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Protocol

Effectiveness of an Ecological Momentary Intervention for Reducing Risky Alcohol Consumption Among Young Adults: Protocol for a Three-Arm Randomized Controlled Trial

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Abstract

Background: Recent research has investigated the utility of mobile phone–delivered interventions for reducing risky single-occasion drinking, also known as binge drinking. In the past five years, focus has been placed on ecological momentary interventions (EMIs), which aim to deliver intervention content in correspondence to real-time assessments of behavior, also known as ecological momentary assessments (EMAs).

Objective: This study aims to assess the effect of a fully automated, tailored, mobile phone–delivered EMI termed Mobile Intervention for Drinking in Young people (MIDY) on young people's risky single-occasion drinking behavior.

Methods: We will use a three-armed randomized controlled trial design to determine the impact of MIDY on peak consumption of alcohol among young people. A list of mobile telephone numbers for random digit dialing will be generated, and researchers will telephone potential participants to screen for eligibility. Participants will be randomized into one of three intervention groups. For 6 weeks, EMI, EMA, and attention control groups will complete hourly EMA surveys on their mobile phones on Friday and Saturday nights. EMI participants will receive personalized feedback in the form of text messages corresponding to their EMA survey responses, which focus on alcohol consumption, spending, and mood. EMA participants will not receive feedback. A third group will also complete EMA and receive feedback text messages at the same time intervals, but these will be focused on sedentary behavior and technology use. All groups will also complete a short survey on Saturday and Sunday mornings, with the primary outcome measure taken on Sunday mornings. A more detailed survey will be sent on the final Sunday of the 6-week period, and then again 1 year after recruitment.

Results: The primary outcome measure will be an observed change (ie, reduction) in the mean peak number of drinks consumed in a single night over the 6-week intervention period between the EMI and attention control groups as measured in the weekly EMA. We expect to see a greater reduction in mean peak drinking in the EMI group compared to that in the attention control group. As a secondary aim, we will assess whether mean peak drinking is reduced in the EMA group compared to the attention control group. We will use a random-effects mixed-modeling approach using maximum-likelihood estimation to provide estimates of differences in peak drinking across time periods between those receiving the intervention (EMI) and attention control participants.

An intention-to-treat approach will be taken for the analysis. Individuals and study groups will be modeled as random and fixed factors, respectively.

Conclusions: This study extends our previous work investigating the efficacy of a mobile EMI (MIDY) for reducing risky drinking among young adults in Australia, and will add to the expanding literature on the use of mobile interventions for reducing risky alcohol consumption.

Trial Registration: Australian New Zealand Clinical Trials Registration (ANZCTR): ACTRN12617001509358p; http://www.anzctr.org.au/ACTRN12617001509358p.aspx

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KEYWORDS

alcohol; brief intervention; young adult; alcohol drinking; prevention and control; mobile phone

Introduction

Recent research has investigated the utility of mobile phone–delivered interventions for reducing risky single-occasion drinking (also known as binge drinking). Smartphones are ubiquitous in the lives of young Australians. A 2017 study showed that 94% of Australians aged 19-25 years spent more than 1 hour on their smartphone each day, with 63% spending more than 3 hours. Over half of the respondents in this age group reported that they check their phone every 15 minutes (27%) or every 30 minutes (25%) [1]. Most mobile phone–delivered alcohol interventions have focused on students and other young adults [2-11] , due to the high rates of alcohol consumption and alcohol-related harm in this population, in conjunction with their high rate of smartphone ownership [12,13].

Among the mobile phone–delivered interventions for alcohol consumption that have been documented in the literature to date, many take a brief intervention approach and provide some form of tailored feedback in response to screening of drinking behavior and other variables. Suffoletto and colleagues conducted several studies in which they recruited young adults from hospital emergency departments and sent them tailored advice via short message service (SMS) text messaging based on reported single-occasion drinking behavior, intentions to drink over the coming weekend, and commitment to reduce drinking and weekly drinking [3-6]. Suffoletto et al [5] reported small reductions in the drinking days and number of drinks per day over a 12-week period in the intervention group compared with those of the control group.

In the past five years, focus has been placed on ecological momentary interventions (EMIs), which aim to deliver the intervention content in correspondence to real-time assessments of behavior, also known as ecological momentary assessments (EMAs) [14]. The difference between EMI-based studies and the aforementioned mobile phone–delivered alcohol intervention studies is the act of interrupting the drinking event in the moment it occurs. EMIs frequently feed off information provided in EMAs, allowing for the intervention to be specifically tailored to the individual's circumstances at the time. The combination of these two factors allows for a highly salient interruption at a time most pertinent to the recipient [14,15]. In our previous work, young adults likened the experience of receiving EMI to having a sober friend or a sober version of themselves pull them out of a drunken haze and gently tweak their behavior to help them avoid going "too far" [16].

Riordan et al [8-10] have focused on EMI for university students, particularly during the orientation week period. In two separate studies, they tested the effect of sending EMAs and EMIs during orientation week, and throughout the university semester; these EMIs were developed specifically for the student population and were informed by formative research. Their results have been mixed, with one study showing an effect in females but not males [8] and a second study showing an effect in one college but not another [9]. Although Riordan et al [17] highlighted a key risk group for alcohol consumption and related harm, many other nonstudent young adults also drink to excess regularly. Therefore, there is a need to test EMIs that focus on more general populations of young adults.

The current study extends our previous work in developing and testing a mobile phone–delivered EMI for reducing risky drinking in the event. Our 2016 study [16] outlined the co-design process taken to develop Mobile Intervention for Drinking in Young people (MIDY), during which 42 young people (adults 18-25 years old) participated in workshops to inform the delivery platform, timing, and frequency of assessment and intervention, questionnaires, tailoring process, and intervention content. The subsequent design included SMS text message–prompted, mobile Web-based EMAs (ie, an SMS text message with a link to a survey that opens in the Web browser of the mobile phone), with text-based feedback sent after each EMA is completed. Our feedback was informed by participants' preferences in addition to motivational interviewing and brief intervention theory [18]. Hourly EMAs were preferred by most of participants, between 6 pm and 2 am on intervention nights. Participants requested feedback messages that were short, practical, and nonjudgmental. The same young people then tested the intervention on one night and completed follow-up interviews. The design was reported to be feasible and acceptable by almost all participants, with a response rate of over 90% for EMAs.

Subsequently, in 2018, we conducted a trial on the implementation of this same intervention among a sample of young people recruited from an existing cohort of young adults with risky drinking behavior [19]. We conducted a three-armed randomized controlled trial (RCT) to compare the full MIDY

intervention with assessment-only and no-contact control groups. Participants were asked to complete the intervention or assessments on 6 nights over a 12-week study period. Our analyses showed a small and nonsignificant increase between baseline and follow-up data with respect to the mean number of standard drinks consumed at the most recent heavy-drinking occasion in the EMI group (12.5 vs 12.7). The EMA and control groups each showed a nonsignificant decrease (EMA 13.8 vs 11.8; control: 12.3 vs 11.6). There were no significant differences in these changes between the groups and effect sizes were small. We also did not observe differences between groups in other measures of alcohol consumption. However, this study was challenged by a small sample size relating to difficulties in recruiting participants from an ongoing cohort study into the intervention study, which affected our ability to detect significant effects. We therefore recommended further research into the efficacy of the MIDY intervention to clarify any effect on alcohol consumption.

Based on the two previous studies [16,19], this study aims to assess the effect of a tailored, mobile phone–delivered EMI (MIDY) on young people's risky single-occasion drinking behavior.

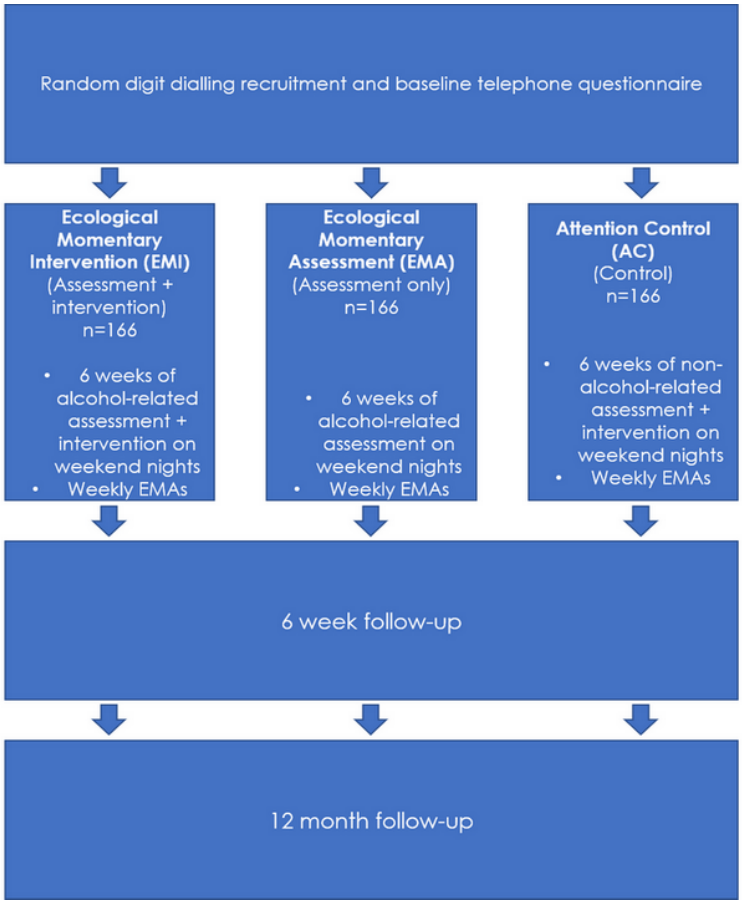
Methods

Study Design

We will use a three-armed RCT design to determine the impact of MIDY on peak consumption of alcohol among young people. The protocol for this study was registered with Australian New Zealand Clinical Trials Registry in October 2017.

The design of the study is outlined in Figure 1.

Figure 1. Study design.



Recruitment and Screening

Participants will be recruited using random digit dialing by trained researchers employed by TKW Research Group, a computer-assisted telephone interviewing (CATI) service provider. A list of mobile telephone numbers for random digit dialing will be generated by TKW Research Group, and their researchers will telephone potential participants to screen for eligibility.

Eligible participants will be Australian residents aged 18-25 years who report drinking at least 8 standard drinks in a single session at least once in the previous 12 months at screening, and possess a mobile phone with internet access. The alcohol consumption eligibility criteria were selected to capture a heavy drinking population of young people, and were based on the Young Adults Alcohol Study conducted by Dietze et al [20].

It is expected to take approximately 4 weeks to recruit the desired sample size of 500 eligible participants, with calls occurring on 5 days of each week in the late afternoon and evening, and a team of approximately 6-10 staff undertaking calls on each shift. TKW Research Group estimated that they will need to make approximately 10,000 calls to achieve this sample size, given that only a small segment of the population will meet the age criterion, and only half of those are expected

to meet the drinking criterion. We have chosen CATI recruitment based on our previous success in using this method with this same age group [20], in which we recruited 800 young adults from Victoria, Australia for a cohort study with a similar length and intensity of recruitment fieldwork. We chose not to use SMS text messaging to directly recruit participants owing to (unpublished) discussions in formative stages of the research with young people who described that they would find being cold-contacted by researchers "dodgy" and that they would likely ignore the message.

When an individual is deemed eligible to be enrolled in the study, researchers will invite them to participate using a standard script to describe the study (ie, all three groups will receive the same information about completing mobile phone surveys on Friday and Saturday nights for the next 6 weeks). If they provide verbal consent, the researcher will administer the baseline questionnaire over the phone on the spot. Reasons for refusal will be documented. Following completion of the interview, TKW Research Group will forward the details of new participants to the Burnet Institute, and we will send a welcome SMS text message with a link to detailed study information relevant to the participants' assigned arm; this will include a plain-language summary of the procedures relating to their trial arm, additional information as per the usual requirements of an "explanatory statement" required by an ethics committee, as well as some frequently asked questions. Participants will be blinded to the purpose of the study. The nature of the intervention means it will not be possible to blind participants to their allocated arm; however, they will remain unaware of the detailed procedures of the other arms.

Event-Based Data Collection

Alcohol Ecological Momentary Assessment and Ecological Momentary Intervention Groups

Each participant from the EMA and EMI groups will fill out the same self-reported mobile phone–delivered surveys on Friday and Saturday nights for 6 weeks. In our previous studies [16,19], participants elected to complete the intervention on nights that they planned to drink. As the current trial includes an attention control (who are not exposed to alcohol questions or related content), this was not feasible, and we instead opted to predefine the intervention nights as the most popular drinking nights of young people based on our previous study. This was restricted to two nights to reduce the burden to the participants.

The design of the data collection procedures and intervention were informed by previous research [19,21,22] showing that this length and intensity of intervention were feasible. Our previous study with a 12-week intervention period retained 87/101 (85%) of the EMI participants at follow up [19]. We shortened this time period in the current study due to the above-mentioned decision to deliver the intervention on two nights of the week, rather than allowing participants to select their own intervention nights. We also found that hourly surveys were perceived as the optimal balance between minimizing the response burden and maximizing memory recall of alcohol consumption [16]. As with our previous study that tested an earlier version of this intervention [19], at 6 pm on study nights, participants will receive a short SMS text message asking them to complete a survey, containing a link to an online questionnaire. This 6 pm presurvey includes questions relating to their intentions for the night, such as their plans for the evening, who they are socializing with (if at all), their location, their mood, and if they plan to consume alcohol. If they plan to drink, they will be asked how much they plan to drink, spend, and eat; a ranked list of particular adverse events they wish to avoid (eg, vomiting, not being able to get home); their planned mode of transport home; next day plans; and any alcohol consumption so far. An addition to this version of the intervention is the ability for participants to set reminders that can be sent throughout the night by SMS text messaging; participants can select from a list of reminders (ie, "You have a study deadline!" or "Don't forget that you have work tomorrow") and can select the time for it to be sent. Multiple reminders can be set to come through between 7 pm that night and 11 am the next day.

Participants will then be sent shorter surveys at hourly intervals between 7 pm and 3 am, which ask about current location type, mood, spending, any alcohol consumption since the last survey, and, if consuming alcohol, their perceived drunkenness. Participants can stop the surveys for the night at any point by selecting an option at the end of a survey, or by replying to the number texting them with the word "stop." Each time a survey is submitted, their GPS location is automatically collected.

At 11 am the next day (Saturdays and Sundays), participants will be sent another survey, which includes questions about any alcohol consumed or money spent after they went to bed, an estimated total standard drinks consumed and money spent for the night, an estimated volume of water consumed for the night, perceived social pressures to drink more and less, reporting of adverse events, "hangover" experienced (if they consumed alcohol), and a "fun" rating of the night.

Alcohol Ecological Momentary Intervention Group

The EMI, including questionnaires, message framing, and content, was developed in a participatory study with a group of 42 young adults in 2014 [22,23]. This three-part study involved half-day workshops to inform the design, individual testing of the intervention on a single night of drinking, and evaluation involving both in-depth interviews and a structured online survey. Further refinements were made following the implementation and evaluation of a pilot RCT [19,24] in 2015-2016. In conjunction with the co-design process, we have refined messages according to principles of motivational interviewing theory [18]. Each message incorporated an aspect of the FRAMES model, which includes Feedback (giving feedback on risks and negative consequences), Responsibility (emphasizing that the participant is responsible for making their own decisions), Advice (straightforward advice on modifying alcohol use); Menu of options (providing a menu of options to choose from), Empathy (demonstrating empathy and a nonjudgmental tone), and Self-efficacy (communicating optimism that the participant can modify their behavior if they so choose). We incorporated advice from participants in the formative stage to reduce the complexity of messages and move toward more straightforward feedback over the course of the

night or as they consumed higher amounts of alcohol. The messages sent the following morning tended to focus more on encouraging the participants to reflect on their behavior and consider what they can choose to do differently the next time.

In line with EMI principles [14], the EMI group will additionally receive repeated interventions by SMS text messages each time they fill in a survey on intervention nights. These feedback SMS text messages comprise tips and advice for having a safe and enjoyable night, along with potential feedback related to cumulative drinking and spending. These messages are tailored to the individual based on their intentions, motivations, and plans reported in the presurvey and their current situation at the time of each hourly EMA during the night. Following completion of an EMA survey, a message is automatically selected from a bank of more than 2500 messages, each of which are "tagged" with particular labels that determine the individual and situations that they are appropriate for. For example, some messages are appropriate for particular locational contexts but not others, such as a message advising participants who are concerned about their spending to take out only a limited amount of cash from an automated teller machine, which is appropriate for venues or public settings but not private homes. Other tailoring variables include gender, their reported priorities for the evening, their transport plans, whether or not they have reported eating dinner, who they are with, how drunk they report feeling, and their mood. Raw data can also be directly dropped into the messages (ie, cumulative standard drinks reported so far) to provide more tailored feedback on drinking and spending.

We used a similar framework for tailoring our messages as adopted in our previous study [24] to determine the type or topic of message sent at each hourly interval, with decision logic based on different variables collected throughout the night. Our SMS text messaging system was developed by Questmetrics, which is linked with SurveyGizmo (the host of our EMA surveys) using webhooks, so that data from the surveys are immediately passed to the Questmetrics database and used to retrieve a relevant tailored message. For each survey filled out, algorithms are run within Questmetrics to match an individual's responses against the logic framework that determines which message to send back to a participant. For example, at 1 am, if the participant has indicated that they plan to ride their bicycle home and that they feel drunk, they will receive a message suggesting that they make an alternative plan such as "It's probably not safe for you to ride home tonight. What's your backup plan?" A participant who reports in their presurvey that they would like to avoid having a hangover the next day and that they have not eaten dinner yet and plan to have more than 2 drinks that night may receive a message such as "Don't want to spend tomorrow in bed? Dinner now is a great idea."

EMI participants who respond to surveys reporting that they have not consumed any alcohol during the night will receive a generic response message such as "Thanks for your time so far!"

Alcohol Ecological Momentary Assessment-Only Control Group

The first control group (EMA) will follow the EMA data collection procedure described above (including registration for 6 weeks and event-based EMA for Friday and Saturday nights during the study period); however, they will *not* receive any feedback SMS text messages. This EMA-only group is required to examine potential reactivity to the EMA; that is, to assess the extent to which completing assessments alone (without any feedback or other intervention) can affect drinking behavior. Although previous studies have not found evidence of reactivity for EMA [25,26], in our pilot randomized control study, we noted a (nonsignificant) greater reduction in the primary outcome measure of peak drinks among participants in the EMA group compared to those in the EMI and no-contact control groups [19].

Attention Control Group

A second control group, attention control group, will fill out nonalcohol-related EMAs on weekend nights during the 6-week study period. We aimed to select a topic that is unlikely to have any influence on alcohol consumption, and instead focused on social interactions and sedentary behavior. Participants will be sent surveys on the same schedule previously described with weekly EMAs and event-based EMAs between 6 pm and 3 am on Friday and Saturday nights during the study period, with the option of opting out during the events. Participants will be asked to report on their plans for the evening, their social circle, social interactions throughout the night (including in person and online), and sedentary behavior such as how many minutes they have spent standing, sitting, or lying down in the past hour. They will then receive feedback SMS text messages in response to their surveys relating to their sedentary behavior, tailored by context such as social interactions and use of social media. There is a bank of several hundred messages available for this attention control group, similarly tagged with tailoring variables. For example, a participant who reported that their main plan for the night was watching TV or Netflix may receive a message such as: "Take a break from the TV every now and then to get up and stretch. You've been sitting down for 2 hours already tonight!" The attention control group will be the primary control group used for comparison to the EMI group in analyses.

Reimbursement

All participants will receive reimbursements that are varied based on the level of participation in the study, with the baseline, 6-week follow up, and 12-month follow up incentivized in addition to the next-day surveys (11 am Saturday following a Friday night event, and 11 am Sunday following a Saturday night event). Each survey is worth AUS$5, with a bonus AUS$10 for completing the final Sunday survey at the end of the 6 weeks, and AUS$10 for the 12-month follow up. Total possible reimbursement is therefore AUS$80.

Ethical Issues

Ethics approval for the RCT has been obtained from the Alfred Hospital Ethics Committee (project 18/18).

There is a small risk that participants will experience discomfort when answering questions about their alcohol consumption and its impacts, and reflecting on their previous weekend night. Participants do not have to answer any question if they feel uncomfortable about doing so.

There is also a small risk of participants feeling inconvenienced at having to answer hourly surveys on weekend nights. The impact is minimal given that the surveys will take only 1-2 minutes each. Participants are also be given the option at each hourly survey to opt out of completing subsequent assessments for that night.

Small payment will also be provided, as described above, to compensate participants for their time.

Primary Outcome Measure

All measures were defined a priori. The primary outcome measure will be an observed change (ie, reduction) in the mean peak number of drinks consumed in a single night over the 6-week intervention period between those receiving the intervention (EMI) and attention control participants, as measured in the weekly EMA. This method improves on our previous study, which only collected this primary outcome measure at baseline and at follow up 12 weeks later.

The primary outcome measure is collected in the 11 am (next-day) survey on Sunday mornings each week during the 6-week study period (total of 6 measurements). The question asks participants to report on the highest number of alcoholic drinks consumed in a single occasion in the past week, and the night of the week alcohol was consumed. This measure will also be collected in a survey 12 months after commencement of the intervention period.

We expect to see a greater reduction in mean peak drinking in the EMI group compared to the attention control group. We also expect that the EMA group will show a reduction in mean peak drinking compared with that of the attention control group. The latter hypothesis is based on findings from our 2018 study, which showed a large but nonsignificant reduction in the EMA group compared to the control group [19]. We also expect to see a greater reduction in mean peak drinking in the EMI group compared to the EMA group.

It should be noted that this outcome is based on reducing peak consumption on a single occasion, rather than the general frequency or quantity of alcohol consumption over a period of time. This outcome is recognized as the most accurate measure of the key aim of binge-drinking interventions, namely to reduce the level of consumption (and harm) in an acute event. This single-item numerical measure has been shown to be reliable when compared to detailed time- and location-specific questioning across the drinking occasion [20].

Secondary Outcome Measures

The following secondary outcomes of interest will be measured at the baseline, 6-week follow up (final Sunday 11 am survey), and 12-month follow up. Secondary alcohol consumption measures include annual consumption of >730 standard drinks per year (which equates to >2 standard drinks per day, in line with the Australian National Health and Medical Research Council guidelines for alcohol consumption) and, as two additional outcomes, monthly consumption of ≥5 and ≥11 drinks in a single session. These three measures will be derived from the graduated frequency measures, which include the following questions: “In the past 12 months, how often have you had 20 or more standard drinks in a day?” with response options including “Every day,” “5 to 6 days a week,” “3 to 4 days a week,” “1 to 2 days a week,” “1 day a week,” “2 to 3 days a month,” “About 1 day a month,” and “Less often than 1 day a month.” The question is then repeated with respect to the frequency of consumption: 11-19 standard drinks, 7-10 standard drinks, 5-6 standard drinks, 3-4 standard drinks, and 1-2 standard drinks. We will also examine changes in hazardous alcohol consumption using the Alcohol Use Disorders Identification Test [27].

We will measure experience of alcohol-related harms with yes/no/don’t know responses as to whether the participant has experienced different types of harm on their heaviest drinking occasion in the past 3 months, including: “Did you get into any verbal arguments or verbal fights on that occasion?”, “Did you fail to do what you intended to do the day after the session?”, and “Did you have any trouble getting home on that occasion?” These items were derived from the GenACIS [28] and VYADS questionnaires [29].

Usability and acceptability will be assessed in the follow-up survey among all groups using a 5-point Likert scale asking participants to rate a series of individual statements pertaining to their experience of undertaking the intervention (eg, “the assessments were easy to complete”). Additional process evaluation measures such as participant levels of response, refusal, and timeliness of response will also be explored to assess feasibility and acceptability.

Randomization

We will use Stata statistical software package version 15 (StataCorp LLC, College Station, TX, USA) to conduct block randomization to ensure balanced randomization to each of the three study arms. Randomization will be undertaken by a researcher external to the study team.

Effect Size and Sample Size

We hypothesize that the intervention will result in a decrease of 2.5 drinks on peak drinking

occasions. In our recent cohort study [17] that utilized similar inclusion criteria, the mean number of drinks consumed on the “most recent big night out” was 13.2 (SD 5.2). Reducing this by a mean of 2.5 standard drinks (Cohen d=0.48) would halve the estimated odds of alcohol-attributable mortality, motor vehicle accidents, and other serious injuries in the population [30,31]. Previous work suggested that this effect size is achievable: a nonrandomized mobile phone intervention found a mean reduction of 2.1 drinks per session following an untailored SMS text messaging–based intervention from a baseline of just 5.2 drinks [3]. This change is also consistent with a meta-analysis of alcohol brief interventions which found a significant aggregate effect size improvement in alcohol consumption of 0.67 (95% CI 0.40-0.95) 3 months after intervention and 0.26 (95% CI 0.20-0.32) 12 months after intervention [32].

Assuming a standard deviation of peak drinking of 5.2, conservative 10% end-point attrition, 90% power, and conservative 1% type-I error rate, we estimate that a sample of

145 participants per group is required at minimum to detect an effect size of this magnitude.

