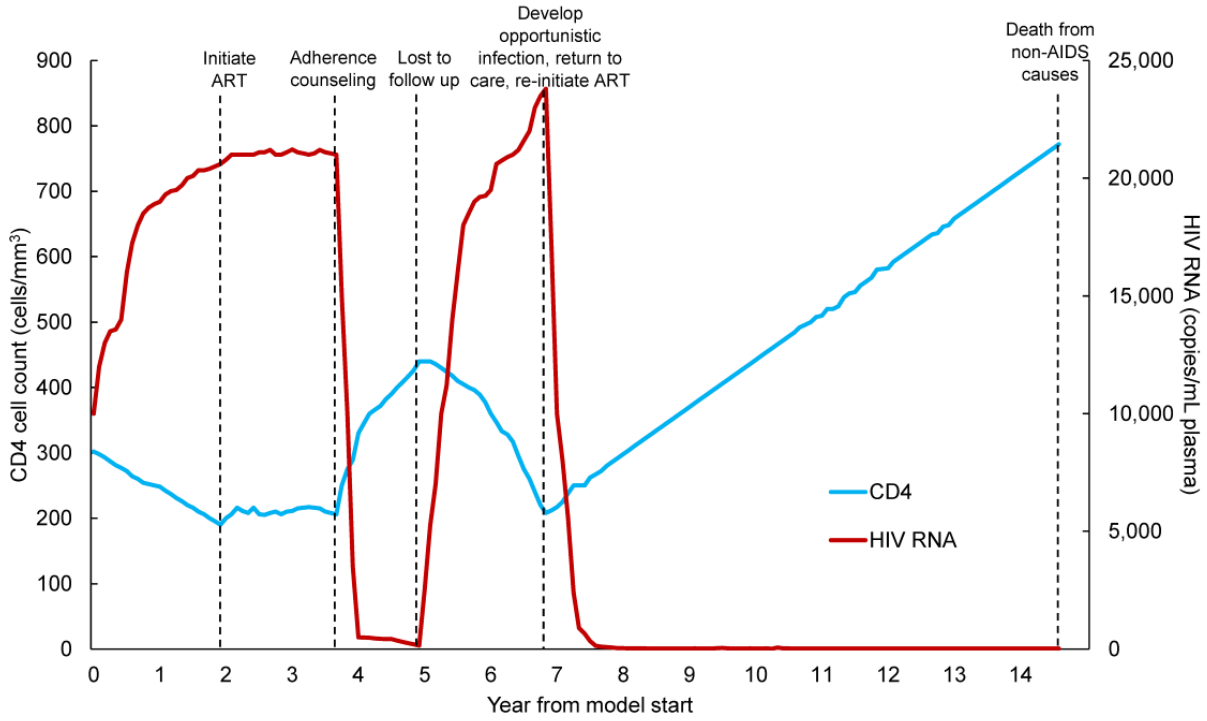
Current Model Structure

The CEPAC-Adult and -Pediatric models are Monte Carlo, state-transition models of HIV disease and treatment [7,8,17,18,29,65]. The models simulate people living with HIV with user-specified characteristics including age, CD4 cell count, VL, and treatment history, from model entry until death. In the absence of effective ART, CD4 cell counts decline monthly; with VL suppression, CD4 cell counts rise at user-specified rates. In each month, modeled patients face risks of key clinical events, such as opportunistic infections, other illnesses, and mortality, determined by current age and current CD4 cell count. Patients can also initiate or continue ARVs, with subsequent VL suppression or virologic failure, and can be lost to follow-up. Onward transmission risk is determined by pooled cohort VL levels using rates derived from published estimates (eg, 2.06/100PY transmission with HIV RNA of 3000-10,000 copies/mL) from adolescents, where available [66,67].

Patients are simulated within the model one at a time; the model tracks their clinical course, from time of entry into the model until death. Upon a patient's death, the model records summary statistics, and a new patient then enters the model. This continues until the last patient in a cohort dies and exits the model, at which time the model tallies clinical events, durations spent in each health state, monthly life and quality-adjusted life expectancies, and costs. State transitions are stochastic and determined by the Mersenne Twister random number generator algorithm [68] that was adapted for use in C++, the programming language of CEPAC. When finished running, model output can be extracted and analyzed by the user, as shown in Figure 2, which traces a simulated patient's CD4 cell count and HIV RNA over the course of several important clinical events.

Adolescent-specific patterns of medication adherence and care engagement will be simulated based on work in Objective 1. Currently, in the CEPAC models, clinical event risk, retention in care, and adherence vary between individual people, but do not vary over time or with changes in development or life events. The new model structure will be developed to reflect age- and time-varying adolescent- and young adult-specific aspects of HIV disease progression and care for YLWH based on these patterns. The model structure will account for heterogeneity—the specific additions to the model structure will be informed by the data generated through activities conducted as a part of Objective 1. Additional details of the existing CEPAC models, including flowcharts, a user guide, and sample patient traces can be found on the CEPAC website [7].

Figure 2. Sample simulated patient trace. CD4 cell count (cells/mm3) is presented on the vertical left-most axis and in the blue line. HIV RNA (copies/mL) is presented on the vertical right-most axis and in the red line. The horizontal axis shows years from model start. The dashed lines mark key clinical events for a simulated patient: initiating ART but failing to suppress HIV RNA and without improvement in CD4 cell count; receiving adherence counseling leading to HIV RNA suppression and improvement in CD4 cell count; becoming lost to follow up with subsequent rise in HIV RNA and decline in CD4 cell count; developing an opportunistic infection resulting in returning to care and reinitiating ART with subsequent HIV RNA suppression and improvement in CD4 cell count; and eventual death from non-AIDS-related causes. ART: antiretroviral therapy.



Translating Objective 1 Data Into Model Inputs

Incidence rates of clinical events (Textbox 1, Objective 1) will be converted into monthly event probabilities. During each patient-month for which a specific set of characteristics apply (age, CD4, and ARV/VL category), these data will be used to assign a modeled risk of each key clinical event over the next 30-day period.

Resource utilization and cost data related to HIV care, ART, and the occurrence of acute events will be derived from adolescent-specific literature when available and otherwise will be derived from adult literature and varied in sensitivity analyses, as in previous work [29]. When specific interventions and studies are identified as candidates for model-based analyses, the Modeling Core will work with study teams to collect the data necessary for future model-based analyses in real time (eg, time and motion studies, activity logs, and costs of personnel and supplies).

Model Validation and Approach to Uncertainty

The model will be internally validated, assessing the accuracy of the model structure by comparing model output (opportunistic infections, viral suppression probability, and survival) with the empiric data in the studies from which model input parameters were derived [69]. As the model projects outcomes over lifetime horizons, the longer-term model results cannot be compared with empiric data; however, as ATN-studied interventions become more widely implemented over time, past model results will be compared with newly available data. The model will next be calibrated to data from the literature and the studies in Objectives 1 and 2 to reflect current populations of YLWH and treatment strategies. One-way, multiway, and probabilistic sensitivity analyses will be conducted, following international guidelines to address uncertainty in data inputs for the model [70,71]. This involves varying single and multiple parameters over wide ranges and reassessing all clinical results and cost-effectiveness outcomes. Sensitivity analyses can inform the potential impact of strategies in scenarios that more closely resemble programmatic rather than trial settings.

Design for Objective 3

The design for Objective 3 was to use the computer simulation model to project the clinical impact, costs, and cost-effectiveness of interventions evaluated in ATN.

Clinical data not specific to ATN interventions will be from Objective 1, reflecting key components of disease progression and treatment for youth with and without VL suppression. Intervention-specific data will be derived from the ATN studies selected for model-based analyses; for ATN interventions, effectiveness, duration of effect, and intervention cost will be parameterized based on data from each modeled ATN trial. Model outcomes will include short-term survival and costs (calibrated to trial results) as well as projected long-term survival and costs, including life expectancy and lifetime per-person costs, and transmissions averted. To compare interventions, incremental cost-effectiveness ratios (difference in lifetime costs divided by the difference in life expectancy, in dollars per year-of-life saved) will be calculated and compared with

commonly used thresholds for the United States [72]. Adolescents comprise only a small fraction of participants in HIV-specific health-related quality of life studies, and emerging data suggest that youth may attach different values to specific health states compared with adults [73-77]. Moreover, one study found that, in general, adults place less weight on impairments in mental health (eg, being worried, sad, or annoyed) and more weight on moderate to severe levels of pain, relative to adolescents [75]. In general, values attached to identical health states are typically lower for younger people in comparison with adults of all ages and may depend on the elicitation method utilized [74]. Where available, adolescent-specific utility weights will be incorporated, and the impact of utility weights on policy conclusions will be examined in sensitivity analyses, as in previous work [29].

Our work in Objective 3 will have the following 4 key areas of emphasis:

1. Work with trial teams to develop study protocols, ensuring collection of data needed for modeling.
2. Conduct pretrial modeling analyses to inform study design and establish benchmarks for interpretation of trial results. For example, to inform study design, detailed simulations of disease progression and clinical events in youth can provide additional input into sample size calculations, and model-based projections can inform study protocol elements such as frequency of study visits and maximal permitted turnaround time for return of diagnostic test results. To establish benchmarks for interpretation, model-based projections under a range of assumptions about efficacy and cost can be used to identify critical thresholds for key study outcomes: how effective and durable would an intervention need to be for that intervention to add benefit to current practice? For any given efficacy and effect duration, at what cost and level of uptake would the intervention be cost-effective?
3. Conduct modeling analyses alongside trials to evaluate the potential clinical impact and cost-effectiveness of trial interventions when implemented at scale for YLWH in the United States.
4. Identify key parameters that may influence policy conclusions such as the cost of electronic dose monitoring bottles or duration of improved adherence after incentives. If data on these key parameters are lacking, this limitation can help identify new research priorities. The Modeling Core will work with ATN leadership to ensure this feedback informs the ATN strategic planning.

Role of the Funding Sources

The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Results

This project was funded as of September 2017.

Discussion

The planned data analyses and model development in Objectives 1 and 2 will position the ATN Modeling Core to evaluate a wide range of new ATN studies and other emerging data. Future work may include new therapies that are likely to be studied in the near future among YLWH, for example, long-acting ART [78]. The Modeling Core also collaborates with the ATN Data Harmonization Working Group to standardize the collection of resource utilization and cost data across all active ATN studies [79].