The study sample size is based on the primary aim, the associated clinically meaningful difference, and the proposed analytical methodology, which includes multiple comparisons of effect across the three groups of the trial. The sample size estimate has been calculated to test for a linear group-by-time interaction (ie, a greater mean reduction in number of drinks across the 6 weeks for those receiving the intervention) from a random-effects mixed-model analysis (6 measurements) and moderate correlations between subject measurements (r=.52, estimated from the variance parameters from our 2018 study [19]. In case of additional attrition, we will aim to recruit 500 participants.

Statistical Analyses

We will use a random-effects mixed-modeling approach using maximum-likelihood estimation to provide estimates of differences in peak drinking across time between those receiving the EMI and attention control participants. An intention-to-treat approach will be taken for this analysis. Initially, individuals and study groups will be modeled as random and fixed factors, respectively, in these mixed-model analyses. Appropriate fixed terms for the functional form of the association between study time and peak drinking will also be estimated in modeling. Additional analyses will explore the model fit of estimation of study group and time factors as random effects. The interaction between group allocation and study time is our primary focus. These analyses will be repeated, as secondary analyses, to determine the impact of the assessments alone (ie, comparison of EMA and attention control groups) using participant observations from the EMA group. Simple main effects for both treatment and time will also be estimated in the models. Distributional assumptions of models will be tested in the data and appropriate transformations applied in cases where these are not reasonably met. All statistical analyses will be performed using Stata statistical software package version 15.

Results

Recruitment for this study began in November 2018, and 601 participants were recruited by March 2019. We expect data collection for follow-up to be completed by March 2020.

Discussion

Overview

This study addresses unanswered questions from our previous research [19] about the efficacy of the MIDY intervention for reducing risky drinking behavior among young people. This research will add to the growing body of literature on EMI for alcohol use. If this intervention demonstrates efficacy in reducing alcohol consumption, we see potential for it to be offered to young people at crucial time points and events where risky drinking commonly occurs, such as during “schoolies” (a celebration following the completion of high school) or “Orientation week” (the first week of university for Australian and New Zealander students). We envisage that this intervention could either be made publicly available for young people to self-select into or be implemented in targeted populations.

Limitations

This study also has a number of limitations. In our previous work, we encountered challenges with respect to recruitment, which participants described as relating to research fatigue after participating in several waves of a cohort study prior to being invited into the trial. However, it is also possible that the intervention itself is deemed unappealing or too burdensome to complete during social events, which could affect our ability to recruit an adequate number of participants.

Due to logistical considerations and funding restrictions, we opted to recruit and administer the baseline questionnaire via CATI, with the subsequent primary outcome assessments performed using mobile Web-based questionnaires. It is possible that changing the mode of administration may induce respondent bias. However, all three groups will be subject to the same biases.

As with most alcohol-related research, this study relies on self-reported data, which is prone to reporting bias; however, this bias is not expected to differ among the RCT arms. The primary outcome will be collected at a time when participants are unlikely to be under the influence of alcohol consumption.

It is difficult to blind participants in this type of intervention study; however, our inclusion of the EMA group should allow us to account for expectancy effects whereby participants may deduce that the purpose of the intervention is to monitor and intervene on drinking behavior.

As is the case for all intervention studies using incentives, adherence to the intervention may not be able to be replicated in real-world settings.

Conclusion

This study extends our previous work investigating the efficacy of a mobile EMI, MIDY, for reducing risky drinking behavior among young adults in Australia, and will add to the proliferating literature on the use of mobile interventions for reducing risky alcohol consumption.

Acknowledgments

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Conflicts of Interest

PD has received funding from Gilead Sciences Inc and Reckitt Benckiser for work unrelated to this study. The authors declare that they have no other conflicts of interest.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 2672 KB - resprot_v9i3e14190_app1.pdf]

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Abbreviations

CATI: computer-assisted telephone interviewing
EMA: ecological momentary assessment
EMI: ecological momentary intervention
FRAMES: Feedback, Responsibility, Advice, Empathy, Self-efficacy
MIDY: Mobile Intervention for Drinking in Young people
NHMRC: National Health and Medical Research Council
RCT: randomized controlled trial
SMS: short message service

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Protocol

Hypothermic Oxygenated Perfusion Versus Static Cold Storage for Expanded Criteria Donors in Liver and Kidney Transplantation: Protocol for a Single-Center Randomized Controlled Trial

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Abstract

Background: Extended criteria donors (ECD) are widely utilized due to organ shortage, but they may increase the risk of graft dysfunction and poorer outcomes. Hypothermic oxygenated perfusion (HOPE) is a recent organ preservation strategy for marginal kidney and liver grafts, allowing a redirect from anaerobic metabolism to aerobic metabolism under hypothermic conditions and protecting grafts from oxidative species–related damage. These mechanisms may improve graft function and survival.

Objective: With this study, we will evaluate the benefit of end-ischemic HOPE on ECD grafts for livers and kidneys as compared to static cold storage (SCS). The aim of the study is to demonstrate the ability of HOPE to improve graft function and postoperative outcomes of ECD kidney and liver recipients.

Methods: This is an open-label, single-center randomized clinical trial with the aim of comparing HOPE with SCS in ECD kidney and liver transplantation. In the study protocol, which has been approved by the ethics committee, 220 patients (110 liver recipients and 110 kidney recipients) will be enrolled. Livers and kidneys assigned to the HOPE group undergo machine perfusion with cold Belzer solution (4-10°C) and continuous oxygenation (partial pressure of oxygen of 500-600 mm Hg). In the control group, livers and kidneys undergoing SCS are steeped in Celsior solution and stored on ice. Using the same perfusion machine for both liver and kidney grafts, organs are perfused from the start of the back-table procedure until implantation, without increasing the cold ischemia time. For each group, we will evaluate clinical outcomes, graft function tests, histologic findings, perfusate, and the number of allocated organs. Publication of the results is expected to begin in 2021.

Results: Dynamic preservation methods for organs from high-risk donors should improve graft dysfunction after transplantation. To date, we have recruited 108 participants. The study is ongoing, and recruitment of participants will continue until January 2020.

Conclusions: The proposed preservation method should improve ECD graft function and consequently the postoperative patient outcomes.

Trial Registration: ClinicalTrials.gov NCT03837197; https://clinicaltrials.gov/ct2/show/NCT03837197 ; Archived by WebCite® at http://www.webcitation.org/76fSutT3R

International Registered Report Identifier (IRRID): DERR1-10.2196/13922

(JMIR Res Protoc 2020;9(3):e13922) doi:10.2196/13922

KEYWORDS

organ grafts; organ transplants; perfusion; kidney transplantation; liver transplantation; hypothermia; clinical trials; temperature; randomized

Introduction

Transplantation is the ideal therapeutic treatment for end-stage liver and kidney disease. However, this treatment seems to be the victim of its own success. Although the number of liver transplantation (LT) and kidney transplantation (KT) procedures is increasing, as recently reported by the Italian registry, we face a dramatic decrease in the number of available organs [1].

Compared with standard donors, extended criteria donor (ECD) grafts are more vulnerable to the intracellular harmful effects of ischemia, such as a decrease in the availability of adenosine triphosphate (ATP), increase in reactive oxygen species, and release of lysosome enzymes with consequent alteration of cell structure and function [2,3]. In addition, hypoxia inhibits glucose oxidative phosphorylation, leaving anaerobic glycolysis as the only source of ATP production, with consequent alteration of the intracellular ionic environment and phospholipid membrane integrity [2,3]. All these events lead to the severe morphological damage that facilitates the onset of graft dysfunction [2,3].

Organ preservation is crucial when ECD transplant grafts are utilized. To date, static cold storage (SCS) is the most widely used method for organ preservation due to its simplicity and effectiveness in reducing metabolism and the associated oxygen need [4]. However, several studies have reported associations between the SCS preservation of ECD grafts and increased rates of delayed graft function (DGF) and primary graft non-function (PNF) in KT, increased rate of early allograft dysfunction (EAD) in LT, and reduced long-term graft survival [5,6].

Over the last decade, researchers have focused their attention on investigating alternative strategies for organ preservation. Preclinical and clinical studies have explored normothermic (35-37°C), sub-normothermic (20-25°C), and hypothermic (4-10°C) machine perfusion with (hypothermic oxygenated perfusion [HOPE]) or without (hypothermic machine perfusion) oxygen [3,7]. Dynamic perfusion improves the quality of high-risk grafts, removes waste products, and provides metabolic substrates for ATP and glutathione generation, which protects against reactive oxygen species–related damage [7]. Several clinical studies have demonstrated how HOPE improves short-term and long-term outcomes of KT and LT recipients [7-11].

In this study, we will evaluate the benefit of end-ischemic HOPE on ECD grafts (liver and kidney) as compared with SCS. Organs will be perfused through a recently developed machine perfusion device from the beginning of back-table procedures until implantation, without increasing cold ischemia time (CIT). The aim of the study is to demonstrate the ability of HOPE to improve graft function and post-operative outcomes of ECD kidney and liver recipients.

Methods

Study Design

In an open-label, single-center, randomized clinical trial, we will compare HOPE (study group) to SCS (control group) in ECD KT and LT. In the HOPE group, 55 livers and 55 kidneys will be preserved by SCS at 4-10°C from the end of organ retrieval until arrival at the transplant hospital. Afterwards, grafts are preserved with HOPE at 4-10°C for a minimum of 1 hour for livers and 2 hours for kidneys until implantation in the recipient. HOPE starts during back-table graft preparation. During the back-table procedure, organs are flushed with a preservation fluid (Belzer solution). Then, the organ is perfused with HOPE through a closed recirculating system.

In the SCS group, 55 livers and 55 kidneys will be preserved by SCS at 4-10°C from the end of the organ retrieval until implantation in the recipient.

In this study, 220 patients will be enrolled, with 55 in each of the following groups: LT-HOPE, LT-SCS, KT-HOPE, and KT-SCS.

The trial design is outlined in Table 1, and the protocol algorithm is shown in Figure 1.

Based on the number of transplants usually performed at the participating center, this clinical study is estimated to be accomplished in 2 years, including 12 months of patient enrollment and 12 months of follow-up. Enrollment at the Bologna Transplant Center started in January 2019 and will end in January 2020 (Figure 2).

Table 1. Trial design to evaluate the benefit of end-ischemic hypothermic oxygenated perfusion (HOPE) on extended criteria donor grafts for livers and kidneys as compared with static cold storage (SCS), N=220.

	Study group (HOPE)	Control group (SCS)
Number of livers	55	55
Number of kidneys	55	55
Process flow		
Step 1.	Preservation in SCS at 4-10°C	Preservation in SCS at 4-10°C
Step 2.	Transfer to the transplant hospital	Implantation in the recipient
Step 3.	Preservation with flushing and HOPE for 30-40 minutes	N/A
Step 4.	Preservation with HOPE at 4-10°C for 1-3 hours	N/A
Step 5.	Implantation in the recipient	N/A

Figure 1. The protocol algorithm for treatment of the study group undergoing preservation with hypothermic oxygenated perfusion (HOPE).

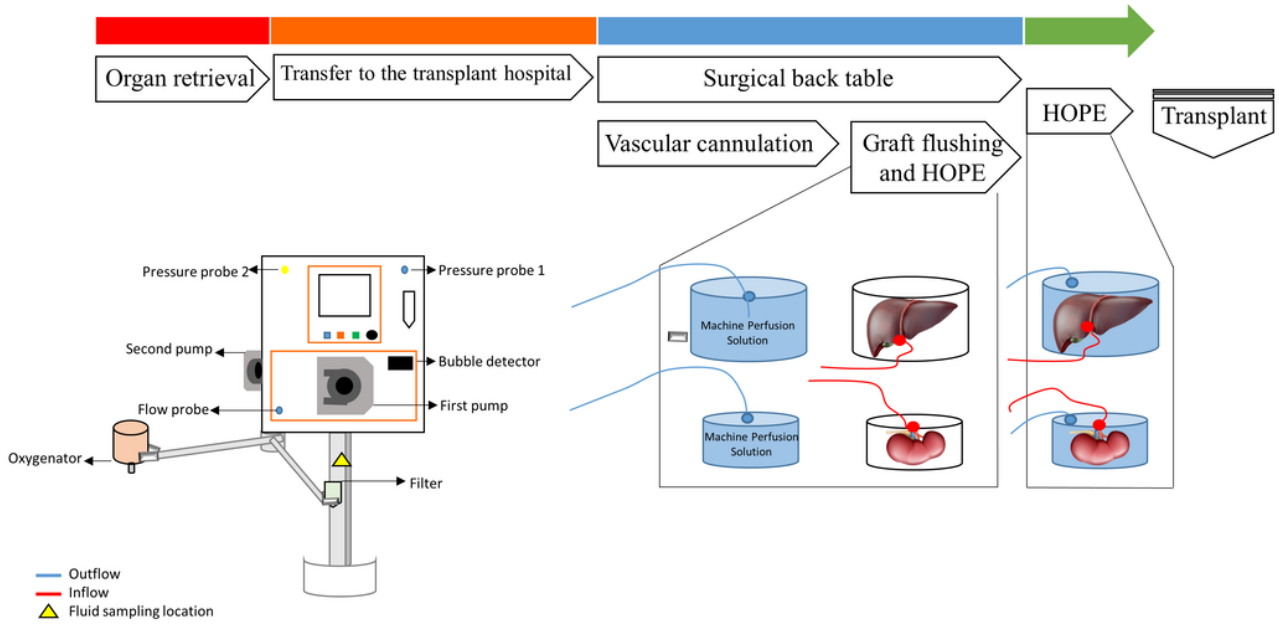
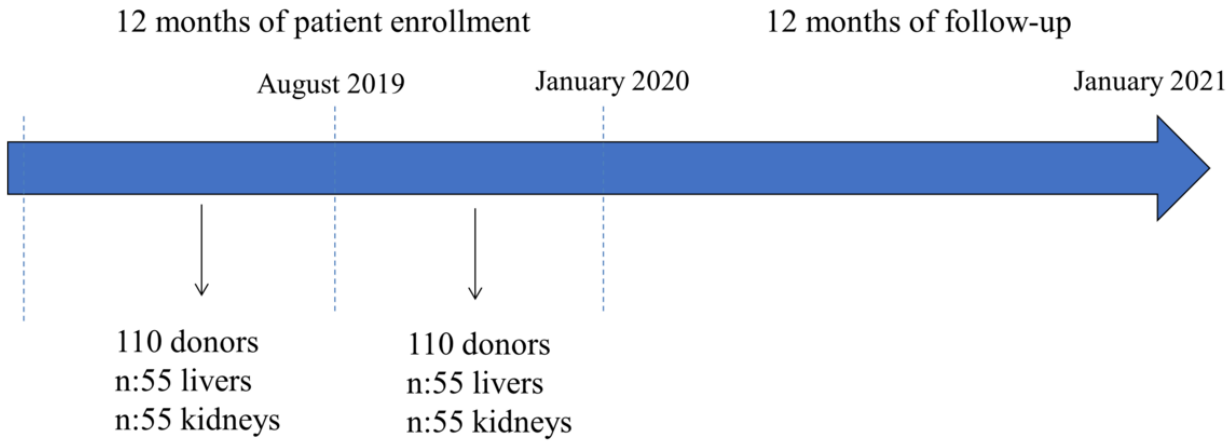


Figure 2. Estimated 2-year timeline to conduct the study, with enrollment at Bologna Transplant center starting in January 2019 and ending in January 2020.



Study Population

Donor and Patient Selection

Donors are considered eligible for the trial if they meet the United Network for Organ Sharing criteria for ECD. For kidneys, these include donor age ≥60 years or 50-59 years plus 2 or more of the subsequent risk factors: death due to cerebrovascular accident, history of hypertension, donor serum creatinine >1.5 mg/dL, or CIT >20 hours. For livers, these include hemodynamic deterioration, donor age >65 years, donor BMI >30 kg/m^2, serum bilirubin >3 mg/dL, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times the upper reference threshold, sodium >165 mmol/L, intensive care unit stay >7 days, steatosis >40%, or CIT >12 hours [12,13].

Exclusion criteria include donor age ≤18 years, split-liver recipients, LT for acute liver failure, pre-emptive renal transplant, and intraoperative surgical complications before the organ implantation. Donors after circulatory death will also be excluded, because Italian law requires 20 minutes of a "no touch period" before the death declaration, causing prolonged warm ischemia and subsequent mandatory perfusion of the organ [14].

All adult (age ≥18 years) patients waitlisted for LT or KT will be enrolled in the study after providing written informed consent.

Randomization

Patients are randomized 1:1 to the HOPE and SCS groups according to the treatment list produced by the randomizer tool. For KT, patients are stratified according to the duration of CIT before HOPE starts (longer or shorter than 12 hours); grafts with CIT >20 hours are excluded from the study. For LT, patients are stratified according to the contemporary presence of ECD liver criteria (more or less than 5 criteria). The study information and informed consent form are distributed to potential recipients. Randomization is performed for patients who sign the consent form after the organ is deemed suitable for transplantation.

To favor comparison between paired kidneys, when both kidneys from the same donor are allocated to the same center, grafts are automatically assigned to a study group and the corresponding control group. Furthermore, in cases where there are multiple transplants occurring at the same time, we prioritize LT over KT, to reduce the CIT.

Organ Retrieval

Organs are procured using the technique developed by Starzl. Following aortic clamping, abdominal organs are flushed in situ through the aorta and portal vein with cold Celsior solution, retrieved, dipped in a bag filled with preservation fluid, and stored on ice (1 L, livers; 0.5 L, kidneys). Pretransplant biopsies are performed according to our retrieval protocol.

Retrieved organs are stored on ice during the transfer from donor to the transplant hospital, during the biopsy analysis, until cross-matched results are returned, and until the final decision regarding donor and recipient eligibility.

Hypothermic Oxygenated Machine Perfusion

Organ perfusion is conducted with the Vitasmart (Medica, Bologna, Italy) machine, expressly designed for ex vivo perfusion of abdominal organs [7]. This machine system consists of two pumps, one heat exchanger, and three flow and pressure probes (Figure 2). The sterile disposable perfusion set is composed of a membrane oxygenator, tubing for vessel cannulation, and surgical cannulas.

Kidney perfusion is performed through the renal artery at a pressure of 25-30 mm Hg. Liver perfusion is performed through the portal vein at a pressure of 5 mm Hg.

Flow, pressure, and temperature are monitored and stored on a USB memory device during organ perfusion. Gas analysis of the effluent perfusate is accomplished at the start of perfusion (T0) and then every 30 minutes to determine carbon dioxide partial pressure, oxygen partial pressure (pO_2), pH, and lactate levels. Two perfusate samples are collected at the beginning and at the end of perfusion to rule out bacterial or fungal contamination.

Graft perfusion is performed in the operating room, from the start of the back-table preparation to organ implantation. First, each organ is connected to the perfusion device through cannulation of the vessels with appropriately sized cannulas. HOPE starts by flushing the organ at low flow values (20 mL/min) with new oxygenated perfusion fluid during the back-table preparation, with the aim of removing waste products and residual microthrombi. After the back-table preparation is completed, the organ is treated with continuous HOPE until transplant. Organ perfusion is continuously monitored. As previously reported [7,8], minimal perfusion time is 1 hour for livers and 2 hours for kidneys.

Belzer machine perfusion solution (2 L, kidneys; 3 L, livers) at 4-10°C, in sterile conditions, and with continuous oxygenation (pO_2 of 500-600 mm Hg) is used for perfusion.

Static Cold Storage

Livers/kidneys undergoing SCS are stored in sterile organ bags with Celsior solution and cooled on ice (0.5 L, kidneys; 1 L, livers).

Transplantation, Immunosuppressive Therapy, and Management During Hospital Stay

KT and LT are performed according to the center's standard techniques. Kidneys are implanted into either the iliac fossa with arterial anastomoses to the external, common, or internal iliac arteries or vein anastomoses to the external or common iliac veins and ureter-bladder anastomoses over a single stent. Livers are transplanted orthotopically preserving the inferior vena cava with a piggyback technique.

Postoperative management, including immunosuppression and antimicrobial, antifungal, and antithrombotic prophylaxis, follows the standard local protocol [15].

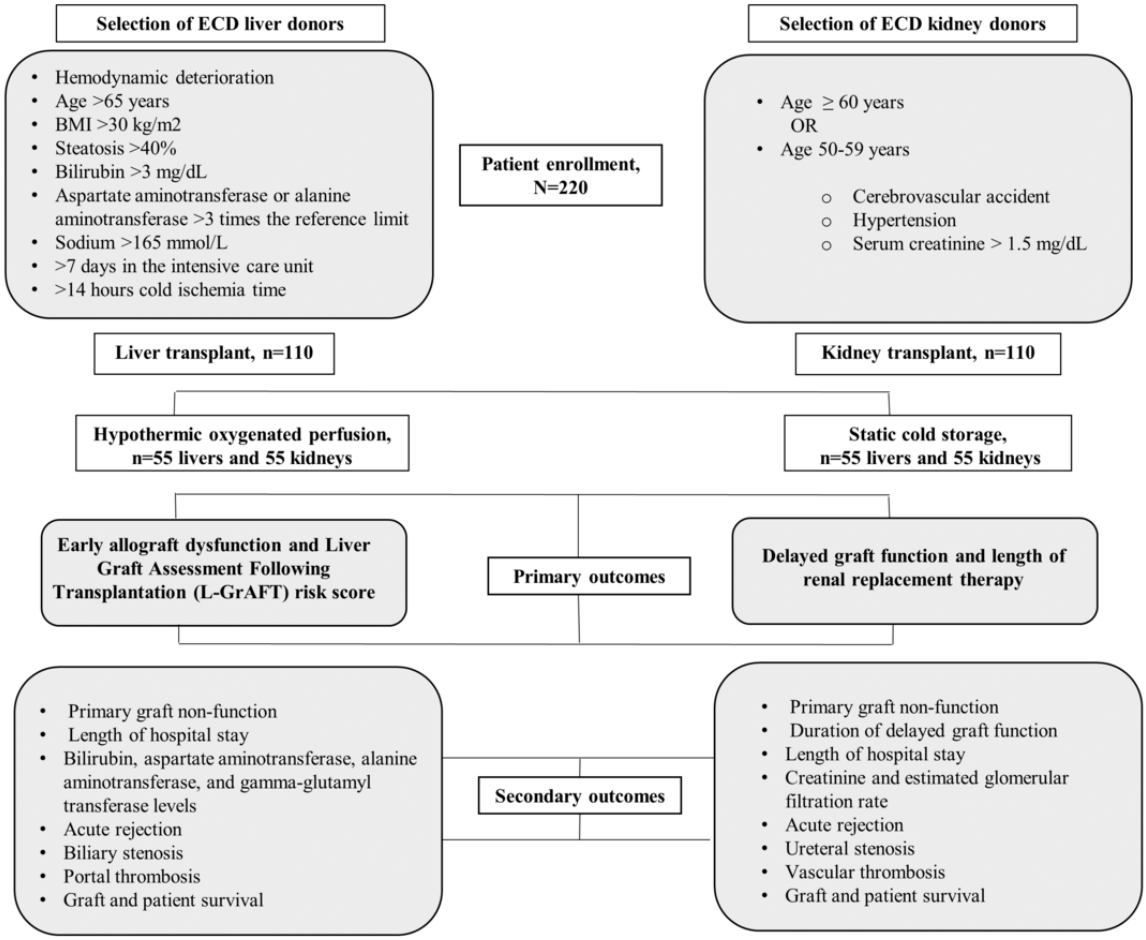
Analyses of Outcomes

Liver Transplant Primary Outcome

The rate of EAD and the Liver Graft Assessment Following Transplantation (L-GrAFT) risk score [16,17] will be analyzed to evaluate the postoperative outcomes of the enrolled liver recipients (Figure 3).

EAD is defined by the presence of at least one of the following lab results: bilirubin >10 mg/dL, international normalized ratio >1.6 on postoperative day 7, ALT >2,000 IU/mL within the first 7 postoperative days, or AST >2,000 IU/mL within the first 7 postoperative days [17]. The L-GrAFT risk score is calculated from the peak AST level, bilirubin levels, platelet counts, and international normalized ratio values from days 1 to 10 post-LT [17].

Figure 3. Inclusion criteria and postoperative outcomes of enrolled extended criteria donor (ECD) liver and kidney recipients.



Kidney Transplant Primary Outcome

The incidence and timing of DGF will be evaluated and correlated with the outcomes of the kidney recipients (Figure 3). DGF is defined as the need for renal replacement therapy during the first week posttransplant [18]. The length of renal replacement therapy is calculated as the interval between the first day and last day of dialysis.

Liver Transplant Secondary Outcomes

Secondary outcome measures in the LT groups are the incidence of PNF, defined as patient death or the need for early retransplantation within the first 7 postoperative days, excluding acute vascular complications [18]; postreperfusion syndrome rate; length of hospital stay (LHS); liver function test values (ie, bilirubin, AST, ALT, and gamma glutamyl transferase) at discharge and 1, 3, and 6 months after LT; occurrence of acute rejection events, biliary complications, portal vein thrombosis, or hepatic artery thrombosis within 6 months from the transplant; graft survival, defined as the time from transplant to retransplant or patient death due to liver failure; and patient survival.

Kidney Transplant Secondary Outcomes

Secondary outcomes for kidney recipients are the incidence of PNF, defined as irreversible graft dysfunction with graft loss, which can also be due to rejection or vascular thrombosis; postreperfusion syndrome rate; number of dialyses required in the posttransplant follow-up; LHS; renal function, as measured using creatinine level and estimated glomerular filtration rate, at discharge, 1, 3, and 6 months posttransplant; occurrence of acute rejection events, anastomotic or nonanastomotic ureteral stenosis, or vascular thrombosis within 6 months from the transplant; graft survival, defined as the time from transplant to graft loss or return to dialysis; and patient survival.

Biomarkers of Oxidative Stress, Inflammation, and Ischemia-Reperfusion Injury

Tissue and perfusate samples are assessed for oxidative stress and metabolic state using reverse transcription polymerase chain reaction (RT-PCR), enzyme-linked immunosorbent assay (ELISA), Luminex technology multiplex assays, and mass spectroscopy analysis. Tissue and perfusate samples are also assessed for the inflammatory markers CD39, CD73, E-selectin, vascular cell adhesion molecule 1, intercellular adhesion molecule 1, hypoxia-inducible factors to tumor necrosis factor-α, interleukin 6, and interleukin 8 using Luminex technology multiplex assays and/or ELISA and RT-PCR.

Specific markers related to renal function and tubular injury, including alpha-1-microglobulin, beta-2-microglobulin, albumin, clusterin, cystatin C, epidermal growth factor, neutrophil gelatinase-associated lipocalin, osteopontin, urinary total protein, trefoil factor 3, hepatocyte growth factor, and macrophage stimulating protein, are measured using Luminex technology multiplex assays and/or ELISA in perfusate and/or ultrafiltrate samples collected before and after ex vivo organ reperfusion.

Adenosine, ATP, adenosine diphosphate, adenosine monophosphate, riboflavin, and succinate levels are measured in tissue, perfusate, ultrafiltrate, and reperfusion fluid using high-performance liquid chromatography.

Finally, miR-21, a small target molecule involved in renal and liver ischemia-reperfusion injury processes, is measured.

Tissue and Vascular Morphology

Tissue injury is evaluated using histopathological analysis before and after ex vivo organ perfusion. Biopsy samples are taken during organ retrieval to assess graft suitability, after graft reperfusion into the recipient, and at the end of the transplant. Pretransplant biopsies are obtained according to our center practice. All tissue samples are sent to Bologna Transplant Center to reduce interlaboratory bias in preparing the slides.

For the livers, parenchymal and vascular damage are evaluated. For the kidneys, glomerular, vascular, tubular, and parenchymal damage are evaluated. Tissue samples are examined by two double-blind pathologists, who grade any damage from moderate to severe.

In addition, we perform immunohistochemical assays to investigate endothelial and epithelial cell injury, ischemia-reperfusion damage, the pro-inflammatory and anti-inflammatory environment, growth factors, dedifferentiation, repair, and apoptosis using specific stainings. Electron microscopy is performed to assess the features of oxidative injury, focusing on preservation of epithelial mitochondria, endothelial cells of the glomerular and peritubular capillaries, and liver sinusoids.

Tissue and perfusate samples are collected and coded to guarantee privacy and data protection in accordance with EU regulations. Perfusate and tissues samples collected for RT-PCR are snap-frozen and stored at –80°C. Tissue collected for immunohistochemical assays are preserved in glutaraldehyde solution.

Posttransplant Follow-up

Postoperative follow-up is carried out according to the local protocol. Hepatic and renal function tests and abdominal ultrasound are performed at each follow-up visit. Follow-up will end at 12 months.

Risk Analyses

Technical assistance by a team of expert technicians is provided during all phases of the machine perfusion procedures.

Vascular endothelial damage is avoided by perfusing the liver solely through the portal vein, leaving the hepatic artery untouched, and keeping the perfusion pressure of the renal artery and portal vein at low levels, which we previously demonstrated as being safe in preclinical and clinical studies [7,8].

Data Management

Demographic, clinical, and biological data of donors and recipients are collected and prospectively entered in the database. The data registration is anonymous, and a study identification code is assigned to each transplant, in accordance with the Helsinki Declaration.

Missing values are handled properly by the researchers to achieve accurate inferences about the data during the analyses of the results.

Statistical Analyses

Sample Size Calculation

The sample size was calculated using the primary outcomes of EAD and DGF for LT and KT, respectively, and the secondary outcomes of PNF and LHS, as reported in similar studies [11,19,20].

In particular, the rates of PNF and EAD are expected to decrease for the LT-HOPE group, thereby improving the postoperative course and LHS. We are expecting the following reductions in these parameters: PNF, 5% (HOPE) vs 10% (SCS); EAD, 10% (HOPE) vs 20% (SCS); and postoperative LHS <21 days, 80% (HOPE) vs 50% (SCS).

In KT, HOPE should reduce the rate of DGF from 50% to 30%, with a general improvement in the postintervention outcomes.

Based on these parameters, the total sample size was estimated at 220 patients, with distribution throughout the 4 groups as already explained (alpha=.05, two-sided test, power of 80%; calculated with nQuery Advisor 7.0, Statsols, Cork, Ireland).

The sample size was calculated to account for a dropout risk of 5-10% for the year.

A preliminary analysis will be performed when half of the enrollment is completed.

Preliminary Analyses

To monitor and optimize the planned surgical and clinical procedures, real-time data analyses are performed before the final data collection. In detail, we are performing two interim analyses on the data from the first 7 posttransplant days. The primary analyses will be performed after the enrollment of 60

patients. The second analyses will be performed after the enrollment of 160 patients.

Statistical Tests

The continuous variables will be compared using parametric (ANOVA) or non-parametric (Kruskal-Wallis) tests according to the data distribution, and the categorical variables will be compared using chi-squared tests. Multivariate analysis will be performed using forward stepwise logistic regression analysis. Survival analysis will be conducted using the Kaplan-Meier method. *P* values <.05 will be considered statistically significant.

Ethical Review

The research protocol, including the forms for data treatment, study information, and participant content forms, were approved by the Emilia-Romagna Region Ethics Committee, which is the ethics committee for the transplant center, and the National Health System Research.

Written, informed consent is obtained prior to final enrollment. Randomization is performed as recommended by the ethics committee, and all members of the research team learns the treatment type of each recipient only after their inclusion. Possible protocol changes will be applied after the approval of their amendments by the National Health System Research and then the local ethics committee.

Recipients are insured against study-related adverse events with a protocol-specific insurance policy.

The principal investigator and all members of our research scientific group have declared no conflict of interest.

Dissemination

We will describe the data and transcribe the results with the aim to develop an original article for submission at a scientific review, national conferences, and international conferences.

Clinical Relevance

With ECD LT and KT, the use of adequate organ preservation techniques may improve posttransplant outcomes without compromising graft function and survival, thereby increasing the donor organ pool.

Results

Dynamic preservation methods for organs from high-risk donors should improve the functional recovery of the graft with a lower expected DGF for KT and EAD for LT.

To date, we have recruited 108 participants. The study is ongoing, and recruitment of participants will continue until January 2020.

Discussion

This study suggests that the use of adequate organ preservation techniques may improve the posttransplant outcomes without compromising graft function and survival, thereby increasing the donor organ pool. The concept of dynamic organ preservation was developed by Carrel and Lindbergh in the 1930s [21,22]. An increasing number of ECDs are used for transplantation, which has triggered an interest in new preservation techniques to improve organ quality and decrease the occurrence of severe complications [23,24]. While the use of oxygen in machine perfusion for liver preservation has been extensively investigated in clinical trials, HOPE has been reported less frequently for KT [25].

An important aspect of this study is the use of the same perfusion device for liver and kidney grafts, which differs from previous studies [11,20,26,27]. With this machine, organ perfusion is a simple procedure that can be started during the back-table preparation of the surgical graft, avoiding an increase in CIT.

Increasing evidence suggests that HOPE of the graft should start immediately after retrieval. This might reduce the accumulation of waste products, such as succinates, and the perfusion should result in better restoration of mitochondrial function [10-25].

Our protocol starts with washing the graft for 30-40 minutes during organ preparation to completely remove the waste elements that were released and accumulated from the start of ischemia. And, the organ perfusion system is equipped with an adsorbing hemofilter to remove cytokines and avoid fat embolism. Following this step, oxygenation and recirculation of the preservation fluid begin. Flow, pressure, and temperature are monitored and stored on a USB memory device during organ perfusion. Gas analysis of the effluent perfusate is conducted at the start of perfusion (T0) and then every 30 minutes to determine carbon dioxide partial pressure, pO_2, pH, and lactate levels. Two perfusate samples are collected at the beginning and at the end of perfusion to rule out bacterial or fungal contamination.

Another important aspect is the simplicity of this organ preservation procedure in terms of organization and management. We do not need a perfusion specialist, and we have had no procedure-related adverse events. In addition, starting from the back-table procedures, CIT is not prolonged.

Advantages of this HOPE system include its simplicity and improved LT and KT outcomes.

In conclusion, we aim to demonstrate the ability of HOPE to improve graft function and postoperative outcomes of ECD kidney and liver recipients.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 6681 KB - resprot_v9i3e13922_app1.pdf]

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Abbreviations

ALT: alanine aminotransferase.
AST: aspartate aminotransferase.
ATP: adenosine triphosphate.
CIT: cold ischemia time.
DGF: delayed graft function.
EAD: early allograft dysfunction.
ECD: extended criteria donor.
ELISA: enzyme-linked immunosorbent assay.
HOPE: hypothermic oxygenated perfusion.
KT: kidney transplantation.
L-GrAFT: Liver Graft Assessment Following Transplantation.
LHS: length of hospital stay.
LT: liver transplantation.
PNF: primary graft non-function.
RT-PCR: reverse transcription polymerase chain reaction.
SCS: static cold storage.

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Protocol

Digitally Enhanced Mentoring for Immigrant Youth Social Capital: Protocol for a Mixed Methods Pilot Study and a Randomized Controlled Trial

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Abstract

Background: There are large disparities between immigrants and native Norwegians in domains such as health, education, and employment. Reducing such disparities is essential for individual and societal well-being. Social capital is associated with positive effects on these domains, and mentoring programs have the potential to boost social capital. However, few studies have assessed mentoring as a social capital intervention among youth or the potential barriers and facilitators of implementing digitally augmented mentoring.

Objective: The goal of this paper is to describe a protocol for assessing the implementation and effectiveness of a digitally augmented mentoring program for immigrant youth as a health intervention to promote social capital. The two-stage analytical framework for a pilot study followed by a randomized controlled trial (RCT) is presented. The pilot aims to assess program fidelity and make necessary intervention adjustments before the RCT. The RCT aims to assess the effects of the implemented intervention program on social capital and the relationship between program fidelity and effects.

Methods: Both the pilot and RCT will use mixed methods with a process evaluation approach used to structure the intervention and a pre-post test survey component to measure social capital and fidelity of program implementation. Interviews will also be used to enrich the quantitative data from the survey.

Results: The pilot study is scheduled to begin in fall 2019. Based on data analyses in spring 2020, potential adjustments will be made to the intervention, with findings used in preparation for the full-scale RCT study.

Conclusions: Digitally enhanced mentoring programs may be a helpful intervention for providing immigrant youth with tools for increasing their social capital and indirectly improving health outcomes. This protocol provides new knowledge about the implementation and evaluation of such programs.

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KEYWORDS

social capital; e-mentoring; youth mentoring; health promotion intervention; mixed methods; randomized controlled trial; immigrant

Introduction

Background and Context

Globally, significant discrepancies exist between immigrant youth and native-born individuals with regards to school dropout, isolation, unemployment, and health. For example, 71% of immigrants in Norway report experiencing at least one of eight listed health problems compared with 49% of the population at large [1]. Relatedly, there is a 26% difference between immigrant and native Norwegian youth with regard to education and employment, with anxiety and depression contributing to these discrepancies [2,3]. These issues also hinder inclusion and integration of new immigrants. Reducing disparities among these vulnerable groups represents an important area of focus, and Norwegian policymakers are increasingly willing to test new approaches.

Social capital, a focus of this study, is associated with a variety of positive health outcomes, including self-reported health [4-6], psychiatric outcomes [7], and mortality [8]. On average, immigrants tend to have less access to certain forms of social capital compared with ethnic Norwegians [9], and investing in social capital can potentially enhance health among immigrant youth. Social capital is multidimensional and has been conceptualized in multiple ways [10-13]. Broadly, it includes relational and cognitive (trust, sense of belonging) and structural (networks or connections among individuals, along with community engagement) dimensions [14]. Analyses can be at the individual or collective level, with focus on different types of social capital: bonding, bridging, and linking [13,15]. With regard to immigrant populations, bonding refers to connection with and support from individuals with a similar ethnic, linguistic, or religious identity, whereas bridging implies connections to those of dissimilar backgrounds, often the majority population [13,16]. Linking relates to vertical relationships between an individual and institutions or individuals in positions of authority [17]. Although bonding social capital is helpful for "getting by," bridging capital is important for "getting ahead" [13]. Bonding is the most prevalent form of social capital among immigrants [18] and can provide social support and belonging, decrease isolation, and allow sharing of local knowledge [9,19]. Bridging includes benefits, such as increased ability to gather information [20], and can facilitate positive labor market outcomes, such as relevant employment [21]. Both bridging and bonding types are important, and bonding appears to facilitate bridging [22]. Immigrant youth are an important target group for study, as they generally have weaker social capital compared with natives [9,22]. This is exacerbated for the unaccompanied refugees in the group who arrive with no family and lack this important aspect of social capital.

Although approaches for strengthening social capital are clearly worth pursuing, interventions to increase youth social capital, such as the one proposed in this paper, are quite new [23]. Little is known about how such interventions might be implemented, and their effects [24]. Although not systematically studied as such, mentoring programs have the potential to act as "social capital interventions" by assisting immigrants in expanding their networks, and thus their social capital [25,26]. In this setting, mentoring can be defined as "taking place between young persons (ie, mentees) and older or more experienced volunteers (ie, mentors) who are acting in a nonprofessional helping capacity to provide relationship-based support that benefits one or more areas of the mentee's development" [27]. Participation in youth mentoring programs is associated with improved outcomes across social, behavioral, and academic domains [28]. Such programs, typically conducted by social entrepreneurs, have few traditions in Norway. For the program described in this paper, coordinators recruit, select, train, and match mentors and mentees, and all mentees receive the same basic program. Main program components include training for both mentors and mentees before program start, mentee and mentor sharing of their achievement story (a proud life moment), identification and discussion of mentee strengths, a "roadmap" selecting a goal and describing tasks for the mentee to achieve it, and a network mapping exercise for the mentees. Additionally, the program requires six face-to-face dyad meetings, with one meeting each month during the six-month program period. Staff members also follow up on the matches monthly. Mentees are recently arrived immigrant youth recruited from local schools; willingness and interest in participating are the main selection criteria. Mentor volunteers are recruited in a variety of ways, including personal connections with program staff, social media, and volunteer recruitment websites.

Although one might assume that digital support for this type of mentoring program holds potential for reach and effectiveness, few programs employ digital tools or have been studied systematically [29,30]. Therefore, a prior study [31] of immigrant mentees' and mentors' experiences and needs was conducted to guide the development of a digital platform. This platform is integral to the mentoring program described in this protocol. The platform was designed to augment and boost, rather than replace, preexisting mentoring program components. Key elements of the platform include a timeline to provide oversight over dates of program events and show program progress, messaging, cards for identifying personal strengths, a forum for mentees and mentors, a network map, and a toolbox containing helpful supplementary resources (eg, information on writing a good resume). Figures with screenshots illustrating planned iterations of the platform are available in Multimedia Appendices 1 to 4. Although the digital platform is expected to enhance social interactions and program fidelity compared with the program without digital support, the protocol does not directly address this issue.

Objectives and Significance

This paper describes a protocol for studying a digitally augmented mentoring program as a social capital intervention for immigrant youth in Norway. The protocol proposes a pilot study followed by a randomized controlled trial (RCT). Ultimately, we are interested in assessing the implementation and effects of mentoring program participation on social capital. A process evaluation framework inspired by a previous study [32] will be applied for investigating the implementation of the mentoring program in this pilot study. This framework consists of (1) contextual factors that affect the implementation, (2) what has been implemented and how, and (3) mechanism of impact

(ie, the participants' responses to and interactions with the program). Thus, the objective of the pilot study is to assess program fidelity and design by investigating the context, implementation process, and mechanisms of impact [32,33]. The questions guiding the pilot study are:

1. What contextual factors affect the implementation?
2. How is the mentoring program implemented (ie, fidelity, dose, and reach)?
3. What are the participants' experiences in the mentoring program?
4. Are the measures used for studying outputs and outcomes valid, and are they acceptable and meaningful to stakeholders?

The pilot allows adjustments of the social capital intervention before full-scale implementation and the RCT. The intention of the RCT is to investigate the effects of the implemented program on the social capital of immigrant youth, guided by the following questions:

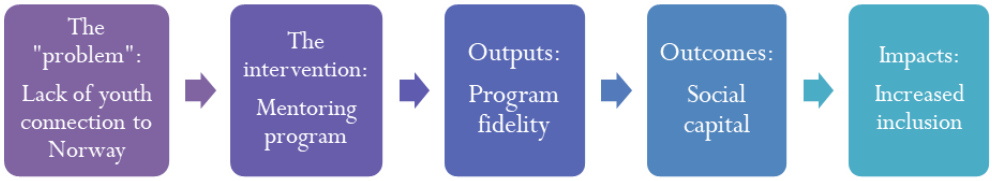
1. To what extent was the intervention implemented (outputs)?
2. What are the effects of the implemented program on social capital indicators (outcomes)?
3. What is the relationship between program fidelity and effects?

The study offers both theoretical and empirical contributions. First, much of the work related to mentoring as an intervention has been done in the United States, with primarily qualitative studies in the United Kingdom [28]. Therefore, this work will contribute by extending the empirical context. Second, few studies have assessed social capital interventions [34], particularly among youth. More commonly, social capital is used as an independent variable (see [35] for a health intervention to increase social capital among Latinx and black adults). Furthermore, little is known about the implementation and effects of such interventions [23], although research indicates potential in this area [25,35]. This study seeks to address these gaps, providing both theoretical and summative insights. The overall objective is to evaluate the intervention in light of challenges and opportunities in implementation and to explore the effects of this implementation.

Analytical Framework

The logic model [36,37] depicted in Figure 1 provides a valuable framework for identifying and illustrating the relationship between clusters of variables in the study. The model identifies a problem (youths' lack of connection to Norway), which requires a response, and specifies activities to address the issue (the mentoring intervention). The implementation of the solution leads to tangible outputs (program delivery) and measurable outcomes (social capital) as the consequence of the outputs; the broader impacts (social inclusion) are the logical effects of the intervention. There is a tight relationship between the identified problem, the intervention, the program outputs, and the outcomes of interest.

Figure 1. Logic model for the protocol (based on [36,37]).



The pilot study focuses on the first three boxes in Figure 1, allowing adjustments before the RCT if certain outputs are not achieved. The full-scale implementation of the intervention will focus primarily on assessing outputs and outcomes. Impacts are often indirect, and there are significant challenges in causal attribution; thus, impacts are not measured as part of this study. However, the implication is that if outcomes are achieved, broader and more distal societal impacts will result.

The framework depicted in Figure 1 provides a general guide for the study. Research suggests that multicultural youth have narrower networks and less access to certain forms of social capital [9], which contributes to higher dropout rates and poorer health than natives. There is evidence that social capital is associated with improvements in these domains and may facilitate integration and inclusion [4,21].

The mentoring intervention seeks to address these discrepancies. An important focus is on how the program can strengthen mentees' networks through information exchange and social contact and increase trust and feelings of belonging (social capital). Thus, the study emphasizes outputs and outcomes, as well as the influence of contextual factors on these.

Methods

Study Design

The first stage is the pilot study, followed by the RCT. A mixed-methods approach will be used combining quantitative survey instruments (pre-post test design) with qualitative data from interviews and focus groups [38]. The survey will measure outputs (program fidelity, dose, and reach); outcomes (cognitive and structural social capital), which are a result of the implementation outputs; and contextual factors (respondents' demographics, school characteristics, and usability of the digital platform). Specific cutoffs for assessing fidelity to the core program components (described in the Background and Context section) and effectiveness will be developed based on pilot study results. Interviews with mentors, youth, and program staff will allow a detailed qualitative understanding of the mechanisms occurring and stakeholder experiences.

Sample and Participant Recruitment

Both stages of the study will be conducted in close cooperation with mentor program staff (the individuals working directly to

coordinate, match, train, and follow up on dyads), and with feedback from the youth. The primary unit of analysis for the study is recently arrived immigrant youth, ages 15 to 25 years, attending school. These youth will be in or have completed their first year of Norwegian schooling; therefore, they will have a minimum basic level of Norwegian proficiency. We will offer interviews in Norwegian and English, but will also consider the use of a translator, as necessary, for the RCT to gain a better understanding of the experiences of participants with varying levels of Norwegian language comprehension. Information from mentors and program staff will also be collected. Informed consent will be obtained and the voluntary nature of participation will be emphasized to the youth, with information that they can end their participation at any time. A video will be used to present the research project, handling of data (confidential, but not anonymous), and privacy issues in youth-friendly language to gain fully informed consent and to increase stakeholder (youth) involvement and interest [39].

For the pilot study, all mentees (approximately 40) participating in four of the mentoring programs will be recruited to participate in the survey at the beginning and end of the program. The majority of these mentees have backgrounds from Syria and Eritrea, and almost all will be attending school. At the end of the six-month program, mentors (approximately 40) from these programs will also be invited to respond to a survey. All mentee respondents will receive small denomination gift cards (approximately $28) on completion of the surveys as a gesture of appreciation for their assistance with the project. We will also discuss how the youth perceive receiving gift cards, with a specific focus on any feelings of coerciveness, to make any adjustments before the RCT. Qualitative respondents will be selected from the individuals providing quantitative information to investigate specific aspects of program fidelity and implementation in more detail.

The full-scale RCT will recruit participants from Norwegian schools and include both a control and an intervention group. The study will try to select similar schools for both groups regarding school size, socioeconomic characteristics, and school type (age range of the student body). Within the intervention group of schools, intervention classes will be drawn randomly, whereas control classes will be drawn randomly from the control schools. Participants and nonparticipants will not attend the same schools to avoid contagion effects. The exact number of individuals will be estimated based on a power analysis of data from the pilot study and is anticipated to encompass several hundred youth. Half will be in the intervention group and half in the control group. Students who are not assigned to the control groups for the study will have the opportunity to receive the intervention after the study has concluded. Although all the youth will have a basic level of Norwegian proficiency, additional potential inclusion and exclusion criteria for the RCT will be developed based on findings from the pilot study. Similar to the pilot study, mentors will be surveyed at program conclusion, and respondents will be invited to qualitative interviews and focus groups, to supplement and nuance the quantitative data.

Data Collection Procedure

Pilot Study

After receiving information about the project in the form of a video and giving informed consent, the mentees will receive an individual link to participate in a Web survey. Questions on the mentee survey at program commencement will focus on social capital in the form of relationships with friends, native Norwegians, connectedness to the school environment, and to Norway more broadly. This will be used to test out and adjust measures for the full RCT study based on feedback from the groups. A Web survey will be administered at program completion, with the same survey questions as on the first survey, supplemented with questions about program fidelity (outputs) and a short battery to assess the relationship with the mentor and implementation. Mentors will receive surveys related to program fidelity and the relationship with mentees and staff. Additionally, both mentees and mentors will respond to survey questions on the usability of the digital platform. To supplement the quantitative survey data, qualitative data will be collected from mentors and mentees in interview form for both the pilot and RCT. Individuals will be selected for interviews based on characteristics such as age, sex, immigration background, and length of time in Norway, with a goal to get a very diverse group [38]. Interview questions will address barriers and facilitators to implementation, possible contextual factors relevant to the implementation and participants' experiences of these factors, and the acceptability and meaningfulness of the measures used in the survey (see Outputs in the Measures section for details on the operationalization of these concepts). Questions to program staff will focus on resources such as program staffing, finances, and technical support for the digital platform.

The pilot study has been approved by the Data Protection Office at Oslo University Hospital. All pilot study data will be stored on a secure remote server as per Oslo University Hospital Personal Data Protection regulations. The pilot study is funded by a grant from the Norwegian Research Council and is a partnership between the Center for Shared Decision Making and Collaborative Care Research at Oslo University Hospital, NORCE-Norwegian Research Centre, Halmstad University, the Norwegian Labor and Welfare Administration (NAV), and Fretex.

Full Study With Randomized Controlled Trial

The effects of the program as a social capital intervention will be studied using a two-level clustered randomized trial, with schools randomly assigned as intervention or control schools. The analyses will be at the individual level. In using a randomized comparison of mentees with non-mentees, the effects of mentoring on social capital can be assessed, also controlling for individual differences.