Strengths and Limitations

This protocol has several limitations inherent to model-based analyses. First, many models necessarily use short-term data to project across longer-term horizons. This extrapolation requires assumptions about whether and how trial-derived clinical risks and costs will change over time. However, when these assumptions are clearly described, examined rigorously in sensitivity analyses, and interpreted appropriately, this ability of models to leverage short-term data into longer-term policy recommendations is one of the key strengths of model-based approaches [4,69]. Second, research participants in Objective 1 studies may not be representative of the larger population of YLWH in the United States. However, these studies remain among the best sources of data for YLWH in the United States. Study-derived risks will be varied widely in model-based sensitivity analyses to examine the potential impact of variations in these results.

Conclusions

In summary, a Modeling Core has been established within ATN 161. A computer simulation model reflecting disease progression, care and treatment outcomes, and HIV transmission among adolescents and young adults will be developed. YLWH are a growing and vulnerable population in the United States, in whom lack of VL suppression contributes to poor clinical outcomes for individual patients, increases health care costs, and drives the ongoing HIV epidemic. Existing data from completed and ongoing NIH-supported studies will be leveraged to develop the adolescent-specific model. The Modeling Core Steering Committee will work closely with ATN leadership and investigators to design and conduct model-based analyses, addressing critical questions about HIV care among YLWH that cannot be fully answered by trials and cohort studies. The Modeling Core will also build a foundation to inform the design of new studies of interventions across ATN and to evaluate the clinical impact and cost-effectiveness of those interventions, directly translating the work of ATN into critical policy recommendations for YLWH in the United States.

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Authors' Contributions

All authors contributed substantively to this manuscript in the following ways: AMN, KP, and ALC contributed to the study design; AMN, KP, and ALC contributed to methods and data analysis plan; AMN and ALC contributed to drafting the manuscript; all authors contributed to critical revision of the manuscript (all authors); and all authors provided final approval of the submitted version.

Conflicts of Interest

None declared.

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Abbreviations

ART: antiretroviral therapy
ARV: antiretroviral
ATN: Adolescent Medicine Trials Network for HIV/AIDS Interventions
CDC: Centers for Disease Control and Prevention
CD4: cluster of differentiation 4
CEPAC: Cost-Effectiveness of Preventing AIDS Complications
IMPAACT: International Maternal, Pediatric, and Adolescent AIDS Clinical Trial
NIH: National Institutes of Health
NPHIVY: nonperinatally HIV-infected youth
PHIVY: perinatally HIV-infected youth
VL: viral load
WHO: World Health Organization
YLWH: youth living with HIV

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Protocol

Dignity Therapy Led by Nurses or Chaplains for Elderly Cancer Palliative Care Outpatients: Protocol for a Randomized Controlled Trial

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Abstract

Background: Our goal is to improve psychosocial and spiritual care outcomes for elderly patients with cancer by optimizing an intervention focused on dignity conservation tasks such as settling relationships, sharing words of love, and preparing a legacy document. These tasks are central needs for elderly patients with cancer. Dignity therapy (DT) has clear feasibility but inconsistent efficacy. DT could be led by nurses or chaplains, the 2 disciplines within palliative care that may be most available to provide this intervention; however, it remains unclear how best it can work in real-life settings.

Objective: We propose a randomized clinical trial whose aims are to (1) compare groups receiving usual palliative care for elderly patients with cancer or usual palliative care with DT for effects on (a) *patient outcomes* (dignity impact, existential tasks, and cancer prognosis awareness); and (b) *processes* of delivering palliative spiritual care services (satisfaction and unmet spiritual needs); and (2) explore the influence of physical symptoms and spiritual distress on the outcome effects (dignity impact and existential tasks) of usual palliative care and nurse- or chaplain-led DT. We hypothesize that, controlling for pretest scores, each of the DT groups will have higher scores on the dignity impact and existential task measures than the usual care group; each of the DT groups will have better peaceful awareness and treatment preference more consistent with their cancer prognosis than the usual care group. We also hypothesize that physical symptoms and spiritual distress will significantly affect intervention effects.

Methods: We are conducting a 3-arm, pre- and posttest, randomized, controlled 4-step, stepped-wedge design to compare the effects of usual outpatient palliative care and usual outpatient palliative care along with either nurse- or chaplain-led DT on patient outcomes (dignity impact, existential tasks, and cancer prognosis awareness). We will include 560 elderly patients with cancer from 6 outpatient palliative care services across the United States. Using multilevel analysis with site, provider (nurse, chaplain), and time (step) included in the model, we will compare usual care and DT groups for effects on patient outcomes and spiritual care processes and determine the moderating effects of physical symptoms and spiritual distress.

Results: The funding was obtained in 2016, with participant enrollment starting in 2017. Results are expected in 2021.

Conclusions: This rigorous trial of DT will constitute a landmark step in palliative care and spiritual health services research for elderly cancer patients.

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International Registered Report Identifier (IRRID): DERR1-10.2196/12213

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KEYWORDS

palliative care; cancer; elderly, religion, therapy

Introduction

Our long-term goal is to improve spiritual care outcomes for elderly patients with cancer. We will use a spiritual intervention, dignity therapy (DT), to help these patients maintain pride, find spiritual comfort, enhance continuity of self, and ultimately explore meaning in the context of their life-threatening illness. "Dignity Therapy, a novel, brief psychotherapy, provides patients with life threatening and life limiting illnesses an opportunity to speak about things that matter most to them. These recorded conversations form the basis of a generativity document, which patients can bequeath to individuals of their choosing" [1]. However, DT has not been viewed as a spiritual intervention or studied with chaplains as the interventionist. Our thesis is that DT will systematize spiritual care processes and improve patient outcomes (spiritual and cancer prognosis awareness). The spiritual outcomes are important because people with advanced illness report that *being at peace with God is as important as freedom from pain* [2]. Spiritual concerns are issues for 86% of patients with advanced cancer [3]. Unfortunately, little research guides interventions for spiritual care. We will address this gap by testing efficacy of DT in a rigorous, multisite, randomized controlled trial (RCT) [4].

Previous studies of DT demonstrated clear feasibility but inconsistent efficacy of DT with virtually no evidence of its mechanism of action. Specifically, the 12 studies of DT (8 uncontrolled feasibility and 4 mostly small sample efficacy RCTs) show DT to be an important intervention when delivered by nurses and mental health professionals. Effects on patients' distressing physical or emotional symptoms of life-threatening illness have been inconsistent. Taking a spiritual perspective for reanalysis of data from the 1 large RCT [1], we found that compared with usual care, patients who received DT reported significantly higher dignity impact ratings [5], which is consistent with the DT focus on meaning making, preparation for death, and life-completion tasks. Evidence from our pilot study also suggests that awareness of cancer prognosis outcomes and will-to-live is facilitated by DT [6]. Of the possible explanations for the lack of DT effect on physical symptoms, 1 could be that symptoms only moderate the DT effect, so conceptualizing symptoms as the relevant outcome is mismatched to the operative DT elements. It is also possible that spiritual distress could moderate the DT effect on patients' sense of meaning and purpose [1], which is an important part of dignity impact.

For this study, we selected 2 disciplines of the multidisciplinary palliative care team to focus on spiritual concerns—nurses and chaplains. A nurse-led or chaplain-led DT study of patients receiving outpatient palliative care is needed to determine the efficacy of DT on key spiritual-related patient outcomes (dignity impact, existential tasks, and cancer prognosis awareness) and explore possible moderators (physical symptoms and spiritual distress) of DT's effects on patient outcomes.

We propose a pre- and posttest, RCT with a 4-step (10 months per step), stepped-wedge design [4] to compare effects of *usual outpatient palliative care (usual care)* and usual care along with either nurse-led or chaplain-led DT on patient outcomes (*dignity impact, existential tasks* [preparation for death and life completion], *and cancer prognosis awareness* [peaceful awareness and treatment preferences]). We will assign 6 outpatient palliative care sites to usual care during the first step, and randomly assign 2 sites per step to begin and continue DT led by either a nurse or a chaplain during each of the next 3 steps. During the usual care steps, 280 patients will complete pretest measures (patient outcomes, covariates *[physical symptoms* and *spiritual distress]*, and *satisfaction* with palliative spiritual care services), receive usual palliative care, and complete posttest measures (patient outcomes, covariates, and satisfaction). During the experimental steps as part of routine palliative care service delivery, 280 patients will complete pretest measures, receive nurse-led or chaplain-led DT, and complete posttest measures. Using a mixed multilevel analysis with site, provider (nurse and chaplain) and time (step) included in the model, we will compare the usual care and each of the DT groups for effects on *dignity impact,existential tasks, and cancer prognosis awareness* and explore the moderating effects of physical symptoms and spiritual distress. We will also determine the effect of usual care and DT on the patient's satisfaction with palliative spiritual care services and the patient's unmet spiritual needs.

Specific Aims

Aim 1

We aim to compare usual care and usual care with nurse-led or chaplain-led DT groups for effects on *(1)patient outcomes* (dignity impact and existential tasks [preparation for death and life completion], cancer prognosis [peaceful awareness and treatment preferences]). We *hypothesize* that, controlling for pretest scores, each of the DT groups will have higher scores on the dignity impact (primary outcome) and existential tasks (secondary outcome) measures than the usual care group. In addition, patients in each of the DT groups will report better peaceful awareness and treatment preferences more consistent with their cancer prognosis (secondary outcomes) than the usual care group; and (2) *processes* of delivering palliative spiritual care services (satisfaction and unmet spiritual needs; and secondary outcomes). We *hypothesize* that each of the DT groups will show increased patient satisfaction with spiritual care services and fewer unmet spiritual needs compared with the usual care group.

Aim 2

We aim to explore the influence of physical symptoms and spiritual distress on the dignity impact and existential tasks effects of usual palliative care and nurse-led or chaplain-led DT. We *hypothesize* that physical symptoms and spiritual distress will significantly affect intervention effects. *This rigorous trial of DT will constitute a landmark step in gero-oncology palliative care and spiritual health services research.*

Research Strategy and Significance

The proposed palliative care research is responsive to PA-13-354/NOT-CA-14-016, *Advancing the Science of Geriatric Palliative Care* for Cancer Patients. It is significant for multiple reasons: it breaks new ground in inquiry regarding spiritual care as a part of patient-centered care for elders with serious illness before they get morbidly ill. The study uses an empirically established intervention (DT), opening chaplaincy in palliative care to rigorous health services research. The study advances palliative care research by leveraging a network of collaborators in a recently formed network for large data, and by making use of a relatively novel method, stepped-wedge design that typically reduces sample size needs and makes recruitment more feasible, especially for those who are frail and stressed by their cancer illness and treatments.