Youth in both the intervention and control groups will complete Web surveys. The youth surveys cover questions related to social capital and will be conducted at baseline (before program commencement), six months after the baseline measurement (at program completion for the intervention groups), and six months after program completion (12 months after the baseline measurement). Surveys to youth in the control group will be

administered at the same time points as for the mentees. Mentors will respond to surveys at program conclusion. Because youth in the intervention group will receive mentoring outside of the school environment, we do not have a specific activity planned for the control group. However, control group youth will be put on a waiting list to participate in the mentoring program after study completion, if they desire. Approval from the institutional ethics board (Data Protection Officer) will be applied for and obtained before RCT study commencement.

The following table (Table 1) summarizes the instruments, respondents, and timeline for data collection.

Table 1. Overview of the study procedure.

Study stage and data collection instrument	Respondents	Description	Time point
Pilot			
Web survey at program start (baseline)	Mentees (approximately 40)	Social capital: cognitive and structural); demographic variables	Program start (fall 2019)
Web survey in program middle and conclusion	Mentees (approximately 40); mentors (approximately 40)	Usability of digital platform	Mid and end of program
Web survey at program completion	Mentees (approximately 40); mentors (approximately 40)	Same as baseline survey; program fidelity	Program completion (6 months after start; spring 2020)
Interviews	Mentees (5-10); mentors (5); program staff (2)	Acceptability and relevance of social capital measures; barriers and facilitators to implementation and fidelity	Midway and at the end of the program (fall 2019, spring 2020)
Randomized controlled trial			
Web survey at program start (baseline)	Mentees; control group youth	Pre-post social capital measurements; demographic variables	Program start (estimated fall 2020)
Web survey at program completion	Mentees; mentors; control group youth	Pre-post social capital measurements; program fidelity	Program completion (6 months after program start)
Postprogram survey after program completion	Mentees; control group youth	Pre-post social capital measurements	Follow-up 6 months after program completion (12 months after program start)
Interviews	Mentees (10-20); mentors (5-10); program staff (4)	Supplementary information on social capital based on survey responses	Midway and at the end of the program (fall and winter 2020)
Pilot and randomized controlled trial			
Qualitative and metadata from the digital platform	Mentees; mentors	App use data (frequency, length of time, particular modules used); content of forum posts	Throughout the programs

Measures

Measures to be used for the study survey are adapted from previous research and large-scale cross-national surveys [40-48]. Where relevant, new items were developed specifically for this intervention context, particularly to measure fidelity of implementation.

Outputs: Intervention Implementation

Outputs are the process and mechanisms by which the "problem" and its consequences are targeted. More specifically, this is the implementation of the intervention. An important emphasis is on fidelity of implementation of core program components (including dose, or the amount of the intervention, and reach), and mechanisms of impact (participants' interactions with the intervention) and the contextual factors that have an impact on the implementation (discussed subsequently). Assessment of fidelity is done using a self-developed scale for the study to match the program environment. Program fidelity is measured using the following indicators (previously described under Background and Context): the total number of dyad meetings held with at least one dyad meeting each month (six meetings in all), participation in training before program start, and execution of the main program components, such as network mapping. The proportion of participants that complete the program (reach) will also be assessed. Identification of any deviations or adaptations to these key program components will be noted. Because the intervention also includes a digital component (forums for mentor-mentee contact), log data from the platform, including the number of log-ins and time spent on different parts of the platform, will be analyzed to assess dosage.

Relationship quality (mechanism of impact) will be measured using the 14-item Mentor Strength of Relationship scale [40], adapted from the Big Brothers Big Sisters mentoring context to this context (eg, terminology such as "my Little" is replaced with "my mentee"). Answers are scored on a five-point Likert scale ("strongly disagree" to "strongly agree"). For mentees, the positive statements from the Youth Strength of Relationship Scale [40,41] will be used; response categories are on a five-point scale and range from "not true at all" to "always true."

The Strength of Relationship scales have been assessed for fit using confirmatory factor analysis, with acceptable results [40]. Little research has been conducted on mentee or mentor relationships with program staff and program training. Therefore, self-developed single items will be used that ask to what extent respondents were satisfied with the program coordinator and the training they received (response categories from 1="very dissatisfied" to 5="very satisfied").

Outcomes: Social Capital

The outcome variable of interest for the RCT—social capital—includes cognitive and structural dimensions [14]. The cognitive dimension of social capital is operationalized to include youth feelings of belonging, support in relationships, and trust. Feelings of belonging will be measured using a question from the European Social Survey (ESS) Round 8 [42] on how connected the youth feel to Norway. The response scale ranges from 0 ("not emotionally connected at all") to 10 ("very emotionally connected").

Youth will also be asked about how often they felt lonely during the previous month (five-point scale: "not at all" to "all the time") (similar to a question from a Statistics Norway survey on social relations [43] and questions in the ESS [42]).

Shared language is another indicator of cognitive social capital related to belonging [44]. This will be measured by using a self-created question asking: How comfortable are you speaking Norwegian? (scale from 1="very uncomfortable" to 5="very comfortable").

Trust will be measured using the question on generalized trust (A4) from the ESS [42] with a response range from 0 to 10 ("you can't be too careful" to "most people can be trusted").

The structural dimension of social capital relates to the presence and patterns of connections between actors or network characteristics (bridging, bonding, linking), school connectedness, and civic engagement or organizational participation. To assess network characteristics, the respondents will be asked about the proportion of their friends with a similar ethnic background and religion (bonding), with an immigrant background (bonding), and with a Norwegian background (bridging). This will be assessed using a five-point scale ("none" to "all"; similar to [22,45]).

Civic engagement will be measured using questions about organizations in which the youth are active. The youth will be provided with a list of different organization types (religious, sports, art and music, volunteer organization) and will be asked to respond if they are a member, have participated previously, or are not a member (similar measures are used in ESS and in the Ungdata survey for Norwegian adolescents [46]).

Patterns and nature of contact with friends and family will be measured in several ways. The youth will be asked if they have at least one good friend that they can fully trust (four-point scale from "no, I have no one I would call a friend at the moment" to "yes, for sure") (questions are taken from Ungdata [46]). Respondents will also be asked about frequency of contact with their friends outside of school or work [42], with responses on a six-point scale from "never" to "every day" (similar to [45]).

To measure school social capital and connectedness, several dimensions (teachers, classmates, school) will be used. Connectedness will be measured using indicators from the Health Behavior in School-aged Children study protocol questionnaire [47], as used in a Swedish study on social capital [4]. Connectedness with teachers will be measured with three items (five-point scale from "strongly disagree" to "strongly agree"); for example, "I feel that my teachers accept me as I am." Connectedness with classmates will be measured using three items (eg, "most of the students in my classes are kind and helpful") with the same five-point scale. These two scales have been validated using confirmatory factor analysis [47]. To assess connectedness with school, three questions from Ungdata [46] ("I am often bored at school," "I don't like going to school," and "It's important to do well at school") will be used, also with a five-point scale. One question from the Health Behavior in School-aged Children [47] ("How do you feel about school at present") will also be used (4-point response scale from "I like it a lot" to "I don't like it at all"). To assess school attachment, a self-developed item similar to that used in Ungdata [46] will be used to assess if and how often the youth have considered dropping out of school in the previous three months. Response alternatives (four-point scale) range from "never" to "very often."

Context and Controls

Demographic characteristics of the youth in the sample, such as age, sex, length of time living in Norway, and economic status (inquiring about their finances during the past year), will also be included in the survey. Characteristics related to setting (school size and centrality) and the digital context in which the respondents participate will also be taken into account. In the pilot study, the usability of the digital platform will be assessed in a survey, which will include questions from the System Usability Scale [48], a robust tool for analyzing usability [49]. The scale has 10 items (eg, "I thought the platform was easy to use") and response choices on a five-point scale from "strongly disagree" to "strongly agree." Assessment of contextual factors will also be collected from mentors and youth in interview form.

Data Analysis

Quantitative data will be analyzed using statistical software packages. Descriptive statistics will be presented and pre-post measures used to determine the impact of the intervention on social capital and more distal outcomes. Additionally, because the literature suggests that mentoring produces better outcomes for some groups (eg, high-risk male youth) over others [50], we will conduct exploratory analyses to investigate differing effects of the intervention based on age, gender, and time in Norway. All interviews will be recorded and transcribed, and qualitative analysis software (NVIVO 12) will be used on the transcribed interviews and forum data. This will entail coding of responses, first extracting broad themes from the data, and then identifying subthemes [51]. This type of qualitative analysis will supplement the data from the surveys, allowing a better understanding of the implementation process and explain why specific outcomes might have occurred [38].

Results

This protocol was informed by a prepilot study conducted from January to June 2019 [31], which focused on the experiences and needs of stakeholders with relation to the digital mentoring platform and perceptions around the concept of social capital. This enabled the identification of areas of focus and strategy for this protocol, particularly in relation to social capital and key components of the mentoring program. Therefore, the resulting protocol is considered well-suited for providing a valid analysis of program fidelity (which the mentoring program is currently working to adhere to) and new knowledge about social capital as a health promotion intervention among immigrant youth.

The pilot study will commence in fall 2019 and conclude in spring 2020. The participants (mentors and youth mentees; approximately 40 of each) have already been identified for the pilot portion of the protocol. Efforts related to recruitment for the RCT will begin after the pilot study is finished.

Discussion

The overall objective of this protocol was to present a plan for evaluating the implementation and effects of digitally augmented mentoring relative to social capital among immigrant youth. The main working hypothesis is that students who receive the intervention will have broader networks and higher levels of trust and feelings of belonging (greater social capital) compared with those students who do not receive the intervention. Considering the paucity of research on social capital interventions, the protocol should be relevant for researchers interested in community-based health promotion and in social capital more broadly. More specifically, it provides a framework for analyzing mentoring programs for immigrant youth to see what works under what circumstances and for whom. However, there are some anticipated limitations.

Because mentees self-select to the program in the pilot study, these findings may not be generalizable to a larger group; however, this is not the primary objective of the pilot. The RCT should ameliorate this issue owing to the random selection of individuals and classes. Another potential limitation relates to language issues, particularly in the survey instrument. The pilot study is intended to assess the relevance and acceptability of the instruments to the target groups; comprehension will also be a relevant consideration at this stage. Thus, this issue will hopefully be minimal in the RCT. Attrition, particularly after program completion, is another potential limitation, as in most survey research.

If this intervention is successful, it may have an impact on the possibility for young people to be better included in Norwegian society. Further work could potentially encompass cost-benefit analyses if there is support for the hypotheses. These preliminary results from the pilot and RCT, if positive, could be promising for a potential expansion of the intervention to other contexts and target groups.

Acknowledgments

The pilot study is financed by a grant from the Norwegian Research Council and by contributions from Oslo University Hospital, Catalysts Technologies, Fretex, the Norwegian Labor and Welfare Administration (NAV), Halmstad University, NORCE-Norwegian Research Center, and the Norwegian Centre for e-Health Research. We also acknowledge the mentees and mentors from the prepilot study for contributing their time and sharing their experiences.

Conflicts of Interest

SP is employed by Catalysts Association, the mentoring organization that is the provider of the programs described in the study, and Catalysts Technologies, a spin-off from Catalysts Association. Catalysts Technologies holds the rights to commercialize any digital tools resulting from this research. The other authors report no conflicts of interest.

Multimedia Appendix 1
Platform screenshot: Log-in screen with code access.
[PNG File , 122 KB - resprot_v9i3e16472_app1.png]

Multimedia Appendix 2
Platform screenshot: Overview of program activities including program "launch" and "achievement story".
[PNG File , 270 KB - resprot_v9i3e16472_app2.png]

Multimedia Appendix 3
Platform screenshot: Overview of program activities including "roadmap", "network mapping", and "reflection exercise".
[PNG File , 306 KB - resprot_v9i3e16472_app3.png]

Multimedia Appendix 4
Platform screenshot: Information on "network building".
[PNG File , 411 KB - resprot_v9i3e16472_app4.png]

Multimedia Appendix 5
Peer reviewer report from the Norwegian Research Council.
[PDF File (Adobe PDF File), 100 KB - resprot_v9i3e16472_app5.pdf]

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Abbreviations

ESS: European Social Survey
RCT: randomized controlled trial

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Protocol

Efficacy of a Green Banana–Mixed Diet in the Management of Persistent Diarrhea: Protocol for an Open-Labeled, Randomized Controlled Trial

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Abstract

Background: Diarrhea is the second-leading cause of death in children under 5 years of age. In low- and middle-income countries, 3%-20% of acute diarrheal episodes become persistent diarrhea (PD) (ie, duration ≥14 days), which results in 36%-56% of all diarrheal deaths. In Bangladesh, PD causes >25% of diarrhea-related deaths. Commensal gut microbiota dysbiosis is increasingly recognized in the pathogenesis of PD. Hospital-based management of PD requires a hospital stay, which increases the risk of infection and hospital costs. The higher cost of treatment and high case-fatality rates reiterate PD as an important public health problem. At the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), for the last two decades, a consensus-based guideline has been followed for PD. Observation has revealed that green banana helps in the resolution of diarrhea. However, no larger prospective study has been conducted to evaluate the efficacy of green banana in the management of PD among children older than 6 months of age.

Objective: Our objective is to assess the efficacy of full-strength rice suji (semolina) with and without green banana compared to three-quarter-strength rice suji in the management of PD in children aged 6-36 months at the Dhaka Hospital of the icddr,b.

Methods: This open-labeled, randomized controlled study aims to enroll a total of 145 children with PD who have not been improving on a diet of milk suji. Children will be randomized into three different diet-specific groups: full-strength rice suji containing green banana, full-strength rice suji alone, and three-quarter-strength rice suji. The primary outcome is the percentage of children who recovered from diarrhea by day 5.

Results: Recruitment and data collection began in December 2017 and were completed in November 2019. Results are expected by April 2020.

Conclusions: This study is expected to provide insights into the incorporation of green banana into the dietary management of PD. This would be the first study to investigate the role of microbiota and metabolomics in the pathogenesis of PD.

Trial Registration: ClinicalTrials.gov NCT03366740; https://clinicaltrials.gov/ct2/show/NCT03366740

International Registered Report Identifier (IRRID): DERR1-10.2196/15759

(JMIR Res Protoc 2020;9(3):e15759) doi:10.2196/15759

KEYWORDS

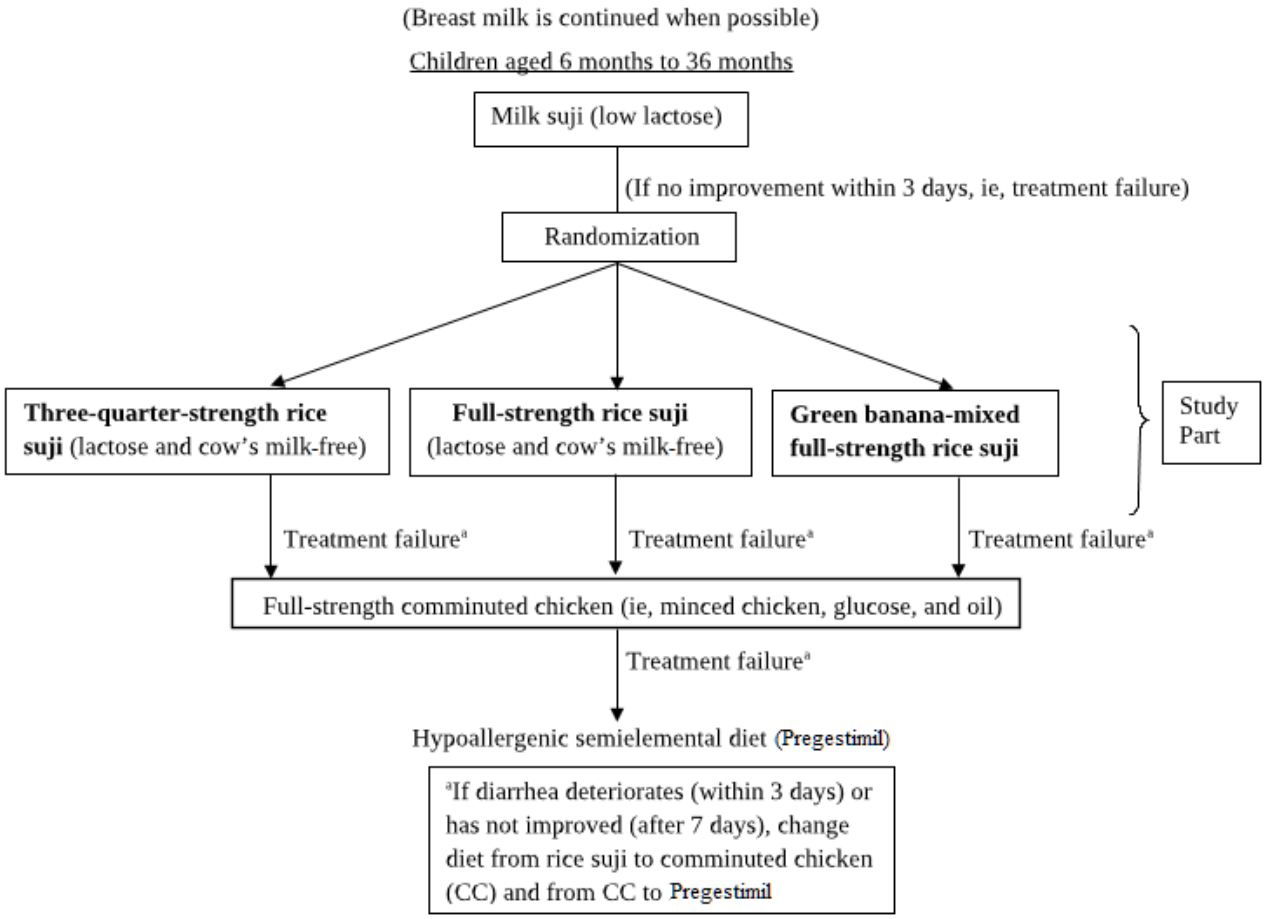
persistent diarrhea; green banana; milk suji; rice suji; microbiota; metabolomics

Introduction

Diarrhea, defined as the passage of loose or watery stool three or more times in a 24-hour period, is the second-leading cause of death in children under 5 years of age [1]. It accounted for 477,293 deaths among 5.4 million people globally and 7062 deaths among 99,608 Bangladeshi children under 5 years of age in 2017 [2]. Use of oral rehydration salt solution and zinc reduced the number of diarrheal deaths to 0.8%, especially from acute diarrhea. However, when diarrhea continues for 14 days or more, not including recurrent or chronic diarrhea as found with celiac disease, cystic fibrosis, or congenital disorders, it is known as persistent diarrhea (PD) [3]. In low- and middle-income countries, 3%-20% of acute diarrheal episodes turn into PD, which is responsible for 36%-56% of diarrhea-associated deaths [3-7]. In Bangladesh, PD accounted for more than 25% of all diarrhea-related deaths among children aged 1-4 years, of which 40% were malnourished [4]. A total of 60% of PD occurs before 6 months of age and 90% below 1 year of age [8]. Along with malnutrition, younger ages, lack of breastfeeding, infection, and inappropriate use of antibiotics are risk factors for PD [9-11]. Due to multifaceted etiology, proper diagnosis and treatment are often warranted for quick recovery from such episodes. In addition, the higher cost of treatment and high case fatality rates reiterate PD as an important public health problem [12]. Every year in Bangladesh, the Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b)—the largest diarrheal hospital in the world—treats a number of children with PD; as well, PD cases peak during the summer [13]. In the management of PD, we follow the algorithm based on earlier studies from the Dhaka Hospital of icddr,b [14,15] and that suggested by the World Health Organization (WHO) [16]. It includes rehydration; control of infection, if present; algorithm-based dietary intervention; micronutrient supplementation; and management of associated complications.

Algorithm-based dietary management increases the duration of hospital stay (see Figure 1). To reduce the osmotic burden to the gut, children are frequently given a diet three-quarters the strength of a regular diet. Though these diets are iso-osmolar, they provide suboptimal energy to the children. Prolonged diarrhea, diminished nutrient absorption [17], and low-calorie intake causes children to be malnourished. Consequently, there is an exaggerated risk of hospital-acquired infections, such as septicemia and pneumonia [18], with unwanted fatal outcomes, which pose a great burden to resource-poor settings. A group of icddr,b scientists have conducted studies to find a remedy for PD that includes green banana [19,20], guar gum [21], and probiotics [22].

Figure 1. Flowchart for the proposed randomized controlled trial.



Several studies demonstrated the beneficial effect of green banana (ie, whole green banana fruit, *Musa paradisiacal sapientum*) in the resolution of PD [19,20]. The antidiarrheal action of green banana is postulated to be mediated by its high

content of amylase-resistant starch, which is not digested in the small intestine of humans [23,24]. On reaching the colon, this starch is fermented by resident bacteria into the short-chain fatty acids butyrate, propionate, and acetate [24]. In the colon, short-chain fatty acids stimulate salt and water absorption [25,26]; they also provide energy and induce a trophic effect on the colonic and the small-bowel mucosa [27].

The human body is home to trillions of microorganisms, primarily bacteria in the gut, which are generally referred to as the microbiota [28]. Commensal gut microbiota dysbiosis is increasingly recognized in the pathogenesis of PD [29]. Therefore, analysis of the commensal gut microbiota and adjusting the intestinal microbiota might be a promising method for the prevention or treatment of PD. In addition, there might be some proteins, factors, or host-pathogen interactions responsible for the continuation of diarrhea, which transform acute watery diarrhea into prolonged diarrhea and finally into PD [29]. Thus, we aimed to acquire knowledge about proteomics and metabolomics related to PD to explore the pathophysiological mechanisms of PD, which could lead to a targeted management strategy.

To address this background and knowledge gap, we have designed this randomized controlled clinical trial to include 6-36-month-old male and female children with PD. Our objective is to compare the efficacy of full-strength rice suji (semolina) containing green banana, full-strength rice suji without banana, and three-quarter-strength rice suji without banana in the resolution of PD in children. In addition, we will be able to evaluate the role of the gut microbiota and proteomics in the pathogenesis of PD.

Methods

Ethics and Research Approval

This study has received approval from the Institutional Review Board (IRB) at the icddr,b (approval No. 17075, version 3.0, dated October 22, 2017). Final data will be publicly disseminated regardless of the study results. A report containing the study results will be submitted for publication in an appropriate journal after completion of data collection and analysis. The study protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidance for protocol reporting [30] (see Tables 1 and 2).

All subjects will need to give written informed consent in accordance with the Declaration of Helsinki. The privacy, anonymity, and confidentiality of data and information identifying study participants will be strictly maintained. All medical information, description of treatment, and results from laboratory tests will be confidential and kept under lock and key; only the research staff will have access to this information. A quality assurance audit and inspection of this study may be conducted by the Ethical Committees of the IRB and will be independent of the study investigators and the sponsor; the quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation relevant to this clinical study. The occurrence of any serious adverse event (eg, death) will be reported to the IRB within 24 hours of the event and their recommendations will be followed.

The study recruited patients and placed them into three different groups. An addendum to the protocol (version 4.0, dated May 5, 2018) has been approved by the IRB and includes a plan to collect stool and blood samples for microbiota and metabolomics analysis, respectively. The funder has not and will not have influence at any stage of the research, from study design to publication.

Traditionally, green banana is used as an antidiarrheal agent in the community. It is also used as a vegetable in Bangladesh, India, and other countries in Africa. Therefore, the IRB from the icddr,b did not direct us to form a data-monitoring committee.

Table 1. Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) schedule of enrollment, interventions, and assessments.

Protocol items	Study period					
	Screening (day -3 to -1)	Enrollment (day 0)	Assessment and allocation (day 0)	Study diets (days 2-7)	First follow-up (days 14±3)	Second follow-up (days 21±3)
Enrollment						
Eligibility screen		x				
Informed consent		x				
Randomization and allocation			x			
Interventions						
Different diets			x	x		
Assessments						
Demographics	x					
Comorbidities	x					
Physical examinations	x			x	x	x
Primary outcome						
Resolution of diarrhea (by day 5)				x		
Secondary outcomes						
Resolution of diarrhea (by day 7)				x		
Consistency of stool				x		
Frequency of stool				x		
Recovery time				x		
Hospital-acquired infection				x		
Relapse at first follow-up					x	
Relapse at second follow-up						x
Enteric pathogen detection by TaqMan assay[a]	x					
Detection of gut microbiota by 16S rRNA sequencing[a]		x		x		
Detection of proteomes and metabolomes from blood[a]		x		x		

[a]According to the addendum (Ethical Committee approval on May 5, 2018), at the end of the study, stored stool samples and blood samples will be processed for the desired testing.

Table 2. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 checklist: recommended items are addressed in this clinical trial's protocol and related documents.

Section or item, item no.	Description	Page no. where addressed
Administrative information		
Title		
1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration		
2a	Trial identifier and registry name; if not yet registered, name of intended registry (ie, ClinicalTrials.gov, ID: NCT03366740)	2
2b	All items from the World Health Organization Trial Registration Data Set	N/A[a]
Protocol version		
3	Date and version identifier	4
Funding		
4	Sources and types of financial, material, and other support	20
Roles and responsibilities		
5a	Names, affiliations, and roles of protocol contributors	1
5b	Name and contact information for the trial sponsor (ie, the icddr,b[b])	N/A
5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	5
5d	Composition, roles, and responsibilities of the coordinating center, steering committee, end-point adjudication committee, data-management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data-monitoring committee) (ie, Institutional Review Board and the icddr,b)	4, 5
Introduction		
Background and rationale		
6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3, 4
6b	Explanation for choice of comparators	3, 4
Objectives		
7	Specific objectives or hypotheses	18
Trial design		
8	Description of trial design, including type of trial (eg, parallel group, crossover, factorial, or single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, and exploratory)	13, 14
Methods: participants, interventions, and outcomes		
Study setting		
9	Description of study settings (eg, community clinic and academic hospital) and list of countries where data will be collected; reference to where list of study sites can be obtained	12
Eligibility criteria		
10	Inclusion and exclusion criteria for participants; if applicable, eligibility criteria for study centers and individuals who will perform the interventions (eg, surgeons and psychotherapists)	13
Interventions		
11a	Interventions for each group with sufficient detail to allow for replication, including how and when they will be administered	13, 14
11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, and improving or worsening disease)	17
11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return and laboratory tests)	N/A
11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	17, 18

Section or item, item no.	Description	Page no. where addressed
Outcomes		
12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, and time to event), method of aggregation (eg, median and proportion), and time point for each outcome; explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	18
Participant timeline		
13	Time schedule of enrollment; interventions, including any run-ins and washouts; assessments; and visits for participants—a schematic diagram is highly recommended (see Table 1)	5, 6
Sample size		
14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	19
Recruitment		
15	Strategies for achieving adequate participant enrollment to reach target sample size	N/A
Methods: assignment of interventions (for controlled trials)		
Allocation: sequence generation		
16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification; to reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions (ie, block randomization)	18
Allocation: concealment mechanism		
16b	Mechanism of implementing the allocation sequence (eg, central telephone and sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	18
Allocation: implementation		
16c	Study members who will generate the allocation sequence, will enroll participants, and will assign participants to interventions (ie, allocation sequence: senior scientist not related to the study; enrollment and assignment: principal investigator and study physician)	18
Allocation: blinding (masking)		
17a	Study members who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, and data analysts), and how (ie, open-labeled trial)	18
17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: data collection, management, and analysis		
Data collection methods		
18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements and training of assessors) and a description of study instruments (eg, questionnaires and laboratory tests), along with their reliability and validity, if known; reference to where data collection forms can be found, if not in the protocol	15, 16
18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management		
19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry and range checks for data values); reference to where details of data-management procedures can be found, if not in the protocol	19
Statistical methods		
20a	Statistical methods for analyzing primary and secondary outcomes; reference to where other details of the statistical analysis plan can be found, if not in the protocol	19
20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
20c	Definition of analysis population relating to protocol nonadherence (eg, as randomized analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: monitoring		

Section or item, item no.	Description	Page no. where addressed
Data monitoring		
21a	Composition of data-monitoring committee, summary of its role and reporting structure, statement of whether it is independent from the sponsor and competing interests, and reference to where further details about its charter can be found, if not in the protocol; alternatively, an explanation of why a data-monitoring committee is not needed	5
21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial—no interim analyses in this trial	N/A
Harms		
22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	5
Auditing		
23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	4
Ethics and dissemination		
Research ethics approval		
24	Plans for seeking research ethics committee (REC) and institutional review board (IRB) approval	4
Protocol amendments		
25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, and analyses) to relevant parties (eg, investigators, RECs, IRBs, trial participants, trial registries, journals, and regulators)	5
Consent or assent		
26a	Study members who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32) (ie, principal investigator and his or her representative)	N/A
26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality		
27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	4
Declaration of interests		
28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Access to data		
29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	4
Ancillary and posttrial care		
30	Provisions, if any, for ancillary and posttrial care and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy		
31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, and other data-sharing arrangements), including any publication restrictions	4
31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices		
Informed consent materials		
32	Model consent form and other related documentation given to participants and authorized surrogates (see Multimedia Appendix 1)	N/A
Biological specimens		

Section or item, item no.	Description	Page no. where addressed
33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable (see Table 1)	5, 6

[a]N/A: not applicable.

[b]icddr,b: International Centre for Diarrhoeal Disease Research, Bangladesh.

Study Location

The study is being conducted at the Dhaka Hospital of the icddr,b, Dhaka, Bangladesh. This hospital provides care and treatment to over 166,624 patients annually of all ages and of both genders. Patients usually come with diarrheal illnesses and/or other associated problems, such as pneumonia, malnutrition, sepsis, and electrolyte abnormalities. In 2018, about 98,308 children under the age of 5 years were admitted. The majority of care seekers were from poor socioeconomic backgrounds and lived in urban and periurban Dhaka. Care is provided by a professional team, including junior and consultant physicians, nurses, counselors, and dietary workers in a multidisciplinary approach. There are different wards to treat patients with respiratory problems, diarrheal diseases, and malnutrition. The laboratory possesses well-equipped facilities capable of performing most of the clinical tests proposed in this study. For critically ill patients, there is an intensive care unit facility present within the hospital, equipped with necessary life support measures, including mechanical ventilators and syringe pumps for vasopressor support.

Study Population

This study includes patients who meet the criteria below.

Inclusion Criteria

1. Children aged 6-36 months, having diarrhea for 14 days or more (up to 29 days), either at admission or developed at some point during their treatment period in the hospital.
2. Children able to take oral feeds at the time of randomization.

Exclusion Criteria

1. Children whose parents or caregivers do not provide consent.
2. Growth of Shigella, Salmonella, or Cholera in rectal swab culture.
3. Children having weight-for-length Z-scores or weight-for-height Z-scores of less than -5 SD or severe or generalized edema.
4. Children presenting with septic shock, convulsion, or any other illness that needs intensive care unit support during admission.
5. Birth defects, such as complex congenital heart diseases, cleft lip and cleft palate, Down syndrome, cerebral palsy, and others, that may themselves cause a digestive problem or failure to thrive.
6. Children diagnosed as having apparent or known tuberculosis, HIV, or chronic (>30 days) or organic diarrhea where the cause is known (eg, Crohn's disease, ulcerative colitis, and celiac disease).

Study Design

This is an open-labeled, randomized controlled clinical trial with three treatment arms (see Figure 1 and Table 3). Children 6-36 months of age admitted to the Dhaka Hospital of the icddr,b with PD or who developed PD during their treatment period and failed to respond with milk suji—a low-lactose formula made from milk powder and rice powder—have been screened and enrolled in this study. The participant enrollment period lasted 18 months.

Randomization

The permuted block randomization technique was followed to select treatment arms for each child. The randomization procedure was planned and set up by a scientist from the icddr,b who was not involved in the data collection. The randomization list containing the subject IDs and the corresponding group allocation remained concealed. IDs were chronologically assigned to each new study participant. After randomization, opaque envelopes containing the names of the allocated diet groups were opened.

Table 3. Proposed dietary composition for this randomized controlled trial.

Ingredients per liter	Three-quarter-strength rice suji	Full-strength rice suji	Full-strength rice suji containing green banana
Green banana, g	N/A[a]	N/A	200
Glucose, g	30	30	25
Rice powder, g	40	60	50
Egg white, g	100	100	80
Soya bean oil, g	25	32	26
Sodium chloride, g	0.1	0.1	0.1
Magnesium chloride, g	0.5	0.5	0.5
Potassium chloride, g	1.0	1.0	1.0
Calcium carbonate, g	2.0	2.0	2.0
Energy, kcal/100 mL	57	70	70
Protein, g/100 mL	1.9	2.1	2.0
Osmolarity, mOsmol/L	296	298	<298
Protein energy ratio, %	13	12	11
Fat energy ratio, %	40	41	35

[a]N/A: not applicable.

Collection of Baseline Information

All children with PD, either at admission or developed at some point during their treatment period, within the defined age group were screened for study eligibility criteria by the study physician. Parents or attending caregivers of those eligible children, depending on the inclusion and the exclusion criteria, were invited to provide their consent for enrollment of their children in the study. Parents and caregivers signed a written informed consent form (see Multimedia Appendix 1) and were provided with information about the study and its interventions, possible benefits and risks, and voluntary nature of participation, including the right to withdraw children at any time after the initial consent without providing any reason; after this, children were enrolled by the study physician. One copy of the signed consent document was given to the caregiver of each participant and another copy was kept for the study documentation. A pretested case record form was used to collect relevant medical history information, including nature and duration of illness and medication for current illness. The form was also used to collect information on sociodemographic characteristics, such as age, sex, religion, gestational age, parental age, parental education, parents' occupations, drinking water source and sanitation, fuel use and smoking history, monthly family income, number of siblings, and number of rooms in the home. Information was also collected about each child's feeding practice, such as their history of breastfeeding, formula feedings, or other complementary feedings, as well as immunization status and each child's past history of pneumonia and diarrhea.

Data on clinical characteristics of participants was also collected. Clinical examination measurements recorded by the study physician included pulse and respiratory rate, axillary temperature, anthropometric measurements (ie, height, weight, mid-upper-arm circumference, weight-for-age Z-score, weight-for-length Z-score, and weight-for-height Z-score), chest auscultation, oxygen saturation, presence or absence of chest-wall indrawing, cyanosis, and mental status (ie, normal, irritable, or lethargic). Weight was measured using an electronic weighing scale with a precision of 0.1 kg; height/length was measured using a locally made length board with a precision of 0.5 cm by a trained and experienced nurse from the Dhaka Hospital of the icddr,b. Fever was defined when the axillary temperature was 38°C or greater. Respiratory rate was counted for a full 60 seconds by exposing the trunk when the child was awake and calm; the presence of lower-chest-wall indrawing was noted at the same time. Frequency and consistency of stool were monitored by either the study physician or a health worker every 8 hours up to the resolution of the diarrhea.

At discharge, caregivers were asked to come back with the children for a minimum of two, weekly follow-up visits.

Laboratory Tests

All laboratory tests were carried out according to the management outline of PD based on the previous studies [31-34], which include the following tests:

1. Stool for routine microscopic examination and culture for Vibrio, Salmonella, Shigella, and Campylobacter jejuni from rectal swab culture.
2. Total and differential blood count.
3. Chest x-ray of anteroposterior view for management of pneumonia.
4. Serum electrolyte and creatinine if there is any clinical evidence of electrolyte imbalance or renal insufficiency.
5. Blood culture for suspected septicemia, typhoid fever, prolonged febrile illness, or hospital-acquired infection.
6. A rapid diagnostic test of stool by enzyme-linked immunosorbent assay (ELISA) for the diagnosis of Cryptosporidium spp and Giardia in selected cases, where the response is delayed or there is strong clinical suspicion.

With the aim to evaluate gut microbiota and proteomics in PD, additional investigations are planned as follows:

1. For gut microbiota analysis, fecal samples (2 g each) were collected from every child over the course of the study as follows: (1) on enrollment day, (2) at any time a diet was changed, and (3) at the time of discharge. Different types of microbiota of diverse groups (eg, Bacteroides, Prevotella, and Ruminococcus) will be tested by 16S rRNA sequencing.
2. For the TaqMan assay to detect other enteropathogens causing PD, a fecal sample (2 g) on screening day was collected.

For proteomic and metabolomic assays, two plasma samples (150 µL each) were collected from 50 children over the course of the study as follows: (1) on enrollment day and (2) at the time of discharge from the study; samples are to be analyzed and tested by a collaborative institute (to be decided).

Clinical Management

Children with PD were admitted to the long-stay unit of the Dhaka Hospital of the icddr,b. Initial routine investigations were completed to identify the etiology of diarrhea by performing stool routine microscopic examinations and rectal swabs; if stool routine examinations were suggestive of invasive diarrhea, an appropriate antibiotic was provided according to hospital protocol. During this period, milk suji, a low-lactose milk and rice flour-based diet containing ~67 kcal and 1.3 g protein per 100 mL, was given as a routine diet. If the PD resolved with milk suji, the child was discharged with health advice. On day 4 (ie, 3 days after milk suji was given), if diarrhea did not resolve, the child was enrolled in the study and randomization was performed. The child received one of the three diets: full-strength rice suji containing green banana, full-strength rice suji alone, or three-quarter-strength rice suji alone. Children on all three diets were followed for 7 days. If there was deterioration of diarrhea (ie, either increased frequency or watery consistency) for 3 days or if the condition remained static for up to 7 days, the child's status was declared as *treatment failure*. Children whose treatment failed received dietary intervention as per the standard management of diarrhea at the Dhaka Hospital of the icddr,b (see Figure 1).

Volume of Diet

In this age group, we usually provide oral feeding equivalent to 60-85 mL/kg/day (12 feeds/24 hours). If breast milk was insufficient or the child was formula fed, the child received 120 mL/kg/day (12 feeds/24 hours). For a severely malnourished child who often did not get sufficient breast milk, the diet volume was 120 mL/kg/day (12 feeds/24 hours). Later, if a child demanded more and diarrhea had not worsened, the amount they were fed was increased to 144 mL/kg/day. The consultant physician made the final decision about the dietary volume, depending on the clinical condition of each patient. The volume offered and actual intake were properly recorded.

Follow-Up After Discharge

Children who were fed full-strength rice suji, with or without green banana, or three-quarter-strength rice suji were discharged and were required to follow up for 2 weeks. At the end of 14 days, they returned to the hospital and if they remained diarrhea free, the diet was switched back to milk suji and caregivers were advised to introduce other family diet items gradually. Children with severe acute malnutrition and severe pneumonia received treatment according to the hospital's standard management protocol [35,36] and WHO guidelines [32], respectively. Last but not the least, it is important to mention that caregivers who were the mothers of the children were encouraged to continue breastfeeding along with providing their children with a specific diet. The food in the study was prepared and provided by health workers under the close supervision of a qualified dietician; the diets were formulated based on locally available, culturally acceptable, affordable foods, quite similar to the WHO's recommendations [3,14,16].

Outcome Measures

Primary Outcome Variable

The primary outcome variable is the percentage of children who recovered from diarrhea by day 5 after being on the study diets.

Secondary Outcome Variables

There were eight secondary outcome variables, as follows: (1) the percentage of children who recovered from diarrhea by day 7, (2) the consistency of stool on different days, (3) the frequency of stool on different days, (4) the outcome after being on the study diets for 1 week (eg, recovery time), (5) the number of hospital-acquired infections, (6) the rate of relapse within 14 days of follow-up, (7) the detection of enteric pathogens via the TaqMan assay and gut microbiota via 16S rRNA sequencing, and (8) the detection of proteomes and metabolomes related to PD.

Sample Size

Rabbani et al [20] conducted a study where they enrolled 5-12-month-old children; they found that their recovery rates from PD by day 4 on the green banana diet and rice suji was 78% and 23%, respectively. However, studies by Islam et al [13] and Mahfuz et al [37] found that a higher percentage of children recovered from PD after being given rice suji. There has been no study conducted where diets of rice suji with or without green banana were given to children 6-36 months of age. Considering these facts, we assumed that in 6-36-month-old children, the rate of recovery from diarrhea by day 5 in either of the intervention diet groups (ie, full-strength rice suji with or without green banana) would be 90% and that the rate of recovery in the control diet group (ie, three-quarter-strength rice suji) would be 65%.

With 80% power and a 5% type I error, and considering three treatment arms, we needed 40 children in each arm. If we enrolled 45 children in each arm, that would accommodate up to an 11% rate of attrition. Therefore, the total target sample size was 135 children (ie, 45 children × 3 arms).

Statistical Analysis

Data has been entered into a personal computer and will be analyzed using SPSS Statistics for Windows, version 20.0 (IBM Corp). Statistical analyses will include descriptive as well as analytical methods. We will compare different characteristics (eg, age, gender, diarrhea and its duration, stool consistency,

presence or absence of blood, fast breathing, lower-chest-wall indrawing, and fever). We will also evaluate the PD outcome as *improved*, *death in hospital*, *relapse*, or *death during follow-up*. Categorical variables will be compared using the chi-square test. When the variables of interest are continuous and parametric, the statistical significance of group mean comparisons will be evaluated by analysis of variance (ANOVA). When the main outcome measures are continuous nonparametric variables, the statistical significance of differences will be determined using the Kruskal-Wallis test. The post hoc test will be done accordingly. A probability of less than .05 will be considered statistically significant. Strength of association will be determined by calculating relative risk and 95% CI. Our primary analysis is an intention-to-treat analysis comparing the groups. Survival analysis will also be carried out. Finally, regression analyses will be performed to reach more definitive conclusions.

Results

Recruitment and data collection began in December 2017 and were completed in November 2019. Results are expected by April 2020.

Discussion

The purpose of this clinical research is to improve the existing standard dietary treatment to manage PD. PD incurs a great amount of morbidity and has accounted for about 36%-56% of diarrhea-related mortality in low- and middle-income countries [3-7]. Current algorithm-based management was developed several years ago; different countries adopted these guidelines with modifications depending on their local and cultural backgrounds. This study will focus on whether a low-calorie, low-osmolarity, or green banana diet works best for the early resolution of diarrhea. The data gathered from this study will hopefully be of great interest to scientists, who may seek to modify the management strategy of PD or to pursue new elements in PD where proteomics- and metabolomics-based studies might provide more answers.

In conclusion, this study is expected to provide useful insights into the efficacy of green banana in the management of PD in children aged 6-36 months. If this diet results in improved outcomes in this setting, then we can assume that it would also be beneficial in other similar health care facilities. We will demonstrate whether this simple yet practical solution for PD works or not.

Acknowledgments

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Authors' Contributions

MS, MIH, TA, SBI, NHA, SAS, and MJC contributed research ideas. MS, MIH, TA, SBI, NHA, SAS, MJC, MMI, SMRI, and MM contributed to the study design. MS, MIH, TA, SBI, NHA, SAS, MJC, MMI, SMRI, and MM contributed to the writing of the protocol. MS, MIH, TA, SBI, NHA, and MJC were responsible for obtaining study approval from the IRB. All authors contributed to and approved the final draft of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Participant consent form.
[DOC File , 45 KB - resprot_v9i3e15759_app1.doc]

Multimedia Appendix 2
Previous peer review reports from icddr,b.
[PDF File (Adobe PDF File), 293 KB - resprot_v9i3e15759_app2.pdf]

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Abbreviations

ANOVA: analysis of variance
ELISA: enzyme-linked immunosorbent assay
icddr,b: International Centre for Diarrhoeal Disease Research, Bangladesh
IRB: Institutional Review Board
PD: persistent diarrhea
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
WHO: World Health Organization

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Original Paper

Impact of Motivational Interviewing on Self-Management in Patients With Type 2 Diabetes: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: The nonpharmacological approach to diabetic control in patients with diabetes focuses on a healthy diet, physical activity, and self-management. Therefore, to help patients change their habits, it is essential to identify the most effective approach. Many efforts have been devoted to explain changes in or adherence to specific health behaviors. Such efforts have resulted in the development of theories that have been applied in prevention campaigns and include brief advice and counseling services. Within this context, motivational interviewing (MI) has proven to be effective in changing health behaviors for specific cases. However, stronger evidence is needed on the effectiveness of MI in treating chronic pathologies such as diabetes.

Objective: This study will obtain preliminary data on the impact of a nurse-led MI intervention in improving glycemic control, as well as clinical, psychosocial, and self-care outcomes for individuals with type 2 diabetes mellitus when compared with usual care, with the aim of improving diabetic control in patients with diabetes.

Methods: An open, two-arm, parallel, randomized controlled, pilot exploratory trial will be performed. Two government outpatient clinics in the New Territories West Cluster in Hong Kong will be involved. In total, 20 to 25 participants will be invited in each arm. Intervention participants will receive face-to-face MI interventions in addition to their usual care from the clinic. Control participants will only receive usual care. Outcomes are assessed at baseline, 6 months, and 12 months. The primary outcome measure is glycated hemoglobin levels. Secondary outcomes include blood pressure, BMI, hip and waist circumference, fasting blood, and psychosocial and self-care measures.

Results: This study is currently underway with funding support from the Hong Kong College of Family Physician Research Seed Fund 2017.

Conclusions: MI skills constitute the main strategies primary care nurses use on their patients. Having economical, simple, effective, and applicable techniques is essential for primary care professionals to help their patients change their lifestyle and improve their health. This study will provide scientific evidence on the effectiveness of MI. It will be performed with strict control over the data collection, ensuring the maintenance of therapeutic integrity.

Trial Registration: Centre for Clinical Research and Biostatistics CUHK_CCRB00614; https://tinyurl.com/v9awzk6

International Registered Report Identifier (IRRID): DERR1-10.2196/15709

(JMIR Res Protoc 2020;9(3):e15709) doi:10.2196/15709

KEYWORDS

motivational interviewing; diabetes; nurse; usual care; self-management; self-care

Introduction

Background

Self-management of diabetes mellitus (DM) requires that patients can reconcile their resources and preferences with the standard therapeutic regimen for diabetes, a task that can be a challenging for many patients [1,2]. It has been widely accepted that diabetes education is not only required in the first few months following diagnosis, but is an important component of ongoing diabetes care because of the demanding self-care requirements, which requires multiple daily decisions to balance diet, physical activity, and medications [3]. There has been a keen interest in examining the impact that different kinds of patient education programs have on diabetes self-management. The findings of several meta-analyses from randomized controlled trials (RCTs) provide extensive evidence for the effectiveness of behavioral and educational intervention on fasting blood glucose and glycated hemoglobin (HbA_{1c}). However, the long-term effects of such interventions are uncertain [4-11]. Knowledge about the effectiveness of behavioral and educational interventions on other diabetes-related outcome measures including blood pressure, lipid profile, body weight, self-management skills, health behavior, and psychosocial aspects are currently inconclusive [3,10-13]. There are few studies that have examined the impact of these psychological interventions among Chinese patients with diabetes. Critical assessment regarding the impact of behavioral and educational programs requires further research that is based on rigorous methods from high quality studies and are adequately powered as well as furnished with long-term follow-ups. The precise magnitude of the effectiveness should be examined, well-defined, and specific to the service recipients when designed [12-14].

Motivational interviewing (MI), described by Rollnick and Miller [15], is a well-defined and scientifically tested method of client counselling that has successfully been used to elicit and sustain a person's behavior changes in a number of health care areas. A recent review of MI showed improvements in health behaviors such as diet and exercise in patients with diabetes [16]. However, studies on the effectiveness of MI have not been able to offer unanimous conclusions on clinical [17-23] and psychosocial attributes [18,21,24-27] in patients with diabetes. Previous reviews emphasize the need for studies of high methodological quality and adequate power to explore the effect of MI on glycemic control and well-being in patients with diabetes [14,16,28].

Given the fast pace of consultation flow in Hong Kong, where consultation time for a general practitioner is around 5 minutes for each patient in government outpatient clinics (GOPC), it is not possible for doctors to carry out MI. Management of diabetes involves a multidisciplinary approach in which allied health professionals such as dietitians, occupational therapists, and physiotherapists are also important team members. Our study will be novel as it is the first RCT using samples of Chinese patients with diabetes. In addition, we invited trained nurses to participate in our intervention.

Knowledge Gap

Evidence-based MI research in various health care aspects is available abroad, but there is a dearth of such research in Hong Kong. It is important to build up local data on MI research.

Objectives

This project aims to obtain preliminary data regarding the impact of MI on diabetes control compared with normal care among patients seen in primary care settings. The outcomes of interest include glycemic control (as measured by HbA_{1c}), blood pressure, BMI, hip and waist circumference, fasting blood, and psychosocial and self-care measures.

The findings could inform the efficacy of MI for diabetes management in patients in family practices and contribute to better disease control.

Methods

Study Design

A pilot multicenter, parallel-group, RCT will be performed. It is an assessor-blinded study, involving two GOPCs in Hong Kong. They will be randomized with one allocated to an intervention group and the other to a control group.

Patients who attend the nurse-led clinic (NLC) in the intervention group will receive up to five individual counselling sessions based on MI in 1 year, in addition to their usual care.

A RCT design was chosen to minimize contamination between the control and intervention participants that could occur if participants in the same health service were randomized to different treatment groups. Furthermore, because the intervention will be targeted at changing the behavior of health professionals, once trained, treatment leakage could occur, as it will be difficult for them to avoid using the intervention techniques with control participants.

Subjects

Inclusion Criteria

Patients are eligible if they were diagnosed as having type 2 DM for at least 1 year and are 18 to 65 years of age with poor DM control (defined as $HbA_{1c} \geq 8$). Patients who have or have not received maximum dosages of oral hypoglycemic agents are equally eligible.

Exclusion Criteria

Patients who are pregnant as well as those with severe debilitating diseases that preclude adherence to recommendations (eg, end stage cancer), cognitive deficits, or medical conditions rendering the individuals incapable of completing informed consent or participating in the study are excluded.

Hypotheses

Our hypotheses are that MI can reduce HbA_{1c} levels, improve clinical and psychosocial outcomes, and increase diabetes self-care when compared with patients' usual care.

Recruitment Procedure

The patients will be informed while participating in the NLC. Advanced practice nurses (APNs) will assist participants in achieving the primary goal of treatment for HbA_{1c} levels less than 7.0%, which is the target defined by the Manual for Risk Assessment and Management Programme (Diabetes Mellitus) in the Primary Care Setting under the Hospital Authority of Hong Kong. This primary goal is applicable for both groups in the study.