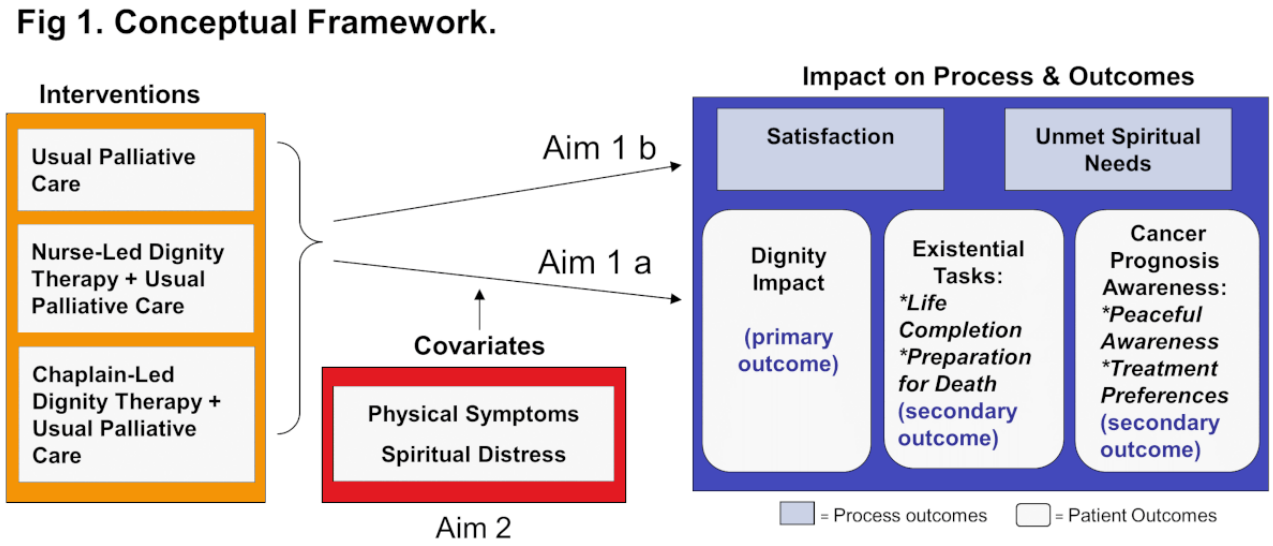
Dignity Therapy: An Effective Intervention in Need of More Study

DT has its conceptual origins in Butler's Life Review [7], which he developed as an antidote to depression in elders and understood as part of a life-cycle task. Both interventions are conceptualized as psychosocial and multidimensional for patient-centered care. But little is known about how DT works and if it can and should be used clinically.

Although DT has been established in RCTs to be beneficial to patients among multiple disease groups in multiple ways, the question of its efficacy when *administered* in a real-life care setting is not established. Pragmatically, within palliative care teams, it is most likely that nurses or chaplains could include DT as part of their routine work, and we, therefore, have designed a trial to assess the efficacy of DT delivered by nurses or chaplains. Considerations for either discipline include the following facts. In a prior RCT [1], a research nurse administered the DT with significant dignity impact findings. Furthermore, the nursing discipline's focus on holistic care inclusive of spirituality makes this discipline a strong candidate. Although the ratio of nurses to patients is suitable, nurses already have a heavy flow of work that may be sidetracked by DT unless carefully scheduled. In addition, recent work indicates that a taxonomy of chaplaincy activities reasonably aligns with DT components [8,9] and recent findings [10] also indicate that clinicians from nursing and medicine look to board certified chaplains (BCCs) as the professionals with the expertise to provide spiritual care. Chaplain-to-patient ratios and their assignments are not currently suitable for routine offering of DT, but chaplains might be more interested in DT than nurses due to alignment of DT with chaplain tasks. If our findings show that DT led by nurses or chaplains has outcomes better than usual care, in the future, DT could be implemented in many places by redeploying current nursing or chaplain resources, based on their availability. Fortunately, *six palliative care outpatient services* are committed to test the efficacy of DT led by either nurses or chaplains and thereby provide evidence about the effects of DT compared with usual care in the context of outpatient palliative care of elderly cancer patients.

As palliative care starts earlier in the course of medical therapy and *geriatric oncology* care continues to seek interventions for ambulatory elders, we have asked if DT can be successfully administered in outpatient settings. The findings from a pilot study conducted in a colorectal cancer clinic indicate *feasibility* in an outpatient setting [6]. This pilot study provides guidance about where DT should be done and when in the sequence of the patient's clinical encounters. Our experience with this study also helped us plan who should transcribe the interview, how to return the legacy document, and how long an interval between transcription and delivery is suitable. None of these decisions are established for clinical practice, but the proposed study will provide evidence from 6 sites to better inform future clinical practice implementation of DT, including the impact on the flow of the team's work and DT's impact on illness acceptance and cancer care goals. Successful completion of the proposed study is likely to have a significant and sustained impact on gero-oncology care in the future.

Figure 1. DT_Fig 1_Conceptual Framework.png.



Spiritual Interventions Are Important to Patients but Understudied

Many *elders becomemore spiritually inclined* as a life-cycle phenomenon [11,12]. However, little research exists on how this inclination relates to their medical care. New evidence suggests that *DT is primarily a spiritual intervention* with implications in the other spheres of a person's experience.

Figure 1 displays the study's conceptual framework including the mechanisms to explore. In this individual-level model, we conceptualize physical symptoms and spiritual distress as moderators of the DT effect on spiritual outcomes, measured as dignity impact, existential tasks, and cancer prognosis awareness, and on process measures (patient satisfaction and unmet spiritual needs).

In a study of factors considered important among 340 patients, with advanced illness, most of whom were elderly, some diagnosed with cancer, *being at peace with God was as important as freedom from pain* [2]. This finding is consistent with the broad consensus that attention to patients' spiritual concerns is 1 of the core dimensions of palliative care and a part of comprehensive geriatrics care [13-15]. Research with terminally ill patients makes clear that, in their view, a good death includes addressing several central spiritual issues and tasks [2,16]. A body of evidence is developing that describes moderate to high levels of spiritual concerns, unmet needs, or struggles among patients in palliative care or with advanced illness [3,17,18]. Existing evidence is limited but points to improved patient illness experience when patients' spiritual needs are addressed, as well as greater use of hospice rather than ICU care at the end of life [19]. Furthermore, when patients feel that their spiritual needs are unmet, they have lower satisfaction with care and increased emotional distress [20,21].

Delivery of spiritual care services is a variable and the evidence-based studies on chaplaincy interventions are limited. There are few published studies of interventions designed to address the spiritual needs of palliative care patients [22] and *no studies of spiritual care provided by chaplains create a* gaping hole in knowledge of the effects of the interdisciplinary team. Fortunately, professional chaplaincy is currently undergoing an important transformation. Until now, chaplaincy practice has been guided primarily by tradition and expert opinion. However, professional chaplaincy associations recently embraced the importance of evidence-based care, as have practicing chaplains [23]. Presently, the major obstacle that prevents chaplains from adopting evidence-based practice in palliative care is the absence of any research about chaplains' interventions. Although much of US health care and elsewhere is shifting from a focus on volume-based metrics (eg, number of patients seen or procedures done) to value-based metrics such as increasing patient satisfaction, chaplaincy has been very slow to make this change particularly with regard to proposing and testing appropriate outcomes. In the proposed study, we begin to fill this gap.

Few protocols- or evidence-based chaplaincy interventions have been used to meet the spiritual needs of people facing aging with chronic or serious illness or to test whether meeting those needs would improve outcomes valued by the elderly patient with cancer. *Therefore, rigorous evaluation of a manualized, evidence-based intervention would constitute a landmark step in gero-oncology and palliative care research and in nursing and especially chaplaincy health services research.* DT is a well-designed, validated, and manualized intervention well-suited for clinical protocolization. For these reasons, we proposed to include both nurse-led and chaplain-led DT with each compared only with usual palliative care and *hypothesize* that each DT group will report higher dignity impact than their respective usual palliative care group, which would mean that either discipline could lead DT when it is implemented clinically in palliative care. Nurses, but not chaplains, have been the DT interventionists in previous feasibility studies; however, we expect both can be trained to competently lead DT in the outpatient palliative care setting with elderly cancer patients. Distinguishing effects between the DT groups is beyond the scope of our application, but our findings will provide effect size estimates for future studies, should such a comparison be warranted by our findings. Both disciplines need to be included

in this study to provide an efficient test of the efficacy of DT and time of delivery in clinical care by the disciplines most likely to be available, an important issue for translation of result findings into practice.

Addressing Intrinsic Limitations to Palliative Care Research by Leveraging Our Network and Using Novel Design

This study is generated from a group of collaborators that came together under the auspices of the Patient-powered Spirituality-and Quality-of-life-focused Advanced-illness Research-network, a group formed in 2013. An open community of 27 organizations (health providers, researchers, patients, and other stakeholders) invited participation in research and health information giving.

Palliative care research is inherently hindered by the patients' severity of illness. High illness burden and short life spans make participant accrual and retention challenging; the participation burden must be minimal. Using a stepped-wedge design, 1 possible design for an RCT [4], will require a *smaller number of participants and allow intervention integration into the care process while maintaining power, data quality, and desirable design features including randomization to control and intervention groups.*

In summary, successful achievement of study aims will have important impact on the fields of geriatrics, comprehensive cancer care, and palliative care by showing whether DT can be optimally used in routine care settings to bring better illness experience to patients. It will further advance understanding of how DT works.

Innovation

This proposed work is innovative in 6 ways. *First*, and most importantly, we primarily conceptualize DT as a spiritual intervention for individuals with serious illness. Other researchers have approached DT as an intervention that broadly improves the dignity of patients nearing the end of life but examined the effects of DT on a variety of outcomes and only psychosocial outcomes showed a significant effect [24,25], In contrast, our *second* innovation is the use of spiritual outcomes as primary and secondary indicators of the DT effect. Our focused conceptualization of DT as a spiritual intervention leads to our choice of unique outcome measures and DT's focus at the level of the individual patient, though it could be conceptualized at the family level, which is beyond the scope of the proposed study. Other DT researchers used multiple measures of physical and psychological symptoms, as well as a broad measure of personal dignity. In contrast, our measures focus on dignity impact and existential tasks that help patients feel prepared for life completion and to have awareness of their prognosis. Furthermore, our measures of these constructs have been successfully used in previous palliative care or DT-related studies, and our recent reanalysis of RCT data shows that dignity impact differed for the DT group compared with usual care and another patient-centered intervention [5]. Although there is consensus about the central role of spiritual care in palliative care, there are few studies about spiritual care and no studies of spiritual care provided by chaplains. Thus, the *third* innovation of our study is that it employs a rigorous research design to test the efficacy of a manualized nurse-led or chaplain-led intervention in the palliative care context. Studies such as this are essential to clarify what spiritual care contributes to palliative care and to advance an evidence-based approach to chaplaincy care. Consistent with our rigorous test of a spiritual intervention, our *fourth* innovation will be to gather detailed information, in both the usual care and DT samples, about the nurses and chaplains' assessments and activities for descriptive purposes. The development of evidence-based chaplaincy has been hampered by the lack of evidence-based assessment instruments and standardized descriptions of chaplaincy care. Our work will employ innovative approaches for nurse or chaplain assessment of the patients' spiritual needs and for nurses' or chaplains' description of the care they provide. Prior studies of DT have focused on its effects on key outcomes and patients' reports of its benefits. They have not proposed or tested hypotheses about the ways that DT improves patient dignity during serious illness like cancer. The *fifth* innovation is the test of 2 new hypotheses about 2 moderators of DT effects, and we will employ rigorous measures to do so. The *sixth* innovation is that we will employ a stepped-wedge design, which has been used in other fields, but is new to clinical trials in the palliative care context and addresses the challenges of recruitment in this clinical setting.

In summary, by focusing on DT as a spiritual intervention, using a new conceptual model and measures consistent with the model to examine its effect, examining several pathways that shape its effect, and using a stepped-wedge design, our study will contribute important novelties to palliative care research. In addition, by testing the effects of nurse-led or chaplain-led DT, we will advance an evidence-based approach to spiritual care in the gero-oncology palliative care context, which is highly responsive to the National Institute of Aging's and the National Cancer Institute's request for palliative care applications (PA-13-354/NOT-CA-14-016) to study elderly cancer patients.

Approach

Study Team

Our study has a high probability of success because we will apply an interdisciplinary approach with highly productive investigators possessing expertise in palliative medicine, chaplaincy health services research, and nursing research focused on palliative care topics. The multiple principal investigators, MPIs (LE, GF, and DW), and coinvestigators, Co-I (MC, GH, and YY) have worked together within the HealthCare Chaplaincy Network and on palliative care research and publications for many years [26].

Preliminary Studies

Harvey Chochinov, MD PhD, originator of DT and lead investigator on many of its main studies, is a highly involved member of our team and provided data analysis of the dignity impact measure [5]. In addition, we and other research groups have established its feasibility among seriously ill patients, including those receiving hospice or palliative care. As we recently reviewed [26], 12 studies of DT established it as an important intervention: 8 uncontrolled feasibility studies (3 with

29 to 100 patients) and 4 efficacy RCTs (3 with less than 65 patients; Table 1). Taken as a group, 2 findings stand out. *First*, DT does not have consistent effects on distressing physical or emotional symptoms experienced by patients with life-threatening illness. As Hall et al [24] noted, 1 possible explanation for these inconsistent findings is that DT does not directly affect physical symptoms and thus it is a mistake for DT research to focus on physical symptoms or related outcomes as primary success indicators. *Second*, patients who receive DT provide uniformly high ratings of satisfaction and benefits for themselves and *report significantly higher dignity impact ratings* than patients who receive usual care or another patient-centered intervention [5]. It is important that *all* the existing studies consistently show feasibility of DT, and 1 study shows promising evidence that dignity impact is an appropriate outcome [5]. These findings are important as dignity impact is important to patients, especially the elderly with life-threatening illness, such as cancer. In addition, DT increased patients' *sense of meaning and purpose and their will to live* [27], which is important for patients continuing cancer treatments and participating in cancer research (both are emphases of NOT-CA-14-016).

In summary, we propose conceptualization of DT as a spiritual intervention that assists with the existential tasks faced by elderly patients as they face a serious illness like cancer. This conceptualization leads us to 2 additional decisions. First, nurses and chaplains are the appropriate members of the palliative care team to offer DT. As prior studies had the DT delivered by palliative care nurses or other health professionals, showing that the efficacy of DT is significantly better than usual care, whether the DT is delivered by chaplains or nurses, would be a scientific and clinical advance for translation of DT into geriatric and oncology practice. Second, although they have not been used in prior DT studies, measures of the existential tasks associated with life-threatening illness, as well as dignity impact, are appropriate DT outcome measures.

Although there is limited research about the benefits of chaplains' care [33] and no research about the benefits of chaplains' care in palliative care, for decades chaplains have understood their important role in helping patients with existential tasks associated with serious illness [34]. As part of a project funded by the Templeton Foundation and led by members of our team (Emanuel, Handzo), 6 studies of chaplaincy care have recently been completed and published [35,36]; others are being prepared for publication. None of these studies tested the effects of chaplain-led DT on patients' existential preparation for death, but one documents that chaplains are willing and able to use a manualized intervention. Thus, our proposed work will fill 2 unique gaps in DT research: the effects of DT on important existential tasks associated with serious illness; and chaplains' contributions to improving the care of those patients.

Under MPI Dr LE'S mentorship, Vergo conducted a feasibility study of DT early in the illness course of outpatients with stage IV colorectal cancer receiving second line chemotherapy (Table 1, study 4) [6]. In addition to outcomes on distress, symptoms, and quality of life; relevant outcomes also included peaceful awareness and treatment preferences. Of patients approached to participate, 88% did so. The findings suggest not only feasibility of DT during cancer care, but some improved physical and emotional symptoms, increased understanding of the terminal nature of their disease, less aggressive end-of-life goals of care, and increased death acceptance over time (11% at baseline; 57% at 1 month post-DT). These results are suggestive of improved spiritual as well psychological, social, and physical states and give our team recent experience with DT for patients with cancer undergoing active cancer treatments.

Working with Chochinov, we recently reanalyzed data from the study of 441 Canadian, Australian, and US hospice or palliative care patients [1] using the 7-item dignity impact scale we propose as our primary outcome. We found strong internal consistency (α=.85) and that the DT group mean score of 21.4 (SD 5.0) was significantly higher than the usual care group mean 17.7 (SD 5.5, P<.001) and a patient-centered intervention group mean of 17.9 (SD 4.9, P<.001) [5]. These preliminary findings provide strong support for our proposed 3-arm efficacy trial because they indicate that the DT affects the dignity impact, not an artifact of the attention provided during individualized therapy because the patient-centered intervention group did not show an effect better than usual care. Our prior studies provide solid evidence that the proposed 3-arm study will be successful: access to an ethnically diverse population of patients with cancer and receiving outpatient palliative care, prior success recruiting and retaining in a DT trial of colorectal cancer during cancer care, a well-tested intervention training program and manualized intervention, fidelity measures, and outcome measures that are robust in detecting the effect of DT. We are now poised to learn if nurse-led or chaplain-led DT is more effective than usual care to improve dignity impact as the primary outcome. Our secondary outcomes were sensitive to other psychosocial interventions [37-39], but have not been used in previous DT RCT studies, which is why we do not propose them as primary outcomes. We also have used the measures for moderator effects. Therefore, our preliminary work is strong and warrants the proposed RCT.

Table 1. Prior trials of dignity therapy.

Study and sample	Design, measures, and interventionists	Findings
Feasibility studies with N≥15		
100 Canadian & Australia terminally ill[28]	Design: Pre-post trial of dignity therapy (DT); Measures: Single item screening measures for 8 factors (depression, anxiety, suffering, suicide, sense of well-being; QoL[a], ESAS[b]; DTPFQ[c]); Intervention: psychiatrist, psychologist, and palliative care nurses	Significant improvement in suffering and depressed mood. High proportions gave positive evaluation to benefits of DT (eg, 91% feel satisfied or highly satisfied with DT, 86% report DT was helpful or very helpful)
80 Danish cancer patients in hospice or palliative care [29]	Design: Pre-post trial of DT; follow up after (T1) & 1 mo after (T2); Measures: SISC[d]; PDI[e]: EORTC QLQ-C15-PA[f]; HADS[g]; PPSv2[h]; DT PFQ; Intervention: psychologists	No change on any measure at T1 or T2 except QoL decreased baseline to T1. At T1 and T2, positive responses on DTPFQ
29 Australian patients with MND[i] [30,31]	Design: Pre-post trial of DT; Measures: Hope; FACIT-Sp[j]; PDI; DT PFQ; ALS[k] measures; Intervention: psychologist	Feasibility and acceptability established. High satisfaction (93%) and helpfulness (89%) for DT. Not significant: hope, spirituality, and dignity.
15 US stage IV colon cancer patients, active cancer treatment [6]	Design: Pre-post trial of DT; follow up after DT (T1) & 1 mo after (T2); Measures: ESAS; distress; QoL; peaceful awareness; advanced care planning; DTPFQ (selected items) Intervention: palliative care oncologist	Feasibility and acceptability established. High satisfaction (100%) and helpfulness (88%) for DT. No significant changes in other study measures.
Efficacy studies		
441 Canadian, Australian, & US hospice or palliative care[1]	Design 3 arm RCT: DT vs client-centered vs standard care; Measures: SISC; ESAS; PDI; QoL- 2 items; HADS; FACIT-Sp; DTPFQ; Intervention: psychiatrist, psychologist, and palliative care nurses	No significant differences on any outcomes. Reanalysis of dignity impact items: DT group has significantly higher scores than standard care (P<.001) or client-centered care (P<.001).
45 UK advanced cancer[24]	Design RCT: Tx = DT plus usual care; Control=usual care (Phase II trial for acceptability and estimates of effect sizes); Measures: Primary: PDI; Secondary: Hope; HADS; EQ-5D[l]; palliative-related outcomes (Hearn); DTPFQ; Intervention: oncologist	No differences on PDI. No differences on any secondary outcomes, except higher hope in group at week 1 (P=.02). Patients in the DT group had higher scores on DTPFQ, some significant.
64 UK patients in older care homes[32]	Design RCT (Phase II trial for potential efficacy, feasibility): Tx = DT plus usual care; Control = usual care; Measures: Primary: PDI; Secondary: GDS[m], HHI[n], EQ-5D, Acceptability: DTPFQ ; Intervention: palliative care nurse	No differences on efficacy outcomes; reduced dignity-related distress on DTPFQ across both groups (P=.03). DT group significantly more likely to feel DT had made life more meaningful at follow up 1 (P=.04).
60 Portuguese terminally ill[25]	Design RCT: Tx = DT+usual care; Control = usual care; Measures: HADS; Intervention: palliative care physician	DT associated with lower depression and anxiety (day 4 and 15, not day 30; all P<.05)

[a]QoL: quality of life.