After randomization, all outcome measures will be assessed at baseline, 6 months, and 12 months in both groups. Randomization is generated by a research randomizer with a 1:1 allocation ratio in both groups. Each GOPC is considered as a single unit of randomization.

Sample Size Calculation

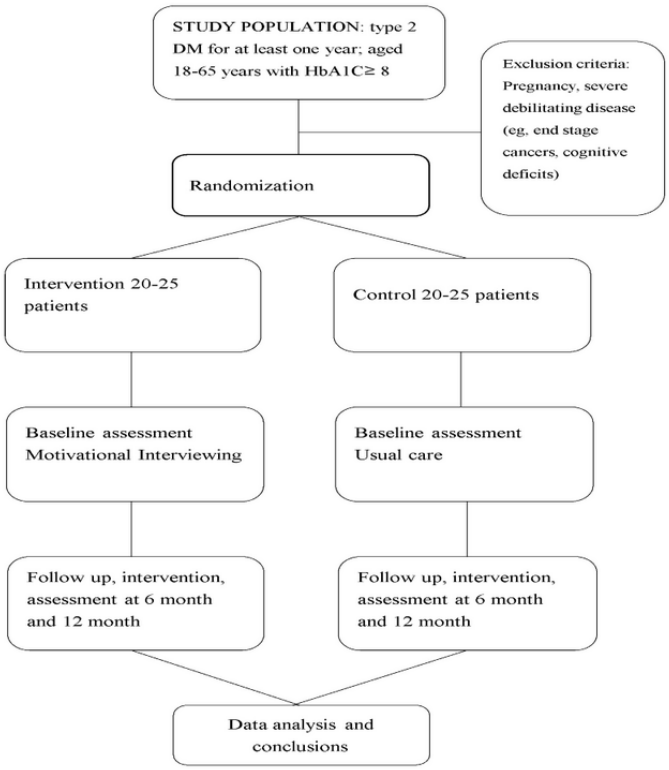
Sample size estimates were calculated using the fixed number of clusters (2) available to the current study. The intracluster correlation coefficient (ICC) accounts for the greater similarity of responses in patients within clusters compared with between clusters, and we could apply an ICC of 0.05 as typical in primary care settings [29]. The effect size for the primary outcome, HbA_{1c}, was anticipated to be 0.32%, based on findings from a published meta-analysis [29]. Using these parameters, a sample size calculator for cluster-randomized trials [29] could estimate a total number of samples that would be required to achieve a power of 80%, while maintaining an alpha of 5% and a participant attrition rate of 20%.

However, since this is a pilot study, we will deploy a convenient sampling of 20 to 25 samples in each arm depending on resources. We anticipate performing a pragmatic cluster RCT in the future when resources are available so that sample size can be calculated with adequate power.

Stratification and Randomization

Participants will be sampled by computerized random allocation software to achieve balance. The sampling procedure produces an ordered list of eligible participants. Then, recruiting officers systematically invite eligible participants into the study. Once a participant declines participation, the recruiting officer will move to the next person on the list. APNs will provide all participants an explanatory statement and consent form in person at their GOPC visit. Participant flow is shown in Figure 1.

Figure 1. Trial participant flow. DM: diabetes mellitus; HbA_{1c}: glycated hemoglobin.



Usual Care

Medical treatment is not a part of the intervention. All participants, irrespective of participation in the intervention group or the control group, will undergo the same routine check-up at the GOPC in charge of their diabetes care. Biochemical tests and examinations will be performed during these visits in accordance with protocols.

Individual counselling and recommendations will be given based on the results of the examinations, biochemical tests, and self-monitoring of blood glucose. Renewal of prescribed medication will also be done at these check-up visits. Patients could be referred to individual counselling for diet modification, optimization of physical activity, smoking cessation if applicable, and minimization of alcohol use if required by their usual health care provider.

Research Intervention

The theoretical approach of the intervention is based on the self-efficacy theory and MI spirit. Perceived self-efficacy is defined as people's beliefs about their capabilities of producing designated levels of performance on exercising influence over events that affect their lives [30]. MI is used as a method to facilitate this process and is a directive counselling style for eliciting behavior change by helping patients to explore and resolve ambivalence [31,32]. In addition to their usual care, patients in the intervention group will receive a 1-year MI program consisting of up to five individual counselling sessions lasting approximately 30 to 45 minutes. Each participant in the intervention group is assigned an APN who has received training in MI. The style of the interview is standardized with the following components: seeking to understand the person's frame of reference; expressing acceptance and affirmation; eliciting and selectively reinforcing the client's own self-motivational statements of problem recognition, concern, desire and intention to change, and ability to change; exploring the client's degree of readiness to change; and affirming the client's freedom of choice and self-direction. Exploring readiness to change is used as a component of the therapeutic process and not an outcome. Each session follows a semistructured MI format, specifically developed for this intervention program. Participants may bring up any concerning issues related to diabetes self-care during the intervention sessions. The participants in the intervention group may be referred by the health care professional to individual counselling for lifestyle modification, which may include dietary changes, promotion of physical activity, and counseling on quitting smoking and minimizing alcohol consumption.

Education of the Health Care Professionals Prior to the Intervention

A number of APNs will be educated to carry out MI, depending on funding and resources. They will be coached by trainers from the Motivational Interviewing Network of Trainers.

The theoretical and practical part of the education includes training in the key elements of MI, which is generally facilitated through eliciting change talk and exploring ambivalence about behavioral change while trying to examine discrepancies between the individual's current behavior and core values or personal goals. The health care professionals will be introduced to MI methods including reflective listening and acknowledgement, so they will be able to clarify the patient's goals and concerns, as well as elicit reasons for change using the patient's own words. The role of the health care professionals is to coach and support the patients in discovering and developing their own resources for change and management at the patient's request.

After the course, the health care professionals will be individually supervised by the MI trainer in 10 real patient situations. The supervision will include audiotaping and evaluation inspired by the Motivational Interviewing Treatment Integrity (MITI) coding system version 4.2.1 [33]. The MITI coding system is divided into a global rating and behavioral counts. The global rating is a 5-point Likert scale, where 1 indicates low competence in MI and 5 indicates high competence in MI. The behavior counts reveal MI behavior in proportion to all behavior, where a high percentage indicates a high competence in MI.

Measurements and Outcomes

The primary outcome measure is HbA_{1c}. Secondary clinical outcomes include systolic and diastolic blood pressure, weight, BMI, waist and hip circumference, and fasting blood samples (fasting plasma glucose, total cholesterol, triglyceride, high-density lipoprotein, and low-density lipoprotein). Additionally, secondary psychosocial and self-care behavior outcomes include: psychological distress (Kessler 10 [K10]; score range 10-50) [34], quality of life (QOL) (WHOQOL-BREF; domain score range 0-100) [35], diabetes self-care activities (Summary of Diabetes Self-Care Activities [SDSCA]; score range 0-7, representing number of days per week) [36], and diabetes management self-efficacy (Chinese Diabetes Management Self-Efficacy Scale [C-DMSES]; score range 0-200) [37]. These surveys have been shown to demonstrate satisfactory psychometric properties.

K10 is a 10-item questionnaire intended to yield a global measure of distress based on questions about anxiety and depressive symptoms that a person has experienced in the most recent 4-week period.

The WHOQOL-BREF instrument comprises 26 items that measure the following broad domains: physical health, psychological health, social relationships, and environment. The WHOQOL-BREF is a shorter version of the original instrument that may be more convenient for use in large research studies or clinical trials. Both the self-administered and the interview version of the Hong Kong Chinese WHOQOL-BREF will be available [38].

The SDSCA measures frequency of self-care activity in the last 7 days for five aspects of the diabetes regimen: general diet (adherence to healthy diet), specific diet (ie, ate fruits and low-fat foods), foot care, blood-glucose testing, exercise, and taking recommended diabetes medication. Participants rate themselves from 0 to 7 on each item. The mean scores of the 11 items are then used to assess a participants' self-care behavior.

C-DMSES assesses the extent that participants are confident they can self-monitor nutrition, blood sugar, foot exams, physical exercise, weight, and medical treatment. Participants rate themselves on an 11-point scale ranging from "0=can't do at all" to "10=certain can do". The mean scores of the 20 items are used to assess participants' self-efficacy.

All patient level outcomes will be assessed at baseline, and again at 6 months and 12 months, during a clinical health check and an interviewer-administered questionnaire. All participants will be instructed to fast overnight for a minimum of 12 hours, and participant fasting times will be recorded prior to each blood test. When fasting times are insufficient, participants will be asked to reschedule their appointment. Intervention and control groups will both undergo the same assessments, and all participants will be informed of their clinical results. Participants who are absent for outcome assessments will be contacted whenever possible by a phone call and asked to reschedule.

Owing to the pragmatic nature of this trial, data collectors will not be blinded to group allocation; however, laboratory technicians will be blinded. Blood samples will be analyzed centrally at the Chemical Pathology Laboratories at Tuen Mun Hospital in Hong Kong.

Fidelity

To externally verify that MI and usual care differ as expected, 2 out of 20 participants (10%) in both the MI and usual care sessions will be randomly selected for coding on adherence to MI principles using the MITI coding system by an expert independent coding group. Coders are blind to the study arm of the session and the study hypotheses. We anticipate that MI sessions will receive scores of 4 or higher on the 1 to 5 global rating and be significantly higher than usual care sessions on ratings of evocation, collaboration, empathy, and autonomous support. With respect to frequency measures for counselor behavior we expect MI sessions to have a higher reflection-to-question ratio and significantly fewer instances of giving information.

Statistical Analysis

Descriptive statistics will be used to summarize the characteristics of the GOPCs and participants with regard to baseline characteristics and patterns of mean change over time. The primary analysis will examine the changes in HbA_{1c} at the 6- and 12-month follow-ups in comparison to the baseline. Secondary analyses will include all clinical, psychosocial, and self-care measures that are continuous outcomes. For data analyses, SPSS (IBM Corp, Armonk, NY) will be used. As this is a pilot study, nonparametric statistical tests will be used. The baseline values will be reported as means (SD). A *P*-value<.05 will be regarded as statistically significant.

Ethical Considerations

This study is in compliance with the Helsinki Declaration and local legislation. Ethical approval was sought and granted by the New Territories West Cluster Clinical & Research Ethics Committee on July 3, 2018, with Ref. No.: NTWC/CREC/18038 at Tuen Mun Hospital in Hong Kong. All participants signed an informed consent from the nurses before participating in the study. This study is noncommercial.

To protect the interest of vulnerable subjects, confidentiality will be ensured according to the guidelines from the Hospital Authority in Hong Kong. For example, the data, including personal information, will be stored in encrypted files during and after the study. The investigators will be responsible for the safekeeping of the personal data, and only they will have access to the personal data during and after the study. The data will be kept in a locked cabinet for 5 years after the study. After completion of this storage period, the data files will be destroyed.

Results

This study is currently underway with funding support from the Hong Kong College of Family Physician Research Seed Fund 2017. Participants could start the study at different times. All testing was completed in mid-November 2019. The results of the study will then be communicated via publications.

Discussion

Impact

Demonstrating which of the two methods tested here is more effective can have a major impact on clinical practices when designing and proposing clinical protocols for the management of diabetes. Clinical interviewing skills and health education are the essential strategies used by nurses with their patients. Obtaining scientific evidence on the effectiveness of MI in primary care through strict monitoring of the training methods and controlling the integrity of the therapies applied will allow us to have economical, brief, effective, and applicable techniques to help patients change their health habits and achieve better health outcomes.

Limitations

This study design has several limitations. First, as the resources for this study are limited, we will not be able to collect a large sample size. Consequently, it might be more difficult to identify statistically significant intervention effects. This issue highlights the importance of preventing dropouts from the intervention. Dropouts will be prevented by sending telephone reminders to participants for follow-ups. In addition, to test our hypotheses, participants will need to fill out many questionnaires, which may cause higher levels of attrition.

Conclusions

This study is one of the first attempts to assess the extent that the MI approach helps in overall diabetic care. The results obtained will help us understand the practical effectiveness of this approach, including its limitations and actual impact on Chinese patients with diabetes. If this method proves to be effective, our intention is to disseminate and promote that intervention used in APN sessions to promote better self-management.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1722 KB - resprot_v9i3e15709_app1.pdf]

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Abbreviations

APN: advanced practice nurse
C-DMSES: Chinese Diabetes Management Self-Efficacy Scale
DM: diabetes mellitus
GOPC: government outpatient clinic
HbA_{1c}: glycated hemoglobin
ICC: intracluster correlation coefficient
K10: Kessler 10
MI: motivational interviewing
MITI: Motivational Interviewing Treatment Integrity
NLC: nurse-led clinic
QOL: quality of life
RCT: randomized controlled trial
SDSCA: Summary of Diabetes Self-Care Activities.

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Protocol

Influence of Cognitive Functioning on Powered Mobility Device Use: Protocol for a Systematic Review

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Abstract

Background: Power mobility devices (PMD) are critical to achieving independent mobility and social participation for many individuals who have trouble walking. Provision of PMDs is complex, with cognitive functioning expressed by clinicians as a major concern. Even if PMD use can be predicted by the level of cognitive functioning, outcome tools used to assess readiness do not consider how cognitive functioning may affect PMD use.

Objective: The specific aims of this review are to identify existing assessments used to assess cognitive functioning and PMD use, classify cognitive functions that are identified within existing assessments related to PMD use, and explore the relationships between cognitive functioning (ie, executive functions and attention) and PMD use.

Methods: A systematic review will be conducted using the electronic databases MEDLINE (Ovid), CINAHL, Embase, PsycINFO (Ovid), and Web of Science based on the concepts of PMD performance and capacity, and cognitive functioning. To be included, studies must have: a sample of PMD users (inclusive of age and diagnoses), an assessment of cognitive functioning, and an assessment of PMD capacity or performance. The International Classification of Functioning, Disability and Health will be used to classify cognitive functions. Study quality will be assessed using the Mixed Methods Appraisal Tool. Qualitative and quantitative studies will be analyzed in a complementary manner depending on their designs; a result-based convergent synthesis design will be applied.

Results: This proposed systematic review protocol has been registered in PROSPERO (CRD42019118957). It was funded by the Quebec Rehabilitation Research Network and approved on February 2019.

Conclusions: Results will inform the development of a PMD driving program that aims to enhance cognition. The results of this study will enhance understanding of the influence of cognitive functioning on PMD use and will support the clinical practice in choosing appropriate evaluative tools.

Trial Registration: PROSPERO CRD42019118957; https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=118957

International Registered Report Identifier (IRRID): DERR1-10.2196/16534

(JMIR Res Protoc 2020;9(3):e16534) doi:10.2196/16534

KEYWORDS

cognitive functioning; power mobility devices; clinicians; nurses

Introduction

Individuals with mobility impairments can benefit from power mobility devices (PMD), such as powered wheelchairs; scooters [1]; and, specifically for children, adapted ride-on toys [2]. A national survey in Canada stated that, in 2016, approximately 160,000 individuals 15 years of age and older used a PMD (42,400 users of powered wheelchairs and 108,550 users of scooters) [3]. The prevalence of PMD use is expected to increase for both older adults, as the population continues to age [3], and children, as recommendations on early PMD provision are increasing [4].

According to the "Convention on the Rights of Persons with Disabilities" PMD use is critical for independent mobility [5]. In the International Classification of Functioning, Disability and Health (ICF) framework, mobility is described within the activities and participation chapter (d4). Mobility requiring use of a PMD is defined in "Moving around using equipment" (d465) as "moving the whole body from place to place, on any surface or space, by using specific devices designed to facilitate moving or create other ways of moving around, such as moving down the street in a wheelchair or a walker" [6]. The impact of PMD use is considerable, including the possibility to move throughout the user's environment [7,8]. Optimal PMD use can also enhance mobility confidence and participation in various occupations [9-11]. Thus, using a PMD facilitates autonomy, independent living, and social participation in all aspects of life for children, adults, and older adults [5,12-14].

For example, the association between PMD use and participation has been demonstrated for older adults. Sund et al [11] conducted a prospective study and investigated the influence of PMDs over a period of 1 year. Among community-dwelling older adults, PMD use was associated with an increased frequency of grocery shopping and going for a walk, as well as other aspects of everyday life such as going to a restaurant, sending letters at the post office, going to the bank, and visiting family and friends became easier after PMD acquisition [11]. Additionally, Rossen et al [15] conducted a qualitative study exploring how PMD users experience their everyday life and how PMDs influence their daily occupations. The study reported that community-dwelling older adults reported a satisfaction with well-being, self-esteem, dignity, and social life that was associated with using a PMD [15].

However, to benefit from PMD use, a person must first obtain the device, which often requires a prescription from a health care professional and adaptations to their environment, and then demonstrate that they have the capacity to use it safely. For the purpose of this systematic review, PMD use encompasses capacity (ie, what a person can do in a standard environment) and performance (ie, what a person actually does in their actual environment) as defined by the ICF [16]. Accordingly, driving a PMD involves complex interactions between the person (social and cognitive factors), the environment, and the device itself. Therefore, PMD provision requires careful consideration of the diagnoses and prognoses; motor, cognitive, and perceptual capacities; and the built and social environments [17]. However, in practice, occupational therapists often report feelings of uncertainty when considering safety, autonomy, and risk through PMD acquisition [18].

Cognitive functioning is the major concern expressed by clinicians who prescribe PMDs [18,19], as learning new skills (ie, capacity) and applying the skills in the real world (ie, performance) requires adequate cognitive abilities. There is evidence to suggest that successful PMD use can be predicted by the level of cognitive functioning [20]. For example, Cullen et al [20] demonstrated that cognitive functions such as memory and visual perception upon PMD provision predicted frequency of PMD use 1 month later. However, one evaluation of cognition was based on an index score that combines multiple tools. Through evaluation of a PMD training program among individuals living in long-term care, Mendoza et al [21] also reported an increased number of accidents among PMD users who had executive dysfunction. Despite the perceived importance of cognition, global or specific cognitive functions required for PMD use remain unclear.

Clear clinical guidelines related to cognition and PMDs are limited by a dearth of literature that has not yet been adequately synthesized. Furthermore, existing PMD use assessment tools focus predominantly on motor skills and performance-based outcomes, and seldom consider how cognitive functions and application of knowledge (ie, executive functioning, problem solving) could influence PMD driving. For example, the Power Mobility Indoor Driving Assessment [22] and the Power Mobility Community Driving Assessment considers whether more training is required; the Wheelchair Skills Test assesses specific driving skills [23]; the Power Mobility Road Test evaluates driving capacities in structured and unstructured environments [24]; and the Wheelchair Use Confidence scale measures self-efficacy for using a PMD [25]. In addition, the Functional Evaluation Rating Scale evaluates driving performance in simulated programs [26]. However, existing assessment tools do not consider how cognitive functioning may affect PMD use [27]. Consequently, subjective clinical judgment often plays a central role in determining if an individual has the necessary cognitive functions for using a PMD [18].

Given that cognitive functioning is fundamental to using a PMD and that decision making around PMD provision often relies on clinical judgement, it is critical to gain a better understanding of the relationships between cognitive functioning and PMD use, which is important for the development of assessment tools and training programs. To our knowledge, there has not been a systematic review describing the relationship between PMD use and cognitive functioning.

The specific aims of this review are to identify existing assessments used to evaluate cognitive functioning and PMD use; classify, according to the ICF, cognitive functions that are identified within existing assessments related to PMD use; and explore the relationships between cognitive functioning (ie, executive function, attention) and PMD use.

Methods

Prospero Registration and PRISMA-P Statement

The present protocol has been registered within the PROSPERO database (CRD42019118957). Given that there are no guidelines for mixed-method reviews [28], this review will follow the relevant domains of the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) statement for quantitative aspects [29] (Multimedia Appendix 1), and the relevant domains of the Enhancing Transparency in Reporting the Synthesis of Qualitative Research (ENTREQ) statement for qualitative aspects [30].

Literature Search

A librarian contributed to the development of the search strategy. Appropriate keywords were selected according to Medical Subject Headings (MeSH) terms, terms used in existing studies on cognition and PMD use, and the "Mental functions" and "Learning and applying knowledge" chapters of the ICF. The search was conducted in online databases including MEDLINE (Ovid), CINAHL, Embase, PsycINFO (Ovid), Scopus, and Web of Science. The search strategy included the concepts: "PMD", "cognitive functioning", and related synonyms. In each database, the subject headings related to the two concepts were used. The keywords and writing rules (eg, truncation, quotation marks, operators) were adapted for each database. An example of the search strategy is provided in Multimedia Appendix 2. The results were searched independently by two authors (AP and MDL) to identify relevant studies. All searches were documented including terms used and the number of hits or studies obtained.

Eligibility Criteria

The PICOS (Population, Intervention, Comparison, Outcomes, and Study Designs) structured approach [29] was used to frame inclusion and exclusion criteria. Included studies must: be scientific peer-reviewed manuscripts, dissertations, or theses (including all quantitative and qualitative methods and study designs); present original data; be written in English or French; include a sample of PMD users (inclusive of age and diagnoses); assess cognitive functioning; and assess PMD capacity or performance. No restriction will be applied regarding year of publication. Studies not involving human subjects will be excluded.

Data Management

The data will be imported from the databases in Endnote reference management software (version X9). Then references will be exported to Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia), where duplicates will be removed automatically based on the title of the references. Remaining duplicates will be deleted during the abstract and title screening.

Screening and Selection Process

Titles and abstracts will be screened for eligibility by two independent reviewers (AP and LK). The full text of all relevant studies will be retrieved and independently assessed for inclusion by two reviewers (AP and LK). Any disagreement in study eligibility will be resolved through discussion with a third reviewer (KB). References of all considered studies will be hand searched to identify any relevant reports missed in the search strategy.

Data Extraction

Data will be extracted independently by two reviewers (AP and LK) into study-specific extraction tables. The same data extraction approach will be applied across all studies following a standard data extraction template, but with flexibility according to various methodologies and designs [28]. Study designs will be extracted according to Portney and Watkins' definitions [31]. All tables will include the following general categories: author; year of publication; country; study design; purpose of study; type of power mobility device (wheelchair or scooter); participant demographics (sample size, sex, age, marital status, diagnosis); primary outcome: cognitive functions (classified using the ICF and including outcome tools when applicable) (Multimedia Appendix 3); and secondary outcome: PMD use (including outcome tools when applicable). Specific tables for randomized control design, pre-post design, and intervention design will include categories such as intervention, control group, and outcome measure. Only select qualitative data will be extracted according to the specific aims of the protocol (ie, cognition and power wheelchair mobility outcomes) [32]. For example, phrase and keywords (codes) related to cognition and PMD capacity and performance will be reviewed and extracted [33]. The authors will read each article repeatedly to ensure that all concepts and relationships are explored [34]. Discrepancies will be identified and resolved through discussion, using a mediator (KB) when necessary. Missing data will be requested from study authors.

Data Analysis

Embracing no restriction related to the study purpose and design assumes complementarity between methodologies, as such a transparent and systematic process will be used [28,35]. The studies will be analyzed in the same time and in a complementary manner depending on their design. Then the results of both syntheses will be integrated during a final synthesis. A result-based convergent synthesis design will be applied [36]. This design implies that qualitative and quantitative studies are analyzed separately using different synthesis methods, and that the results of the qualitative synthesis informed the quantitative synthesis [37]. First, qualitative and quantitative data will be analyzed separately. Codes extracted from all qualitative studies will be organized accounting for similarities and differences in the study findings and will lead to new interpretations of the phenomena studied [30]. For quantitative data, if studies are sufficiently homogenous, quantitative synthesis will be used (aggregate level data) and correlations between cognitive functioning and PMD measures will be calculated with SPSS Statistics (SPSS Inc, Chicago, Illinois). Second, a narrative synthesis will be integrated to merge the results of both qualitative and quantitative syntheses, which will then be combined using a third synthesis in a convergent manner [36]. Throughout analyses multiple researchers will be involved in peer debriefings. Consensus will be reached among three researches (AP, LK, and KB) to assure

reliability and trustworthiness. The interpretation of the results will occur in the discussion section.

Critical Appraisal

The studies will be organized by study design in descending order from the highest level of evidence to the lowest level according to an evidence-based practice toolkit [38]. The methodological quality of each included study will be appraised using the Mixed Methods Appraisal Tool (MMAT), evaluating qualitative and quantitative designs [39]. It is noteworthy that this tool is currently being updated; if the new version is available during this study, the most recent version will be used. Methodological limitations identified in primary studies will be taken into account to discuss the results and conclusions regarding the relationship between cognitive functions and PMD use. This systematic review does not have restrictions related to the study designs; therefore, the methodological quality of each article will be essential to the interpretation of the results. The two appraisals will be completed independently by two authors (AP and LK). Discrepancies will be identified and resolved through discussion with a third author (KB) when necessary.

Ethical Considerations

There are no ethical issues of concern in this secondary analysis of published evidence.

Results

The review has been designed according to the Cochrane method [40], such that each step will be performed in duplicates (screening and selection, data extraction and data analysis). Transparency will be enhanced by regular team meetings and presentations on emerging findings at internal seminars, as well as by sharing the findings with an advisory group. All steps and decisions such as discussions about keywords or the exclusion of a study will be recorded in a logbook. None of the authors have conflicts of interest that would affect their interpretation of evidence.