[b]ESAS: Edmonton System Assessment Scale.

[c]DTPFQ=DT patient feedback questionnaire.

[d]SISC: Structured Interview for Symptoms and Concerns.

[e]PDI: Personal Dignity Inventory.

[f]EORTC QLQ-C15-PA: European Organization for Research in Cancer Quality of Life Questionnaire-C15-Palliative.

[g]HADS: Hospital Anxiety Depression Scale.

[h]PPSv2: Palliative Performance Scale.

[i]MND: motor neurone disease.

[j]EQ-5D: EuroQol group's five dimensions.

[k]FACIT-Sp: Functional Assessment of Chronic Illness Therapy-Spiritual Well-being.

[l]ALS: amyotrophic lateral sclerosis.

[m]GDS: Geriatric Depression Scale.

[n]HHI: Herth Hope Index.

Methods

Design

We propose a 6-site, pre- and posttest, randomized, controlled 4-step, stepped-wedge design to compare the effects of usual outpatient palliative care and usual outpatient palliative care along with nurse-led or chaplain-led DT on patient outcomes and palliative care processes. We will assign the 6 sites to usual care during the first-step period (10 months), and randomly assign 2 sites per step to begin and continue DT during each of the next 3 steps (10 months each). Figure 2 shows the stepped-wedge study design with projected numbers of completed patients needed per site, step period, and group (usual care, DT led by either a nurse or a chaplain). Dr. Yao, a highly qualified statistician, will conduct the randomization of site from steps 2 to 4. Each step will be 10 months long, with DT training during a 1-week period between steps. For each site and step, a quota of 50% of the participants will report low or high distress on the Personal Dignity Inventory to assure that we recruit a sample with a range of problems threatening their dignity. Each patient will participate for 4 to 6 weeks. During the 10 months at each step, we expect 23 to 24 patients to participate at each site (93 to 94 total patients per site).

Setting

For this efficacy study, the settings will include Northwestern University Hospital, Rush University Medical Center, MD Anderson Cancer Center, Emory University, University of California San Francisco, and University of Florida Health. The clinical resources of each of these settings are strong. Our team members have extensive experience recruiting and retaining elderly patients with cancer for studies, including palliative care and chaplaincy research.

Sample

We will recruit the study sample from the populations receiving care at settings across the United States. For the patients who meet the eligibility criteria, we anticipate a 50% to 60% enrollment rate and a 20% to 30% attrition rate. We based these estimated numbers on accruals, withdrawals, and deaths in previous palliative care studies conducted at study settings and those in prior studies of DT. During the 40 months devoted to data collection, we anticipated a total available population of 3126 from the outpatient palliative care services of the 6 sites. From this sample, 560 patients will complete sufficient data for the planned analysis, 140 per each of 2 DT groups and 280 total control group. Therefore, we expect each of the 6 sites to complete at least 2 to 3 patients per month and a final total of 93 to 94 patients per site with data for analysis. On the basis of ethnic and racial distribution of patients served at the 6 sites, we expect the final sample to be 50% female, about 3% Asian American, 21% African American, 73% Caucasian, and 3% unknown race and 8% Hispanic ethnicity, representing substantial cultural diversity for this study of DT.

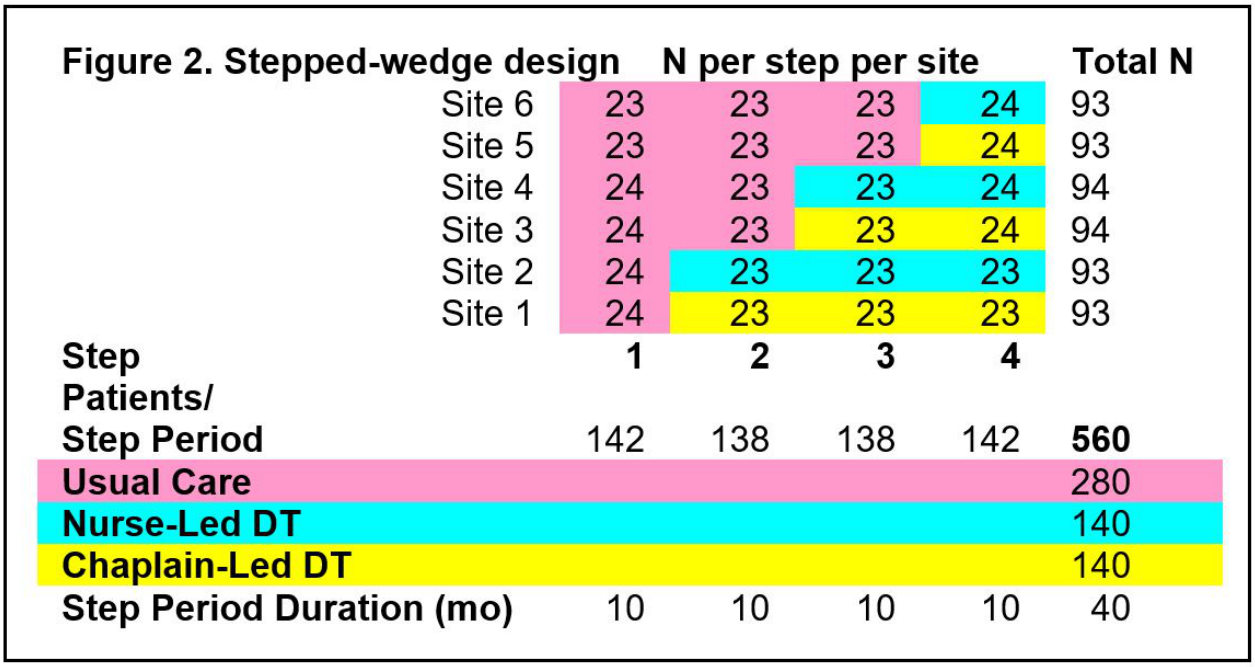
Eligibility Criteria

Inclusion criteria for study participation require that the patient (1) has a cancer diagnosis (receiving cancer therapy or cancer control care to be responsive to NOT-CA-14-016), (2) is receiving outpatient palliative care, (3) is aged 55 years or older (responsive to PAR-13-354), (4) is able to speak and read English, and (5) is physically able to complete the study (Palliative Performance Scale [PPS]>50 [40-45], suggesting a mean in life expectancy of greater than 53 days at the time of enrollment) [45]. Patients will be *excluded* if they: (1) are legally blind, (2) are cognitively unable to complete study measures (Mini Mental Status Exam [MMSE] <24), (3) have history of psychosis (medical record review), (4) have a Patient Dignity Inventory (PDI) or Religious and Spiritual Struggles Scale score that indicates their distress level falls outside the remaining quota for a given step; quota is 50% of sample, site, and step with low distress (≤ 2 problems rated >2) and 50% with high distress (≥ 3 problems rated >2 or 1 rated>3), or (5) are enrolled in another intervention study that is focused on concepts similar to the proposed study.

Retention Strategies

Retention strategies are vital to engaging participants as active research partners. Researchers in this study will always use respectful, empathic communication and schedule data collection at convenient times for participants. We will collect multiple contact information (email, cell phone, home, and extended family phone) to maximize our ability to contact them for final appointments. We also will offer a total of US $50 per patient to cover time and travel expenses to complete the study measures.

Figure 2. Stepped Wedge Design.



Sample Power

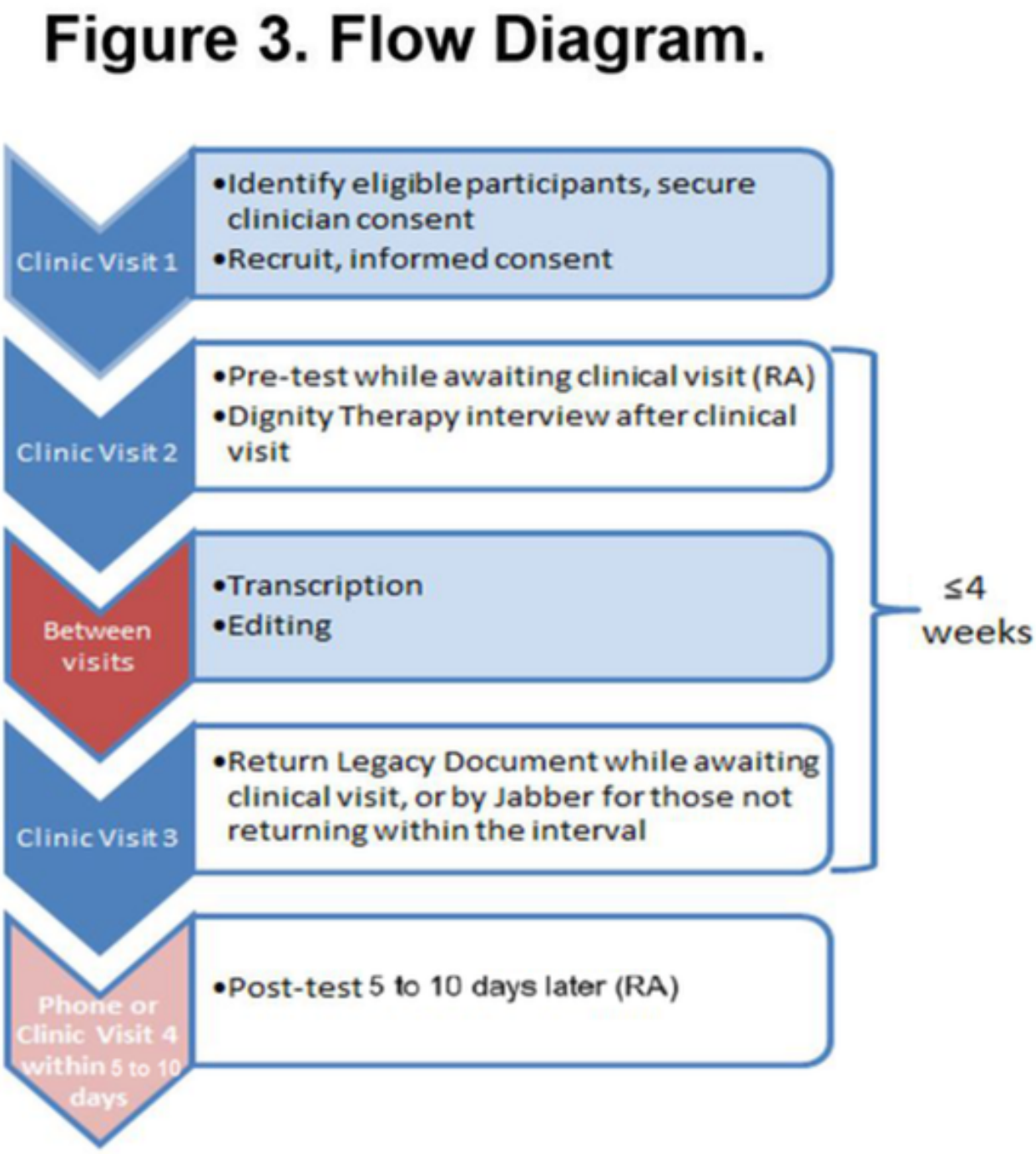
Aim 1 focuses on whether DT has an effect on patient outcomes and palliative spiritual care processes. For the 4-step, stepped-wedge design and the sample size of 23 to 24 patients per site per step (93 to 94 total), we determined from the minimum intervention effect size that the proposed study has at least 80% power to detect given a 2-sided significance level of .5. This minimum detectable effect size depends on disparity between sites as indexed by the intraclass correlation (ICC). With no site disparity (ICC=0), we can detect an effect size of 0.5 or above for either the nurse-led or chaplain-led DT intervention; with a more severe disparity (ICC=.4), we can detect an effect size of 0.6 or above. The *primary outcome* for this study is the 7-item Dignity Impact scale. Using Dignity Impact scale data from the preliminary study [1], the effect size of DT (relative to usual care) was 0.7 [5]. Therefore, we expect this study to have sufficient power to detect the intervention effect on the primary outcome. We do not have preliminary DT data on the secondary outcome measures; however, based on other psychosocial interventions with the measures [37-39,46], our power analysis indicates that as long as the intervention effect on these outcomes is of medium size (0.5 as defined by Cohen) or larger, they can be detected in the proposed study. Our study aims to focus on differences between the control group and each DT group, but do not focus on differences between the provider groups because, with the proposed sample, the *effect size difference between the nurse-led and chaplain-led DT groups needs to be large (0.7 when ICC=0 and 0.9 when ICC=.4)* to be detectable (with 80% power). As prior research shows an effect size of 0.7 between control and DT groups, it is highly unlikely that there will be a significant difference between the provider groups with the proposed sample. *Aim 2* seeks to explore whether or not patient distress (physical or spiritual) moderates the effect of the intervention. The intervention effect size of patients with high distress will be compared with that of patients with low distress level. The study has power (80%) to detect an effect size difference of 1.0 if there is no site disparity (ICC=0) and 1.3 if there is severe site disparity (ICC=.4). Assuming an average effect size of 0.8 and group balance, we can detect a moderation effect if the intervention effect size for the less receptive group is 0.15 or lower.

Procedures

Figure 3 shows the general flow of patients through the outpatient palliative care clinics and study procedures for this study of nurse-led or chaplain-led DT over 4 to 6 weeks. Before participant recruitment, the research assistants (RAs) will be trained in all study procedures. The investigators will introduce the study to the palliative care team members. Members of the palliative care team will refer patients to the RA on the day the patient is seen in the palliative care clinic.

The RA will recruit and consent the patient for screening. For those eligible, the RA will provide informed consent and schedule time before the next clinic visit for the patient to complete the pretest self-report measures using a tablet with smart pen. Then, the RA will inform the nurse and chaplain that the patient is available for care (usual care or DT, depending on the study step and site). The nurse or chaplain will provide the designated care on the same day as the pretest data collection. When the nurse or chaplain sessions are completed, the nurse or chaplain will inform the RA that he or she has completed all nurse or chaplain sessions. Either in-person if the patient has a clinic visit or by telephone contact, the RA will schedule the follow-up appointment and complete the posttest measures within 5 to 10 days. Upon completion of posttest measures, the RA will provide a US $50 cash per card to the patient for time and travel expenses to complete study measures.

Figure 3. DT Study Flow.



Textbox 1. Examples of the Dignity Therapy Question Protocol.

1. Tell me about your life history; particularly the parts that you either remember most or think are the most important? When did you feel most alive?
2. Are there specific things that you would want your family to know about you, and are there particular things you would want them to remember?
3. What are the most important roles you have played in life (family roles, vocational roles, community service roles, etc)? Why were they so important to you, and what do you think you accomplished in those roles?
4. What are your most important accomplishments, and what do you feel most proud of?
5. What are your hopes and dreams for your loved ones?
6. What have you learned about life that you would want to pass along to others?
7. What advice or words of guidance would you wish to pass along to your [son, daughter, husband, wife, parents, other(s)]?
8. Are there particular things that you feel still need to be said to your loved ones, or things that you would want to take the time to say once again?
9. Are there words or perhaps even instructions you would like to offer your family, in order to provide help to prepare them for the future?
10. In creating this permanent record, are their other things that you would like included?

Interventions

In this trial, we will compare the efficacy of 2 interventions, both provided either by palliative care nurses or chaplains. The nurses will be the registered nurses who are trained and working with the palliative care team. Chaplains will be BCC. To become a BCC, a person must have completed a graduate-level theological education as well as 1600 hours of supervised practice in an accredited program of clinical pastoral education. BCCs must be in good standing with, and endorsed by, their faith group. In their application for Board Certification and interview, BCC candidates must demonstrate competence in 29 areas. BCC chaplains adhere to a code of ethics that includes "respect for the cultural and religious values of those they serve and refrain from imposing their own values and beliefs on those served." BCCs must complete 50 hours of continuing education annually and a peer review every 5 years [47].

Usual Care

Palliative care nurses usually see patients each clinic visit to assess vital signs, function, symptoms, and to provide patient and family education. They document findings and interventions in the electronic health record (EHR). Although, usual care for palliative care chaplaincy in the outpatient setting varies by site, chaplaincy care for usual care patients in this study will follow the usual practice.

Dignity Therapy

The DT intervention is detailed in Chochinov's manualized guide; he serves as a coinvestigator. He advised the development of this application since its inception and gave us permission to use the manualized intervention as it appears here in abbreviated form. The basic questions of the DT interview appear in Textbox 1. The nurse-led or chaplain-led DT intervention involves 3 sessions, each of which follows a set process (Table 2). Nurses are familiar with use of manuals. Chaplain use of manuals is not common, but Dr. Karen Steinhauser (personal communication, February 2014) confirmed that trained chaplains used a manualized intervention guide with high fidelity. Table 3 lists exemplars of the dignity repertoire (perspectives and practices) facilitated by the interview and document preparation process. The standardize approach to the delivery of the intervention facilitates a personal process of reflection and recognition that allows the patient to make meaning of their experience.

Dignity Therapy Training

Dr. Chochinov, who developed DT, will provide standardized training for the study nurses and chaplains at one of the study sites on 3 separate occasions; each training session will be 2 days in duration. Nurses and chaplains at all sites will be prepared to participate in the DT training during the 3 training dates that will be set early in year 1 but will first occur at the end of year 1. Only those nurses or chaplains at the randomized sites randomized to begin DT at the next step will be trained at any one date, and they will be notified before the training date. By the 4th step, all nurses and chaplains will be trained, assuring competency of all interventionists to deliver DT with fidelity. If there are new nurses or chaplains at a site randomized to the DT step, they will be allowed to attend remaining training sessions. In addition, 2 weeks before the end of each step, the statistician will divulge the 2 sites randomized to the next step. Before training, the MPI will inform the team members about the randomization. To reduce potential influence of the nurse or chaplain anticipating the training and thereby altering usual care practice, we will suspend recruitment, pretest data collection, and intervention delivery during the training periods; posttest data collection will continue.

Intervention Fidelity

The second RA, who is not involved with data collection, will complete the DT Adherence Form as a measure of intervention fidelity for all DT patients. Members of our team used this tool in previous studies with excellent results. The RA will read each original DT transcript and use this measure to document the nurse's or chaplain's adherence to the DT protocol. Scores range from 0 to 10, with 10 representing complete adherence. We will monitor the adherence scores to determine if a nurse or chaplain requires additional training by Rev. Handzo (those with scores <8).

Table 2. Dignity therapy intervention ingredients.