Discussion

This paper describes the protocol for a systematic review aiming to identify the cognitive functions that are currently assessed before PMD provision and to explore the relationships between cognitive functions and PMD use. Results of this study will improve knowledge about the assessment of cognitive functioning and the relationship between cognitive functions and PMD use. It is apparent that cognitive functioning is required for PMD use. For example, Bottos et al [41] assessed the effects of early provision of a powered wheelchair, and found that children classified as “normal” or “mild learning disability” according to their IQ achieved independent use of PMD easily and rapidly. However, there is a need to better understand the influence of specific cognitive functions on PMD use, and to determine cognitive functions that predict successful PMD use. There is little evidence describing an explicit relationship between cognitive functioning and PMD use. Moreover, the most commonly used assessments of readiness for PMD use [27] focus on PMD capacity or performance outcomes (ie, assess *activity and participation* of a wheelchair user) [19], and may overlook modifiable cognitive functions.

Existing assessments of PMD use and assessments of cognitive functioning identified in this systematic review will be classified according to the ICF. Therefore, the results of this systematic review may guide therapists in the selection of outcome tools for PMD screening and assessment. Moreover, identification of important cognitive functions may provide valuable insight into the development of new PMD driving interventions, and specific cognitive functions (eg, problem solving and executive functioning) may be directly targeted using safe and specialized approaches such as wheelchair simulator environments and virtual reality.

Realization of the proposed systematic review is the first iterative step within a larger program of research that will lead to the development of a PMD training program that targets cognitive functioning. The Medical Research Council methodological framework will guide the development and the evaluation of a novel PMD training program that considers important cognitive functions [42]. This framework follows four phases for the development of complex interventions including: the theoretical and developmental phase (phase I), the feasibility phase (phase II), the evaluation phase (phase III), and the long-term implementation phase (phase IV) [43]. The theoretical phase suggests conducting a systematic review to synthesize existing knowledge. Findings from this review will be used to design the prototype for a new PMD training program that targets cognitive functioning, which will then be refined and evaluated with key stakeholders and experts (eg, PMD users, caregivers, clinicians) through focus groups and Delphi surveys.

The results from this systematic review will enhance the understanding of the influence of cognitive functions on PMD use, which is critical for the development of assessment tools and training programs. Results of this systematic review may inform the development of clinical practice guidelines and training programs that consider cognition and the development of smart wheelchairs. There may be practical applications for PMD users, caregivers, and clinicians.

One limitation of this review is that the strategy will not include literature. Moreover, the broad population being targeted (ie, individuals with cognitive and physical impairments) may pose some challenges. However, we chose to include participants of all ages and diagnoses to not restrict or exclude relevant studies. If data are available, subgroup analyses and descriptions will be considered to describe specific relationships between cognitive functioning and PMD use in different populations (ie, age, sex, diagnoses). The anticipated high variability between existing assessments such as qualitative descriptions versus quantitative outcome tools may also limit the ability to make comparisons between studies and to synthesize findings. Finally, inclusion of qualitative and quantitative studies will potentially limit our ability to make any conclusions regarding strength and magnitude of relationship between cognitive functions and PMD use.

This systematic review will aim to explore the relationships between cognitive functioning and PMD use. The results of this

study will improve knowledge about the influence of cognitive functions on PMD use. This protocol provides a detailed description of the methods that will be used to conduct the systematic review thus ensuring transparency and a priori directions for future research.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Prisma P Checklist 2015.
[DOCX File , 34 KB - resprot_v9i3e16534_app1.docx]

Multimedia Appendix 2
Example of search strategy in MEDLINE/Ovid database.
[DOCX File , 30 KB - resprot_v9i3e16534_app2.docx]

Multimedia Appendix 3
Classification of cognitive functions (mental functions) according to different levels of the International classification of functioning.
[DOCX File , 19 KB - resprot_v9i3e16534_app3.docx]

Multimedia Appendix 4
Previous peer-review report from PROSPERO.
[PDF File (Adobe PDF File), 55 KB - resprot_v9i3e16534_app4.pdf]

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Abbreviations

ENTREQ: Enhancing Transparency in Reporting the Synthesis of Qualitative Research
ICF: International Classification of Functioning, Disability and Health
MeSH: Medical Subject Headings
PICOS: Population, Intervention, Comparison, Outcomes, and Study Designs
PMD: power mobility device
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols.

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Protocol

Effectiveness of Conversational Agents (Virtual Assistants) in Health Care: Protocol for a Systematic Review

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Abstract

Background: Conversational agents (also known as chatbots) have evolved in recent decades to become multimodal, multifunctional platforms with potential to automate a diverse range of health-related activities supporting the general public, patients, and physicians. Multiple studies have reported the development of these agents, and recent systematic reviews have described the scope of use of conversational agents in health care. However, there is scarce research on the effectiveness of these systems; thus, their viability and applicability are unclear.

Objective: The objective of this systematic review is to assess the effectiveness of conversational agents in health care and to identify limitations, adverse events, and areas for future investigation of these agents.

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols will be used to structure this protocol. The focus of the systematic review is guided by a population, intervention, comparator, and outcome framework. A systematic search of the PubMed (Medline), EMBASE, CINAHL, and Web of Science databases will be conducted. Two authors will independently screen the titles and abstracts of the identified references and select studies according to the eligibility criteria. Any discrepancies will then be discussed and resolved. Two reviewers will independently extract and validate data from the included studies into a standardized form and conduct quality appraisal.

Results: As of January 2020, we have begun a preliminary literature search and piloting of the study selection process.

Conclusions: This systematic review aims to clarify the effectiveness, limitations, and future applications of conversational agents in health care. Our findings may be useful to inform the future development of conversational agents and promote the personalization of patient care.

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KEYWORDS

conversational agent; chatbot; voice recognition software; speech recognition software; artificial intelligence; virtual health care; avatar; virtual assistant; virtual nursing; virtual coach; intelligent assistant; digital health

Introduction

Digital technologies are driving transformation in the health sector and show promise in contributing to the resolution of major challenges facing health care systems worldwide, including the provision of personalized medicine, prevention of chronic conditions, care of an increasingly elderly population, and provision of health care to hard-to-reach populations. Intelligent digital platforms with a conversational user interface (ie, conversational agents) constitute a representative technology that has been investigated in these contexts [1-4]. Conversational agents mimic human interaction using natural language processing to analyze user inputs and respond appropriately using human language via auditory or textual methods [5].

The first technology of this kind emerged in 1966, constituting a text-based platform that mimicked a psychotherapist, "ELIZA", using prerecorded answers selected based upon user input [6]. Over the past two decades, developments in natural language processing and deep learning have contributed to the development of more sophisticated artificial intelligence technologies, many of which employ conversational functions. Current agents are available via multiple digital platforms, including telephones, mobile phones, tablets, and computers, and in many virtual formats such as chatbots, embodied conversational agents, and three-dimensional avatars [2,7,8]. The input channels have similarly expanded in recent years; notably, conversational agents have evolved to integrate movement analysis and gesture or eye movement recognition, which may enhance the user-agent interaction by integrating multimodal signals as is the case in human-human interactions [9]. Within the health care field, conversational agents have been designed to automate specialized tasks to support health care professionals, patients, or at-risk populations [2,10-12]. The investigated uses for these systems include triage, diagnostics, counseling, health promotion, and training of health care professionals [1,4,11-16]. The widespread availability of the digital platforms through which these conversational agents operate enables populations with limited health provision or health literacy to access these services [14,17]. Finally, these agents are helping to provide patient-centered care by increasing the patients' involvement in their health care and decision making [2,17,18]. Personalization features have also been integrated into conversational agents to improve user satisfaction, user engagement, and dialogue quality [19].

Despite a wealth of literature on conversational agents and their application to health care, the majority of reviews on the topic focus on a specific therapy area or function, whereas few reviews have comprehensively examined the overall scope and progress in the field [20-23]. Laranjo et al [24] conducted a systematic review of conversational agents in 2018, in which they investigated the characteristics, applications, and evaluation measures of conversational agents; however, this was limited to agents with unconstrained natural language input and systems that had been tested with human participants. Similarly, in 2019, Montenegro et al [25] surveyed the literature related to conversational agents applied to health care with a focus on their patterns, goals, and interactions. Although they described a general taxonomy detailing the functions and architecture, the implications for the users were not addressed.

There is a clear need to understand the effectiveness of current conversational agents to achieve their intended outcome and facilitate the user experience with these agents. This information can then be used to determine the direction that these technologies are most likely to follow in health care and identify the functions or populations that will derive the most benefit from these resources. Furthermore, these conversational agents have potential to alleviate current health care resource burdens by automating functions that previously required face-to-face interaction; thus, it is important to identify whether this is an observed outcome of the use of these technologies.

Thus, the aim of this systematic review is to evaluate the effectiveness and implications of conversational agents in health care. This review will focus on three main questions. First, are the intended health-related outcomes of current conversational agents being fulfilled, and does the effectiveness vary depending on the population or function of the agent? Second, what are the capabilities of health-focused conversational agents, and how might the availability of these agents impact the use of health care resources? Finally, what are the current limitations and gaps in the utility of conversational agents in the health care field that could inform future research?

Methods

Study Design

We will use the Population, Intervention, Comparator, Outcomes (PICO) template and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines [26] to identify appropriate Medical Subject Headings (MeSH) for the literature search and to structure the review. This systematic review will be composed of a literature search, article selection, data extraction, quality appraisal, data analysis, and data synthesis.

Eligibility Criteria

The following PICO framework is based on our three main research questions stated above.

- Population: The population will include the general population, patients, students, and health care professionals of any age who have interacted with a conversational agent for any health-related purpose.
- Intervention: Interaction with a conversational agent that utilizes natural language processing via any interactive device.
- Comparator: No comparator is required for the studies to be included in this systematic review.
- Outcomes: The main health outcomes assessed will be those related to improvements in clinical, behavioral, and psychosocial parameters, along with health literacy, shared decision making, practical improvement in health care provision, or user-based evaluation outcomes, including acceptability, usability, engagement, and satisfaction.

Search Strategy

We will search the following databases: PubMed (Medline), Embase, CINAHL, ACM Digital, and Web of Science. Key terms relating to conversational agents were extracted from an initial review of the literature, and specific search terms and strings were chosen in consultation with a medical librarian. Search terms will include MeSH terms and keywords related to conversational agents, natural language processing, health care, and evaluation. A draft of the search terms that will be used in this review are grouped into four themes in Table 1. All terms in the MeSH and keywords columns are included with the structure: (conversational agents [MeSH OR keywords] OR natural language processing [MeSH OR keywords]) AND (health [MeSH OR keywords] OR health-related education/training [MeSH OR keywords]) AND evaluation (MeSH OR keywords). We will adapt the search strategy as needed to return a breadth of papers without retrieving an unmanageably large number of irrelevant articles.

Table 1. Search terms.

Category	MeSH[a]	Keywords (title, abstract)
Conversational agent	Speech recognition software	"Conversational agent*" OR "embodied conversational agent" OR chatbot* OR avatar OR dialog* system OR "virtual assistan*" OR "virtual nurs*" OR virtual patient OR virtual coach* OR intelligent assistan* OR "relation* agent" OR "assistance technol*" OR "voice-based interfac*" OR "virtual coach" OR speech recognition software OR voice recognition software
Health	Healthcare facilities OR health services OR health communication OR health services accessibility OR delivery of healthcare OR health behavior OR simulation training OR health education OR health literacy OR patient acceptance of healthcare OR health knowledge, attitudes, practice OR asthma OR sex education OR exp aged OR exp counseling OR smoking cessation OR exp diet OR exp education, medical OR exp substance-related disorder OR social skills OR autism spectrum disorder OR patient education as topic OR exercise OR diabetes mellitus OR cardiovascular disease OR pulmonary disease, chronic obstructive	Health OR healthcare OR "health behavio?r" OR hospital OR exercis* OR diet OR healthcare delivery or healthcare access or simulation training or education or elderly care or sex* education or health literacy or counsel?ing or well-being or smoking cessation or cognitive dysfunction or mental health or social skills or autism spectrum disorder OR diabetes OR heart health OR chronic obstructive pulmonary disease OR COPD OR sun protection OR physical activity
Evaluation	Outcome assessment (Health Care) OR program evaluation OR feasibility studies OR pilot projects OR diffusion of innovation OR cost-benefit analysis OR reproducibility of results	Feasibil* OR usabil* OR evaluat* OR outcome* OR acceptability OR acceptance OR treatment adherence OR effectiv* OR adoption OR assess* OR user experience* OR efficacy OR utility OR utili?ation OR patient* acceptance OR patient* acceptability OR user* acceptance OR user* acceptability OR user* perce* patient* perce* or user perspective* OR patient* perspective* OR user* view* OR patient* view* OR cost*

[a]MeSH: Medical Subject Headings.

Inclusion Criteria

The main criteria for inclusion will be interventional studies, including randomized controlled trials and non-randomized studies (eg, non-randomized controlled trials, before-and-after studies, and interrupted time-series studies), and observational studies, including cross-sectional surveys, cohort studies, and qualitative studies. Only studies published in English will be included.

There will be no restriction regarding the year of publication of studies to provide a comprehensive overview of the evolution of conversational agents in health care and the obstacles or successes that these agents have met to inform future research. Studies that evaluated at least one conversational agent will be included. Any population groups, geographical locations, or function intending to influence any aspect of physical or mental health or provide health-related education or training will be included to enable an assessment of the breadth of applications of conversational agents. Studies of conversational agents acquiring information via any input will be included; however, the agent must interact with a human user and adapt the response according to user input.

For an initial search, all study designs will be included; however, the studies included in the final review may be refined based on the initial results. An evaluation of the number of studies that are retrieved from an initial search may result in the exclusion of quasi-experimental trials or other study types.

Exclusion Criteria

We will exclude studies that are not published in English and studies of conversational agent interventions that have no health-related function. Studies of conversational agents that utilize the Wizard of Oz technique, whereby a human operator is involved in response generation, or those not utilizing natural language processing will be excluded, as these do not constitute autonomous conversational agents. Conversational agents solely producing proactive communication will also be excluded (eg, reminder texts or electronic messages that cannot be responded to). Studies that report no evaluation of the conversational agent,

such as papers discussing solely the design, development, or intention of the agent, will also be excluded.

Screening and Article Selection

All articles identified from the database searches will be stored in the citation management software Mendeley (London, UK), which will be used to eliminate any duplicates. Two independent reviewers will screen the titles and abstracts of all studies. Studies that fail to meet the eligibility criteria will be excluded, with any disagreements being discussed until consensus is reached. The full text of the remaining articles will then be examined to determine final eligibility.

A PRISMA flow diagram will be used to record the details of the screening and selection process so that the study can be reproduced.

Data Extraction

To extract data from the included studies, we will use a standardized Excel form that includes general information (title, author[s], year, country of study), study characteristics (study design, aim, study population, duration of study), risk of bias or quality assessment (depending on study design), details of the conversational agent (developer, architecture, intended application, design features), outcomes (including but not limited to health outcomes, user perception, usability, feasibility, and resource implications), limitations (including functional and user-reported limitations or potential improvements), and adverse events (such as data breaches, misinformation, or improper use). We will pilot the data extraction form on a small number of studies to develop the final data extraction form. One reviewer will review the full text of all the papers included in the final selection and extract data that will be validated by a second reviewer. Disagreements will be resolved by discussion, and if consensus cannot be reached, a third reviewer will be consulted.

Quality Appraisal and Risk of Bias Assessment

After the final selection of the studies, two independent reviewers will assess the risk of bias of the included studies. If there is disagreement in judgment, the reviewers will discuss before consulting a third reviewer. The Cochrane Collaboration Risk of Bias tool will be used to assess any randomized controlled trials included in the review [27]. Since many of the included papers are anticipated to assess nonrandomized interventions, the Risk Of Bias in Non-randomized Studies of Interventions (ROBINS-I) will also be used [28]. The National Institutes of Health - National Heart, Lung, and Blood Institute's quality assessment tool [29] will be used for observational cohort and cross-sectional studies. A table will be created summarizing the quality of all included studies.

Data Analysis and Synthesis

It is unlikely that a meta-analysis will be feasible owing to the anticipated variety of study aims, methods, and reported outcomes. Therefore, we will conduct a descriptive analysis to summarize the extracted data. If possible, we will provide a narrative overview of results by subgroups. The discussion will synthesize the data to describe the effectiveness of current conversational agents as well as comment on the scope of the field; draw conclusions about their feasibility, usability, and acceptability; identify limitations and adverse events; and establish directions for future research and development.

Results

As of January 2020, we have begun a preliminary literature search and piloting of the study selection process.

Discussion

We will perform a systematic review and do not anticipate any issues with the implementation of the proposed protocol. This systematic review of the literature reporting the evaluation of conversational agents will offer new insight into the viability and progress of conversational agents in health care, and uncover challenges and limitations that have been encountered in order to inform the future development and evolution of these agents. This research will also add to the growing body of evidence and understanding of how health care can be further personalized. Our findings may also identify potential obstacles to the widespread implementation of these technologies, and aid in the future integration of conversational agents in clinical practice.

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Authors' Contributions

CdC and EM conceived the study topic and research questions, and designed the review protocol. CdC prepared the first draft of the protocol with revisions from MI, CL, MV, and EM. AA contributed to the development of the first draft of this protocol.

Conflicts of Interest

None declared.

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Abbreviations

MeSH: Medical Subject Headings
PICO: Population, Intervention, Comparator, Outcomes
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
ROBINS-I: Risk Of Bias in Non-randomized Studies of Interventions

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Protocol

Three Decades of Internet- and Computer-Based Interventions for the Treatment of Depression: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Depression is one of the leading causes of disability worldwide. Internet- and computer-based interventions (IBIs) have been shown to provide effective, scalable forms of treatment. More than 100 controlled trials and a growing number of meta-analyses published over the past 30 years have demonstrated the efficacy of IBIs in reducing symptoms in the short and long term. Despite the large body of research, no comprehensive review or meta-analysis has been conducted to date that evaluates how the effectiveness of IBIs has evolved over time.

Objective: This systematic review and meta-analysis aims to evaluate whether there has been a change in the effectiveness of IBIs on the treatment of depression over the past 30 years and to identify potential variables moderating the effect size.

Methods: A sensitive search strategy will be executed across the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and PsycINFO. Data extraction and evaluation will be conducted by two independent researchers. Risk of bias will be assessed. A multilevel meta-regression model will be used to analyze the data and estimate effect size.

Results: The search was completed in mid-2019. We expect the results to be submitted for publication in early 2020.

Conclusions: The year 2020 will mark 30 years since the first paper was published on the use of IBIs for the treatment of depression. Despite the large and rapidly growing body of research in the field, evaluations of effectiveness to date are missing the temporal dimension. This review will address that gap and provide valuable analysis of how the effectiveness of interventions has evolved over the past three decades; which participant-, intervention-, and study-related variables moderate changes in effectiveness; and where research in the field may benefit from increased focus.

Trial Registration: PROSPERO CRD42019136554; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=136554

International Registered Report Identifier (IRRID): PRR1-10.2196/14860

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KEYWORDS

depression; internet-based interventions; meta-analysis; review

Introduction

Background

Depression is one of the leading causes of disability worldwide, with global prevalence rates estimated at 4.7% [1,2]. Depression has been identified as a risk factor for many chronic health conditions [3], is associated with poor quality of life [4], has a significant burden of fatal and nonfatal disease [5], and a highly negative economic impact [6].

Cognitive behavioral therapy (CBT) is the most widely practiced and researched form of psychotherapy for depression, with an extensive body of research supporting its efficacy in reducing depressive symptoms [7,8].

Despite the demonstrated efficacy, the World Health Organization estimates that approximately 34 million people suffering from major depressive disorder go untreated each year in Europe and the United States alone, representing a treatment gap of more than 56% [9]. Barriers to effective care include difficulty accessing a nearby provider, the prohibitive cost of treatment, lack of insurance and trained health care providers, long waiting list times, and the social stigma associated with mental disorders [10,11].

The development of internet- and computer-based therapy has provided an effective method of meeting some of these challenges. Emerging in 1990, the first version of computer-based CBT (cCBT) was effectively a CBT manual delivered via a CD-ROM [12]. However, with the development and widespread adoption of the internet in the 1990s, internet delivery became the norm [13].

During an internet- or computer-based intervention (IBI), patients typically log in to a website to read, watch, hear, and download materials arranged into a series of lessons or modules. They receive homework assignments and regularly complete computer-administered questionnaires relevant to their presenting problems, allowing a therapist or other support person to monitor their progress and outcomes [14,15].

There are a number of advantages offered by IBIs over traditional forms of face-to-face therapy [14]. First, in the case of online interventions, the ability for patients to access IBIs at anytime and from anywhere with an internet connection significantly lowers the barrier to access. Second, the anonymity of IBIs allows patients to circumvent the stigma surrounding mental disorders, which prevents many from even mentioning their problems when consulting general practitioners. Finally, the time savings associated with internet-delivered therapy has enabled health care providers to increase the delivery of therapy and reduce wait-list times, making it a highly scalable form of therapy.

Over the past 30 years, IBIs have been developed and tested for a range of mental disorders, the most common of which are anxiety and depression disorders [16]. Interventions have employed a variety of therapeutic approaches—from CBT [16] to acceptance and commitment therapy [17], psychodynamic approaches [18], and interpersonal psychotherapy [19].

Effectiveness of Internet- and Computer-Based Interventions

The most widely researched type of IBI is internet-delivered cognitive behavior therapy (iCBT), with more than 100 randomized controlled trials (RCTs) and a growing number of effectiveness studies [20-22] and meta-analyses [8,23-35] demonstrating its efficacy. One of the earliest meta-analyses by Spek et al [23] found a moderate posttreatment effect size across 12 RCTs for participants with depression compared with control groups. Subsequent reviews have reported similar findings, with pooled standardized mean differences ranging from Cohen *d*=.32 [23] to Hedges' *g*=0.78 [25] for interventions compared with placebo, treatment as usual, and wait-list. A particularly important comparison for IBIs is traditional, face-to-face therapy. Although there have been few trials to date, a meta-analysis by Carlbring et al [35] indicated that there was no significant difference between iCBT and face-to-face treatments, a finding supported by Webb et al [36]. In addition to RCTs, a number of effectiveness studies have demonstrated that iCBT can be effectively delivered in routine clinical practice, with effects similar to those observed in efficacy trials [21,22]. One notable (although widely debated) exception to these findings was the large-scale REEACT (Randomised Evaluation of the Effectiveness and Acceptability of Computerised Therapy) trial, which compared two iCBT interventions (Beating the Blues and MoodGYM) with usual general practitioner care in a primary care setting in the in which it was concluded that the benefits of IBIs demonstrated in efficacy trials may not transfer to clinical settings [37].

Finally, small but significant effect size superiority has been shown at both 3- to 6- and 9- to 18-month follow-ups indicating the potential for IBIs to deliver sustained benefits over time [26].

Despite these positive findings, the growing number of RCTs and meta-analyses conducted to date only provide a pooled estimate of effect size at a singular point in time. To the best of our knowledge, no research has been published that evaluates how the effectiveness of IBIs has evolved over time. That is to say, have outcomes improved, deteriorated, or remained the same? Therefore, the primary aim of the proposed study is to examine the effect of time on the effectiveness of IBIs in the treatment of depression, in which the term "effectiveness" will be used to encompass both efficacy and effectiveness trials [38]. As a result of significant advances in digital technology over the past 30 years, together with a greater understanding of the moderators of change in IBIs, we hypothesize that the effectiveness of IBIs has increased with time.

Factors Influencing the Effectiveness of Internet- and Computer-Based Interventions

As the field of IBIs has developed over the past 30 years, an increasing number of studies have looked at the factors influencing effectiveness. Researchers have identified a broad range of factors related to (1) participant characteristics, (2) intervention components, and (3) study design and quality.

Regarding participant characteristics, marital status, education level, gender, and pretreatment depression severity have all

been shown to influence outcomes [39-42]. However, it is important to note that methodological and power limitations may affect the reliability of these findings, which may also account for the considerable variability found across studies [43,44]. In a small but growing number of trials looking at age, IBIs have also been shown to be effective in the treatment of depression for both children and older adults [45,46].

When it comes to intervention components, IBIs vary considerably in the therapeutic approach adopted, the design of the platform, the content used, and the mode of delivery. Perhaps the most significant and consistent finding regarding the impact of intervention components on effectiveness is the role of human support or "guidance," in which a number of RCTs and meta-analyses have demonstrated that guided interventions lead to greater effect sizes than unguided interventions [15,32,33,44,47]. Additional research has also studied the impact of the amount of guidance received (the dose-response relationship), the qualification of those providing guidance (eg, therapist versus administrative personnel), the communication mode (email, phone, video chat) [15,32,34], and the acceptability of guided and unguided interventions compared with other delivery formats [47].