Session	Timing	Purpose	Key Ingredients (Features)	Process Considerations and Issues
First: nurse-led or chaplain-led Diginity Therapy (DT) contact (information session)	Visit 1	To establish relationship with patient; to explain DT history and procedures	DT is based on piloted studies. Sessions are tape-recorded, transcribed, edited, and returned to the patient for feedback. Process is iterative. Purpose is a legacy generating document for family or friends. DT can be free form, guided, or both. Guide questions may be provided before second meeting upon request. Recording session is scheduled.	Rapport must be established with patient. Patient must understand the process. Nurse or chaplain should be knowledgeable of process. Nurse or chaplain should have guide questions available for patient.
Second nurse-led or chaplain-led dt contact (recording session)	Visit 2: + 2 weeks	To provide DT; to record DT session	Tape-recorded DT session begins with either patient directed content or guide questions. Session takes about 60 minutes and is highly flexible, accommodating the patient's desired discussion content. Nurse or chaplain takes an active role, forming a therapeutic alliance while delivering and organizing the structured intervention. Legacy document session is scheduled.	Nurse or chaplain must maintain respect, empathy, support, and dignity.
Intermission (No contact)	Nonvisit: 2-4 weeks	To transcribe the session; to edit the manuscript; to revise the manuscript; to produce a legacy document	Nurse or chaplain must guide without providing judgment statements. Tape recorder should be tested before session. Recording session is transcribed by a professional transcriptionist. Three copies are kept: a) unedited complete transcript, b) 'tracked' version of the edited transcript, and c) final edited version. Single editor initially edits the manuscript: cleaning up the colloquialisms and nonstarter stories, adjusting the chronology, and removing stories that may be hurtful or harmful. Nurse or chaplain reviews the document, making changes with the editor. Final edited manuscript will end with a summary phrase driven by the patient's story.	Nurse or chaplain read transcription copy for accuracy before editing. Editor must remain unbiased while editing, making sure the themes come through without changing the content. Editor must choose an ending to summarize the patient's story without biasing content. Timeliness is important.
Third nurse-led or chaplain-led DT contact (Legacy document session)	Visit 3: +4 weeks	To deliver edited legacy document; to receive feedback from patient	Nurse or chaplain delivers final edited legacy document to the patient. Nurse or chaplain reads it to the patient or the patient will read it alone. Patient may request editorial changes which will be completed within 24 hours. If revisions are necessary, nurse or chaplain makes arrangements for the final delivery of the legacy document within 24 hours. Patient makes arrangements to deliver the legacy document to loved ones.	Editing may not satisfy the patient. Theme may not be approved by patient. Patient may not be able to provide feedback
Final editing (if necessary)	Nonvisit: 24 hours post Visit 3	To make final revisions to legacy document	Nurse or chaplain makes final revisions based on patient feedback and delivers the final legacy document to the patient.	Final revisions are not approved by patient (process closure)

Table 3. Dignity therapy: exemplars of repertoire (perspectives and practices) facilitated by interview and document preparation process.

Dignity conserving Repertoire	Ways of looking at one's situation, or personal actions that can bolster or reinforce a sense of dignity
Dignity conserving perspectives	Internally held qualities, often based on long standing personal characteristics, attributes, or world view
Continuity of self	A sense that the essence of who one is continues to remain intact, in spite of one's advancing illness
Role preservation	Ability to continue to function in usual roles to maintain a sense congruence with prior views of self
Generativity and legacy	The solace and comfort in knowing that something lasting will transcend their death
Maintenance of pride	The ability to maintain a positive sense of self regard or respect
Hopefulness	An ability to see life as enduring, or having sustained meaning or purpose
Autonomy and control	A sense of control over one's life circumstances
Acceptance	The internal process of resigning one's self to changing life circumstances
Resilience or fighting Spirit	Mental determination to overcome illness-related concerns and optimize quality of life
Dignity conserving practices	Variety of personal approaches or techniques that patients use to bolster or maintain their sense of dignity
Living in the moment	Focusing on immediate issues in the service of not worrying about the future
Maintaining normalcy	Continuous or routine behaviors, which help individuals manage day-to-day challenges
Seeking spiritual comfort	Turning toward or finding solace in one's religious or spiritual belief system

Measures

All our measures have been used among palliative care populations, summary of timing of these measures is shown in Table 4. To collect these data, we will create a REDCap study site using the UF REDCap system, which the UF CTI supports and makes available for NIH funded studies without cost. All data collection sites will use this secure data collection site. Patients will use a tablet with a smart pen to enter the data into the REDCap system. Wilkie et al are successfully using this cost-effective approach to data collection for another palliative care study [48] focused on African American caregivers and the data manager is well versed with REDCap and current mobile devices. Wilkie et al is also successfully using mobile tablet or pen devices in a study of hospice patients in their homes and replicating prior findings of the clear feasibility of elderly patients with cancer near the end of their lives using the tablet technology, especially with use of a smart pen device [49]. We expect that patients will take 30 to 45 minutes to complete the measures at pretest and 15 to 20 minutes at posttest.

Patient Outcomes

The primary study outcome is dignity impact with all study measures. The secondary outcomes are existential tasks and cancer prognosis awareness.

Dignity Impact

Our primary outcome measure is a 7-item Dignity Impact Scale [5]. We took the items from the DT Patient Feedback Questionnaire that has been used in a number of studies of DT [50]. The 7 items addressed the concept of DT and showed significant differences between those who received DT and those who did not in an RCT [1]. The items have been used in many DT studies with evidence of their validity in the target population. We modified the wording of the items to fit our pretest and posttest study design. A sample item is "The care I received during the past month has increased my sense of dignity." The items are scored on a 5-point scale from "strongly disagree" (1) to "strongly agree" (5). The Cronbach α from a preliminary study was .85 [5]. Scores ranged from 7 to 35 in the DT group and 7 to 29 in the usual care group and showed sensitivity to DT effects at posttest with an effect size of 0.7 [5]; it was not measured at pretest, but we will do so to increase power and potential for inferences.

Existential Tasks

The existential tasks of importance in the proposed study are preparation for death and life completion. Our measures of preparation and completion are taken from the QUAL-E, a measure designed to evaluate the quality of life at the end of life and to assess the effectiveness of interventions targeted to improve the quality of life at the end of life [46]. The 4-item Preparation subscale assesses an individual's sense of integrity and concerns about being a burden to significant others. A sample item is "I have regrets about the way I have lived my life." The 7-item Completion subscale assesses an individual's sense of meaning and peace, as well as any unfinished interpersonal business. A sample item is "I have been able to share important things with my family." The items are rated on a 5-point scale from "not at all true for me" (1) to "completely true for me" (5). The items in the Preparation subscale are reverse scored. The Preparation and Completion scales have demonstrated good reliability and validity [46]. Validity of both measures was shown by correlations in expected directions with other measures of quality of life (FACT-G; Missoula-Vitas QOL) and spiritual well-being (FACIT-Sp). In a diverse sample of 248 patients near the end of life, the Cronbach alphas were .68 and .80 for Preparation and Completion, respectively. The 1-week ICCs for participants with no changes in health status were .73 for Preparation and .72 for Completion.

Table 4. Measures, time points, and person who completes.

Measure (concept-aim); [number of items]	Pretest	Posttest
Dignity impact (Aim 1)	X[a]	X
Quality of Life at End of Life (QUALE-E) Existential tasks-aim 1)	X	X
Cancer prognosis awareness (Aim 1)	X	X
Treatment preferences (Aim 1)	X	X
Patient satisfaction with chaplain and nurse care (Aim 1)	X	X
Edmonton symptom assessment scale (physical symptoms-aim 2)	X	—[b]
Religious and spiritual struggles scale (spiritual distress-aim 2)	X	X
Demographic and patient characteristics	X	—

[a]X: data collected.

[b]—: data not collected.

Cancer Prognosis Awareness

Two measures will provide data for peaceful awareness and treatment preference. Our approach to measuring terminal illness awareness (peaceful awareness) is taken from a study of 280 patients with advanced cancer who participated in the Coping with Cancer Study [51]. In that study, 17.5% of the sample reported being both peaceful and aware of their prognosis. Peacefully aware patients had lower rates of psychological distress and higher rates of advance care planning than those who were not peacefully aware. Peaceful awareness is also associated with modifiable aspects of medical care (eg, discussions about terminal treatment preferences).

Treatment preferences will be measured with a standardized and validated Hypothetical Advanced Care Planning Scenario that assesses scenario-based goals of care and treatment preferences. This approach, based on work by MPI LE [52], was used successfully in the study of DT in patients with advanced colorectal cancer [6]. Patients will be considered as making "life prolonging" treatment choices if they selected "I want" or "I want treatment tried. If no clear improvement, stop (only for mechanical ventilation)" for either CPR or mechanical breathing. Patients will be considered as making "non-life prolonging" treatment choices if they selected "I do not want" to both CPR and mechanical breathing. Patients selecting "I am undecided" to either CPR or mechanical ventilation and not considered "life-prolonging" in their treatment choices will be categorized as "undecided."

Palliative Care Spiritual Service Processes

We will measure 2 indicators of palliative care spiritual service processes. They are patient satisfaction with spiritual care and unmet spiritual needs.

Patient Satisfaction

The items in our 7-item measure of Patient Satisfaction with Nurse or Chaplain Care are taken from the work of 2 leaders in chaplaincy research. VandeCreek [53] developed the 23 item Patient Satisfaction Instrument-Chaplaincy (PSI-C) that he administered to a sample of 1440 patients who had been treated in one of 14 different US hospitals. In their study of patient satisfaction, Flannelly et al [54] used 7 items from VandeCreek's PSI-C as well as 7 new items they developed. In their study, with 250 patients at 1 hospital, the validity of their items was supported by positive correlations with other items that assessed patients' perception that their spiritual and emotional needs had been met. Following the work of Flannelly et al [54], we will assess 2 aspects of satisfaction; satisfaction with the process of nurse or chaplain care and satisfaction with the impact of the chaplains' care.

Unmet Spiritual Needs

As clinicians embraced an evidence-based approach to spiritual care, 1 of the challenges they faced is developing instruments that can be used for spiritual assessment [55].

Covariates

The covariates for this trial include physical symptoms, measured by the revised version of the Edmonton Symptom Assessment Scale (ESAS-r), and spiritual distress, measured by the Religious and Spiritual Struggles Scale as described in the previous section. The ESAS-r is a well-validated and widely used instrument to assess common symptoms (eg, pain, fatigue, loss of appetite, and shortness of breath) in palliative care patients [56,57]. Each symptom is rated on a scale ranging from 0 to 10, where 0=no symptom and 10=worst possible symptom. The assessment is usually completed by the patient independently. However, the RA will help the patient complete the assessment if he or she is unable to rate all the symptoms.

Descriptive Variables: Characteristics of Patients and Nurse or Chaplain Spiritual Activities

Via self-report or medical record review, we will collect the patient demographic variables: age, sex, ethnicity, race, education level, marital status, medical diagnoses, health problems, cancer diagnosis date, type, and stage (at diagnosis and at study enrollment), and ongoing cancer treatments (eg, radiation, surgery, chemo, and immunotherapy). We will collect information about the participant's religious and spiritual involvement (eg, religious affiliation and frequency of prayer) using standard items [58].

Screening for Eligibility and Exclusion Criteria

The PPS, a modified version of the Karnofsky Performance Scale [59], measures 5 functional domains: ambulation, activity

and evidence of disease, self-care, intake, and level of consciousness. Its scores range in 10% increments from 0% to 100%, with a score of 0% indicating death, 10% indicating a totally bed-bound patient who is unable to do any activity and needs total assistance, and 100% indicating the patient is able to carry on normal activity and to work without any special care. The findings from studies conducted around the world and 4 regions of the United States [45] support very strong validity with the KPS [43] and adequate interrater reliability [45]. The PPS has predictive validity for average survival of 53 days at the eligibility score for the proposed study (>50) [40-45]; study participation is 28 to 42 days maximum.

We will use the MMSE for cognitive status screening. The MMSE [60] is a valid and reliable quantitative measure of the patient's cognitive performance and capacity. Rated by the trained RA, it measures on a scale of 0 to 30 a variety of cortical cognitive functions. An MMSE score of 26 to 30 represents a normal range, 20 to 25 represents mild cognitive impairment, and scores below 20 represent moderate to severe impairment. Patients with MMSE scores of <24 [61] will be excluded.

We will use the PDI to assess the level of dignity-related distress in the participants to ensure that a reasonable number of patients experiencing some dignity-related distress are recruited at each step. The PDI contains 25 items that assess a broad spectrum of end-of-life distress including physical, psychological, existential, and spiritual sources of distress [62]. The construct and face validity, test-retest reliability, and factor structure of the PDI have been established [62]. Patients rate each item on a 1 to 5 scale (1=not a problem, 2=somewhat of a problem, 3=a problem, 4=a big problem, and 5=an overwhelming problem). Using a score >3 to indicate a problem for that item, 253 patients receiving palliative care reported an average of 5.7 problems (SD 5.5, range 0-24 problems) [63].

Statistical Analysis

Data management and preliminary data analysis procedures will be supervised by MPI DW and conducted by Dr. YY, the Co-I, and statistician, using statistical software R version 3.5.2 (R Foundation for Statistical Computing). Data will be stored in a REDCap database and will be exported to R. In the case of missing data, multiple imputations will be used to generate multiple complete datasets on which statistical inference will be performed and then aggregated. Missing at random assumption will be assessed and if necessary sensitivity analysis will be performed using pattern mixture methods. We will consider a *P* value less than .05 as statistically significant.

Descriptive statistics (ranges, frequencies, means, and SDs) and graphic summary (box plots, histograms, bivariate scatterplots, etc) will be first generated for both patient covariates and outcome measures. We will check patient characteristics to see if there is notable imbalance between the 3 arms, as well as whether there are significant variations between sites or over time. Descriptive statistics of patient outcomes and process data will reveal patients' spiritual state, identify potential areas for improvement in nurse and chaplain service, and provide information on nurses' and chaplains' workload both in usual care and when dignity therapy is added and on family related variables (eg, legacy document disposition).

Aim 1

Linear mixed effects models will be used to compare the effects of usual palliative care with usual palliative care with nurse-led and chaplain-led DT groups on (1) *patient outcomes* and (2) *processes* of delivering palliative spiritual care services. Random effects terms will be used to model the variations between sites. A main challenge of data analysis of a stepped-wedge design is the modeling of potential time trends. We plan to treat time as a continuous variable and utilize smoothing splines to model potential time trends. Smoothing splines is a nonparametric method that allows flexibility to model different time trends without overfitting by enforcing a smoothness constraint. Likelihood ratio tests will be used to determine the statistical significance of the intervention effect on various outcome measures. We hypothesize that, controlling for pretest scores, patients in both nurse-led and chaplain-led DT groups will have higher dignity impact scores, higher preparation for death and life completion scores, better peaceful awareness, and treatment preferences more consistent with their cancer prognosis than the usual care groups. We also expect the patients in the DT groups to be more satisfied with the palliative care and have fewer unmet spiritual needs than the usual care groups. We do not expect significant difference between nurse-led and chaplain-led DT interventions. Note that, this does not necessarily mean that the 2 interventions are equally effective. We do not seek to test the equivalence of the 2 intervention arms. At this point, it is premature to speculate on their relative efficacy. We expect most patients in this study to have metastatic cancer. If a sizable portion of our sample has nonmetastatic cancer, we will explore if they respond to DT differently than those with the metastatic disease.

Aim 2

The effect of physical symptoms and spiritual distress on the dignity impact and existential tasks will be modeled nonparametrically using smoothing splines. Our models will include both main effect for physical symptoms and spiritual distress and their interactions with the intervention. This analysis will provide insight on the type of patients most in need of and most likely to benefit from the DT intervention. Likelihood ratio tests will be used to determine the significance of the interaction. We hypothesize that patients' levels of spiritual distress and physical symptom scores will moderate the intervention effect.

Timeline

Table 5 presents the basic timeline for general activities to achieve study aims. We will prepare study materials, train, and calibrate staff upon award. DT training will commence at the end of month 15. The step-up to step2 occurs in month 16 (12 months per step). Data will be collected from months 4 to 54, processed starting month 4, analyzed for baseline comparisons starting month 16 and outcomes months 55 to 60.

Table 5. Projected timeline for study aims.

Study task	Study month								
	1-3	4-11	12-19	20-27	28-35	36-43	43-48	49-54	55-60
Staff preparation	X[a]	—[b]	—	—	—	—	—	—	—
Participant recruitment: 70-142 patients per year	—	X	X	X	X	X	X	X	—
DT training for nurses or chaplains (before DT; ongoing for fidelity)	—	—	X	X	X	X	X	X	—
Data Processing	—	X	X	X	X	X	X	X	X
Data Analysis, reports, and manuscripts	—	—	X	—	—	—	—	—	X

[a]X: data collected

[b]–: not applicable.

Results

Funding was obtained in 2016 with participant enrollment starting in 2017. Results are expected in 2021.

Discussion

Potential Problems and Alternate Plans

This rigorous trial of DT will constitute a landmark step in palliative care and spiritual health services research. We designed this study mindful of a number of threats to study validity as we implement the study within the workflow of outpatient palliative care in 6 sites and present plans to achieve study aims.

Recruitment

Anticipated numbers of potential participants are based on prior studies among similar patient populations both in in-patient and out-patient settings. However, recruitment is always difficult, especially in palliative care settings. We recruited 6 sites to ensure a generous pool of eligible patients and to use a stepped-wedge design for efficiency in the required sample size. Also, the stepped-wedge design allows flexibility in that, if recruitment proves difficult as proposed, we can add steps and sites to ensure a sufficient sample**.**

Differences Between Sites

We include 6 sites and will recruit participants from outpatient services only. We carefully selected sites with consideration of geographic and population diversity, but our analytic model will include random effect terms to account for site differences, should they occur.

Attrition

Attrition due to illness burden and death is inevitable in this population. We will monitor attrition carefully throughout the study. If the estimates we have used prove inaccurate we will adjust recruitment numbers accordingly to meet benchmarks throughout the study at each site. We will also analyze data from participants who did not complete the DT to check for differences in patient characteristics and to verify that there is no association between attrition and intervention group assignment.

Patients Not Returning to Clinic

Including these patients limits potential loss of patients before they can complete the intervention, for instance, during the interval between the first interview and returning the legacy document. Patients' will be located through the doctor's office or family; those in the hospital at posttest will finish their intervention at the hospital or by phone with electronic or express mail delivery of the legacy document and will still be included in the study. Including these patients will minimize any potential bias. Furthermore, it ensures that the intervention effect size we estimate will reflect the average effect on a realistic patient population, a portion of which will decline in health status before the intervention is complete.

Data Integrity

We will collect preintervention data using self-report on a tablet with a smart pen. Participant operation of the device may limit data entry, but we will use Dr. Wilkie's extensive expertise in using tablets in the homes of elderly hospice patients with cancer. The RA will be present to assist with data collection if needed. We will track incomplete data patterns and raise the topic at regular study meetings to brainstorm solutions such as an improved user interface or directions. We will collect postintervention data by phone or in-person, if the participant has a clinic visit. Obtaining correct phone information in an era when landlines are rare and patients may not be next to their cell phones may be challenging. We will ask for a backup phone number for this reason. Survey responses by phone may be particularly challenging for our sick population; our training will include protocols for taking a break and repeating questions that allow for the illness burden of our participants.

Availability of Nurses or Chaplains

Each site has a chaplain available to the palliative care service, but others are available to cover for absences (vacation, illness, etc). Similarly, nurses are available. For each site, at least two interventionists will be trained and immediately replaced by another should there be an absence, resignation, or retirement.

Summary

We have exceptionally strong research and clinical environments to support the proposed study, and a strong, collaborative, interdisciplinary team distinguished by its rare combination of chaplaincy, nursing, and palliative care researchers. We are

noted for a history of excellence in palliative care research in elderly cancer patients, including a Templeton Foundation grant to stimulate chaplaincy research in palliative care and several funded R01 level studies focused on palliative care populations. We propose a highly significant and high-quality study in which we will apply rigorous science to an area that sorely needs it: spiritual care research. Studying 560 participants in a pre- and posttest, randomized, controlled 4-step, stepped-wedge design, we will compare the effects of usual outpatient palliative care against the same plus either nurse-led or chaplain-led DT on patient outcomes (dignity impact, existential tasks, and cancer prognosis awareness). Using a multilevel analysis with site, provider (nurse and chaplain), and time (step) in the model, we will determine the efficacy and mechanism of DT when delivered by nurses or chaplains as a spiritual care therapy. Success in this landmark study will yield the first manualized intervention for chaplaincy services, its potential efficacy compared with nurse-led DT, and insights into its mechanisms of action related to spiritual care, an area of great importance to elderly cancer patients receiving palliative care. We will *disseminate* study findings in a variety of venues for presentation and publication to reach palliative care, oncology, gerontology, chaplaincy, nursing, and other audiences.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Untitled.

[PDF File (Adobe PDF File), 165KB - resprot_v8i4e12213_app1.pdf]

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Abbreviations

BCC: Board Certified Chaplain
Co-I: coinvestigators
DT: dignity therapy
EHR: electronic health record
ESAS-r: Edmonton Symptom Assessment Scale
ICC: intraclass correlation
MMSE: Mini Mental Status Exam
MPI: multiple primary investigators
NCI: National Cancer Institute
NIH: National Institutes of Health
NINR: National Institute of Nursing Research
PDI: Patient dignity inventory
PPS: Palliative Performance Scale
PSI-C: Patient Satisfaction Instrument-Chaplaincy
RA: research assistants
RCT: randomized controlled trial

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