Another important factor influencing the reported effectiveness of IBIs is study design and quality. Researchers have long been aware of the substantial heterogeneity between studies in the field, leading to inconsistent effect sizes. In recent years, concerns over a number of methodological shortcomings affecting much of the research have been raised. A meta-analysis by Richards and Richardson [15], for example, revealed a high risk of missing data in RCTs as well as possible publication bias. In an in-depth review of study design and quality, Arnberg et al [48] reported on the lack of proper quality assessment and objective outcome measures, the paucity of noninferiority trials, the relatively small sample sizes in most trials, a focus on short-term outcomes, the failure to report on deterioration and adverse events, and the overrepresentation of trials conducted in a limited number of countries threatening generalizability. The type of control used in the study has also been shown to have a significant impact on effectiveness. As Webb et al [36] pointed out, the majority of iCBT studies have used a wait-list as their control condition, which a number of researchers have demonstrated leads to a significantly greater effect size than care as usual [49-52]. If this is indeed the case, research would benefit considerably from understanding whether any potential increase in the effectiveness of IBIs over the past decades is a result of an improvement in the interventions themselves or simply a result of changes in study design and quality. In so doing, we would also reveal how methodological standards in the field have developed over time, exposing potential shortcomings that need to be addressed.

Aims and Objectives

Using a meta-regression analysis, this study will examine whether there has been a change in the effectiveness of IBIs for the treatment of depression over the past 30 years independent of study-related moderating variables. It will also describe relevant developments in the field over time (eg, populations studied, changes in intervention design, study quality, and sample size).

Methods

This protocol has been developed in line with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) protocols statement [53]. The systematic review and meta-analysis has been registered with the PROSPERO (International Prospective Register of Systematic Reviews) database (registration number: CRD42019136554).

Eligibility Criteria

In accordance with the PRISMA checklist recommendations, this review will use the participants, interventions, comparators, and outcome(s) process for framing and reporting the review criteria, and the study design of the included studies will be reported (Textbox 1).

Textbox 1. PICOS (participants, interventions, comparators, outcomes, and study design) elements of the study inclusion criteria.

Participants

- Individuals of all age groups and gender with depressive symptoms

Interventions

- Internet- and computer-based psychological interventions (IBI) (eg, IBI with guidance, IBI without guidance)

Comparators

- Wait-list
- Treatment as usual
- Attention control
- No treatment

Outcomes

- Symptom-specific: depression severity
- Intervention-related: acceptability

Study design

- Randomized controlled trials published in peer-reviewed journals

Participants

We will include studies of people of all age groups and genders with depressive symptoms. No restrictions regarding ethnicity and cultural background will be applied.

Interventions

Included studies must report on one or more interventions that are based on psychological interventions. A multitude of different psychological interventions are available. Following Kampling et al [54], we differentiate between (1) CBT (eg, problem solving), (2) psychodynamic psychotherapy (eg, psychoanalytic therapy), (3) behavior therapy or behavior modification (eg, exposure therapy), (4) systemic therapy (eg, family therapy), (5) third-wave CBTs (eg, acceptance and commitment therapy), (6) humanistic therapies (eg, Rogerian therapy), (7) integrative therapies (eg, interpersonal therapy) and other psychological-oriented interventions (eg, bibliotherapy) [54].

Interventions must be provided via a computer or mobile device (eg, tablet or mobile phone) in either an offline or online setting, defined as computerized-, online-, internet-, or Web-based. Interventions that are delivered solely via mobile apps will be excluded due to differences in the way they approach diagnosis and delivery of the intervention compared with IBIs, as well as significant heterogeneity between the apps themselves (eg, the use of ecological momentary assessments, duration of tasks or modules, and use of conversational agents) [14,55]. We will include both guided and unguided interventions. Guided interventions will refer to interventions that are primarily based on self-help material but accompanied by some form of minimal human guidance related to the therapeutic content. In line with Karyotaki et al [44], guidance will be considered minimal if it is provided at low intervals and through electronic means, such as email, phone, and online messaging (eg, brief email feedback on weekly homework). We will consider an intervention unguided if it is self-help with no human guidance or support relating to the therapeutic content. Studies involving "blended therapy" (where computerized therapy is combined with face-to-face therapy) will be excluded because the therapeutic support here differs substantially from minimal therapeutic contact provided in guided interventions.

Comparators

We will include all RCTs with an inactive control condition (eg, treatment as usual, attention control condition, wait-list control, or no treatment). Studies will be excluded if they compared the intervention to an active control (eg, face-to-face therapy or pharmacotherapy). In cases of multiple comparators or multiple interventions and one comparator in one study, all comparisons between intervention group(s) and comparator(s) will be included separately. We will use a three-level meta-regression model to account for dependencies (see Data Analysis).

Outcomes

The primary outcome will be effect size in depressive symptomatology measured by validated self- or clinician-rated depression scales. Multiple effect sizes (eg, multiple outcomes or multiple groups) will be included separately. Resulting dependencies will be accounted for in the three-level meta-analysis [56].

Intention-to-treat data, if available, will be used for the primary analysis. Secondary analyses will be reported for per-protocol data. The per-protocol analysis will be based on the sample of participants who adequately adhered to the intervention protocol by completing at least 80% of sessions [57].

As a secondary outcome, we will include acceptability of treatment, operationalized as the proportion of patients who left

the study early for any reason during the acute phase of treatment [58].

Study Design

Parallel RCTs will be included. Published, peer-reviewed, full-text articles in all languages will be included.

Predictors and Moderators

This study will investigate the following potential moderators of effect size over time: (1) pretreatment depression severity, (2) guidance, (3) comorbidities, (4) control group, and (5) study quality. Time will be operationalized as the year of publication.

Pretreatment depression severity will be operationalized using the sum score of a validated rating scale. Preference will be given to the measure reported by the majority of the included studies. In studies using different outcome measures, the score will be converted into the most commonly used scale using the established conversion algorithms [59]. If this approach does not cover a substantial proportion of the obtained data, scale scores will be transformed into *z* scores to create a standardized common metric for pretreatment depression severity [34,60].

Guidance will be operationalized as being either "guided" or "unguided" interventions. *Guided* interventions will be defined as support related to the therapeutic content provided by a human at low intervals during the intervention and delivered through electronic means, such as email, phone, and online chat. *Unguided* will be defined as an intervention that that does not provide support related to the therapeutic content but may involve support related to the intervention itself (eg, instruction on how to use the program) and/or automated feedback. "Blended" interventions or those involving any face-to-face support during the intervention will be excluded from either definition.

Comorbidities will be defined as target populations with a comorbid somatic disorder. Control group will be operationalized according to the Comparators section and study quality according to the Risk of Bias section.

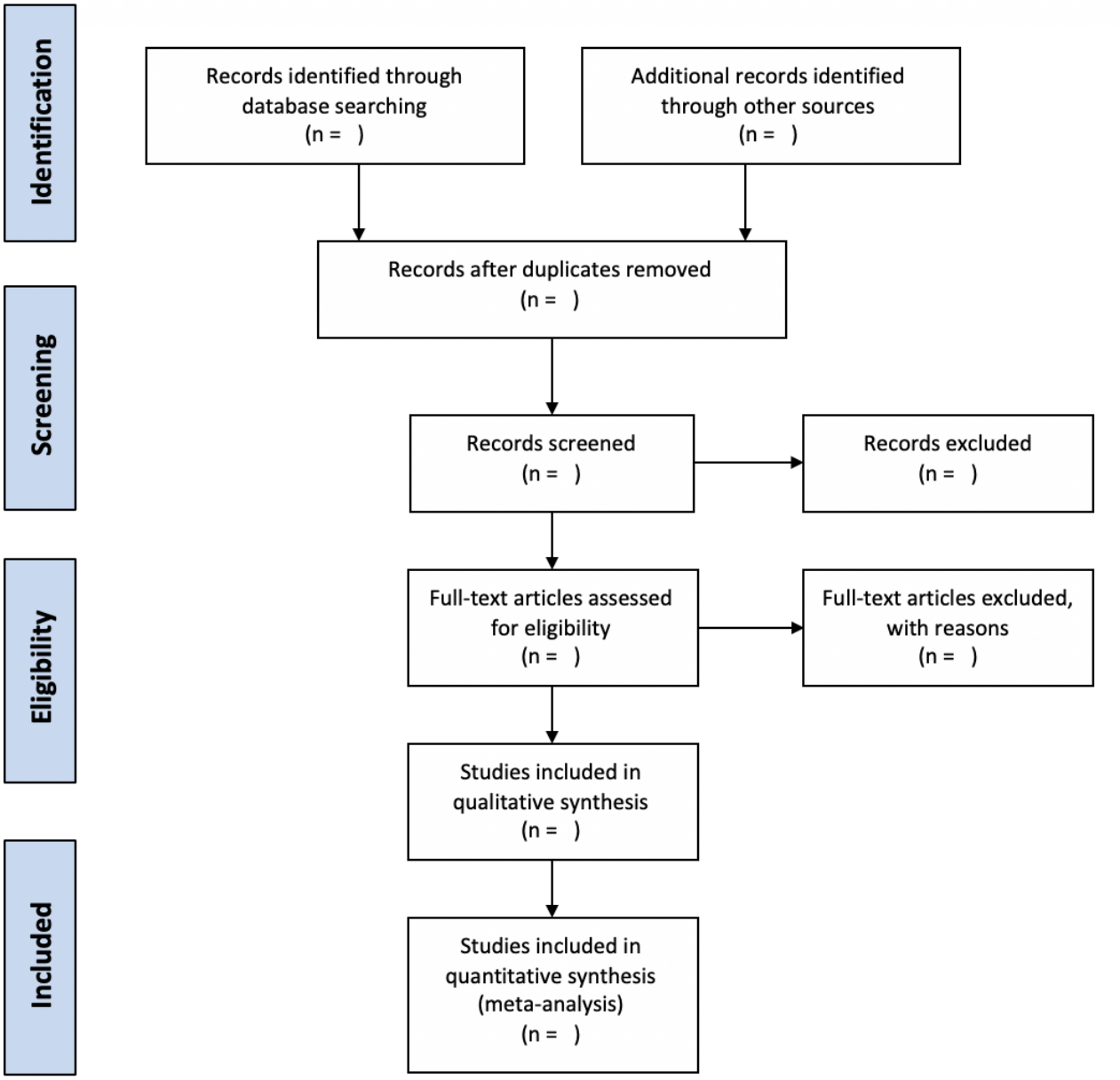
Study Identification and Selection

Relevant articles will be identified according to the following steps. First, a database search will be conducted using a sensitive search strategy for the Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO, EMBASE, and MEDLINE. The sensitivity of the strategy will be validated a priori using a sample set of articles from previous meta-analyses. In a second step, studies included in reference lists of relevant existing systematic reviews and meta-analyses will be checked for eligibility. In a third step, a hand search will be conducted of the reference lists of all included studies.

In the case of missing data, we will contact trialists for information on unpublished or ongoing studies, or to request additional trial data and determine eligibility for inclusion in this review. The search will be restricted to studies published in the 30 years from January 1990 to April 2019.

The selection of articles will be conducted by two independent reviewers (IM and IC). In the first step, they will screen all titles and abstracts yielded by the database search. In the second step, full texts of the selected articles will be retrieved and screened in terms of the aforementioned eligibility criteria. Disagreement will be resolved by a discussion among the reviewers. When needed to resolve a disagreement, a third reviewer (LS) will be consulted. We will identify and exclude duplicate records, and we will collate multiple reports that relate to the same study so that each study rather than each report is the unit of interest in the review. We will record all decisions made during the selection process in sufficient detail with numbers of studies and references to complete a PRISMA flow diagram and "characteristics of included studies" and "characteristics of excluded studies" tables at the end of the review (see Figure 1).

Figure 1. PRISMA flow diagram.



Data Collection

We will use a data extraction spreadsheet to extract study characteristics and outcome data. Two review authors (IM and IC) will extract study characteristics and outcome data from the included studies. Individuals involved in the data extraction process will not be blinded regarding study authors, journal, or institution. We will extract the following study characteristics:

1. Study identification items: description of trial, including primary researcher and year of publication;
2. Study design: sample size, methodology, target mental disorders, control group, and duration of intervention;
3. Study setting: nationality, environment (community, primary care, secondary care), and specific population groups (eg, worker population, students, diabetes patients);
4. Participants: N, mean age, gender, primary diagnosis, comorbid diagnoses, and severity of condition;
5. Interventions: therapeutic theoretical approach (eg, CBT), guidance (guided or unguided); and
6. Outcome measures: primary and secondary outcomes as listed in Main Outcomes and Additional Outcomes herein.

Risk of Bias (Quality) Assessment

To evaluate the quality of the research, two independent reviewers will assess the risk of bias for each study using the criteria outlined in the risk of bias tool for randomized trials [61,62]. Any disagreement will be resolved by a discussion among the reviewers. When needed to resolve a disagreement, a third researcher (LS) will be consulted.

Risk of bias will be assessed in the following domains: (1) selection bias, (2) performance bias, (3) detection bias, (4) attrition bias, (5) reporting bias, and (6) other bias. Risk of bias in each domain will be judged as “low,” “unclear,” or “high.” We will summarize the risk of bias judgments across different studies for each of the domains listed. Overall risk of bias will

be derived based on the risk of bias tool for randomized trials; a score of low=1, unclear=2, and high=3 will be given for each domain. The sum of all domain scores will be used as the overall risk of bias indicator.

Study heterogeneity will be calculated with the I^2 statistic. A random-effects model will be assumed. A value of 0% indicates no heterogeneity; higher values indicate higher heterogeneity. A heterogeneity of 25% is defined as the threshold for low, 50% for moderate, and 75% for high [63]. To account for uncertainty, 95% confidence intervals will be calculated for I^2. In addition, predictive intervals will be reported to estimate the range of the true effect [64].

We will use a funnel plot and Q-Q plot to detect potential biasing effects. Asymmetry will be tested using the Egger test [65].

Strategy for Data Analysis and Synthesis

Interrater Reliability

Cohen kappa will be calculated to assess interrater reliability for categorical variables and intraclass correlation for continuous variables [66,67]. Disagreements will be solved by discussion.

Effect Sizes

Cohen *d* will be used for between-group effect size [68]: Differences in groups' means will be divided by their pooled standard deviation. If *d* is not reported, available coefficients (eg, *r*) will be transformed or *d* will be calculated based on given information (eg, *t* value, N, *F* value, beta). If insufficient information is provided for the calculation, the corresponding author will be contacted [69].

Quantitative Data Synthesis and Statistical Calculations

The meta-analytic effect size will be estimated using a three-level meta-regression model with random effects [70,71]. By assuming a three-level structure, we account for three different variance components distributed over the three levels in the model. This includes sampling variance of the extracted effect sizes at level one, variance between the extracted effect sizes from the same study at level two, and variance between studies at level three [56]. The three-level model will be compared with a two-level model by information criteria to evaluate the need for a three-level structure.

To investigate the development in effect size over time, the primary moderator of interest will be time. Both linear and quadratic time trends will be assumed. In addition, moderators, as outlined previously, will be inserted in the model. Two regression models will be used: (1) a parsimonious model, in which only single meta-regression significant predictors are included ("parsimonious model") and (2) a model including all predictors. Models will be compared using information criteria.

All analyses will be conducted using R [72]. The package "metafor" will be used as the primary analysis package [71,73].

Results

The search was completed after submitting the protocol in mid-2019. Data analysis was completed at the end of 2019. We expect the results to be submitted for publication in early 2020.

Discussion

This systematic review will address a significant lack of research examining the field of IBIs for the treatment of depression from a temporal perspective. Specifically, it will provide valuable analysis of how the effectiveness of interventions has changed over time and identify relevant moderators and study characteristics that may be related to possible changes in efficacy. This is especially important given the rapid rise in internet-based interventions for the treatment of depression over the past decade and the challenges that exist in treating the enormous disease burden of depression.

To the best of our knowledge, this is the first planned study that will review the field of IBIs from a temporal perspective. In so doing, it will shed light on where research has been both over- and underfocused over the past three decades, alert researchers and funding bodies to important research questions that have not been given sufficient attention, and expose methodological shortcomings affecting research to date, thus providing valuable guidance on next steps for the field.

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Authors' Contributions

IM and LS initiated this study and developed the concept and design. YT made a major contribution to methodological aspects. PC and IC added their expertise to the study design and methodology. IM wrote the draft of the manuscript. All authors provided valuable revisions and approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CBT: cognitive behavioral therapy
IBI: internet- and computer-based intervention
iCBT: internet-based cognitive behavioral therapy
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews
RCT: randomized controlled trial
REEACT: Randomised Evaluation of the Effectiveness and Acceptability of Computerised Therapy

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Protocol

Efficacy of Functional Foods, Beverages, and Supplements Claiming to Alleviate Air Travel Symptoms: Protocol for a Systematic Review

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Abstract

Background: Airline passengers often experience symptoms when travelling on long and ultra-long flights. These range from minor discomforts such as gastrointestinal symptoms to more serious life-threatening clinical conditions such as deep vein thrombosis. The food and supplement industry have responded with a plethora of products that claim to prevent one or more of the physiological or psychological symptoms associated with air travel.

Objective: The aim of this literature review is to evaluate the efficacy of functional foods, beverages, and supplements that claim to address the unwanted effects of air travel in healthy adult populations.

Methods: This research is a two-stage process. The first step is a scoping review of the functional foods, beverages, and supplements making claims that they lessen or prevent the physical or psychological symptoms associated with commercial air travel. Databases (ie, Medline, Embase, PsycINFO, and Web of Science), gray literature (ie, the flight catering magazines PAX International, APEX, and Onboard Hospitality), and search engines (ie, Google and Bing) will be used to identify products and generate a database. The second stage is a systematic literature review of the evidence supporting any health claims made for such products. The search will be conducted in Medline, Embase, PsycINFO, Cumulative Index to Nursing and Allied Health Literature, and Cochrane Central Register of Controlled Trials. Additionally, gray literature that includes the reference list of studies included in the systematic literature review and scientific articles referenced by the products within our database will be hand searched. Randomized and nonrandomized controlled trials reporting on changes in flight-related physical or cognitive symptoms in healthy adults that were conducted in commercial flight or flight simulation settings will be included. Two authors will independently screen, extract data, and assess the strength of evidence and risk of bias of the studies. The strength of evidence will be judged using the Grading of Recommendations, Assessments, Developments, and Evaluations approach, and the risk of bias will be assessed using the appropriate Cochrane Collaboration tool (Risk of Bias for Randomized Control Trials II or Robins I for Nonrandomized Interventions).

Results: The scoping review of available functional foods, beverages, and supplements was conducted from March 6, 2019, to August 31, 2019. The systematic literature review commenced on October 1, 2019. The review is expected to be completed in 2020.

Conclusions: The review findings will help consumers and employees of commercial airlines make informed decisions on their use of functional foods and beverages for alleviating air travel–related symptoms.

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KEYWORDS

aircraft; dietary supplements; functional food; functional beverage; jetlag syndrome; sleep

Introduction

With the increasing popularity of international air travel, more people are exposed to extended flight conditions. Long (12-16 hours) and ultra-long (16+ hours) range flights [1] have been associated with several physiological and psychological symptoms that can affect both the air travelling public and commercial cabin crews.

Jetlag, the desynchronization of the normal circadian rhythm due to rapid travel through multiple time zones, is perhaps the most iconic condition associated with prolonged flight [2,3]. Typical symptoms of jetlag include fatigue, sleep disruption, hindered capability to perform cognitive and physical tasks, and mood disturbances [3,4]. The severity of these symptoms is related to the number of time zones crossed and the direction of travel, especially for eastward travel over multiple time zones [3-5].

Prolonged flight conditions can also produce physical symptoms. The average cabin air pressure at typical cruising altitudes results in a 35% expansion of gases within the gastrointestinal tract causing the sensation of abdominal distension and bloating [6,7]. Low cabin humidity combined with the diuretic effects of alcohol and caffeinated beverages commonly consumed preflight or in-flight contributes to dehydration [8], dry skin [9], and irritation of the mucosal membranes in the nose and throat [7]. Compromised mucosal membranes and the proximity of passengers may increase passenger susceptibility to upper respiratory tract infections [7,10]. The mildly hypoxic conditions in pressurized cabins combined with dehydration and reduced physical activity increases the risk of developing deep vein thrombosis, pulmonary embolism, and edema [7,8]. Of concern to cabin crews and frequent travelers, the high altitude of flights increases individual's exposure to cosmic radiation and reactive oxygen species [11].

A number of pharmacological and nonpharmacological treatments exist to lessen the symptoms associated with flight, such as light therapy for jetlag [12] and high-efficiency particulate air filters to improve air quality [7,10]. In addition, the food and supplement industries have responded with a plethora of products claiming to reduce or relieve one or more of these physiological or psychological symptoms. These products include melatonin to improve sleep and reduce jetlag, caffeine to address fatigue, herbal extracts to improve immunity or reduce risk of thrombotic events, and various vitamins and minerals for hydration or as protection against DNA damage from cosmic radiation. However, companies may fail to provide evidence from in-flight settings or flight simulations to justify their claims, and an evidence-based approach is required to provide appropriate advice for passengers and produce guidelines for airlines.

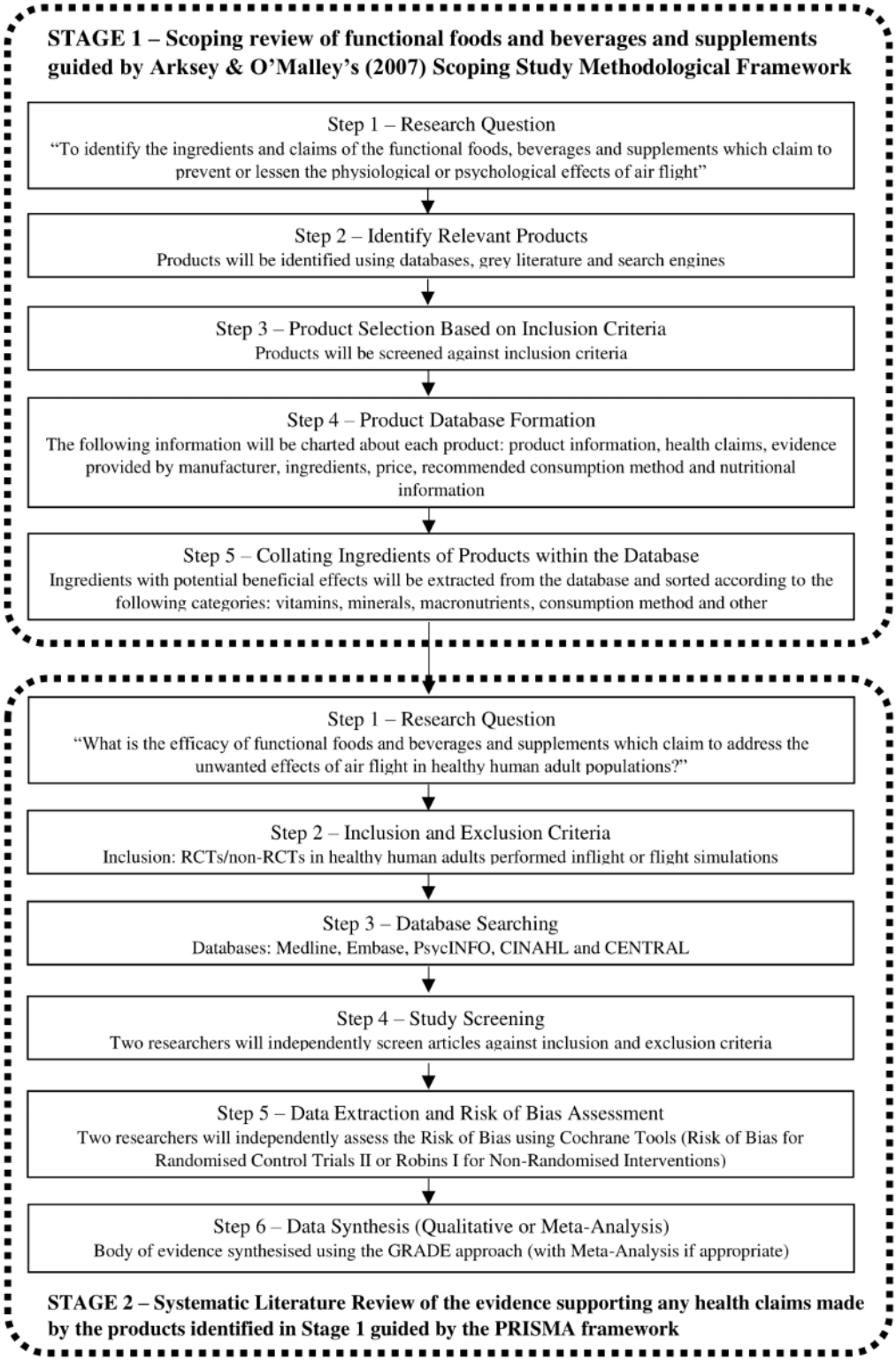
This study aims to evaluate the efficacy of functional foods, beverages, and supplements that claim to alleviate the effects of air travel in healthy populations.

Methods

Study Design

This study is a two-phase process outlined in Figure 1. The first phase is a scoping review of functional foods, beverages, and supplements that claim to alleviate the physical or cognitive symptoms associated with commercial air travel. This stage will be guided by Arksey & O'Malley's (2007) Scoping Study Methodological Framework [13], and the identified products will form the database. The second stage is a systematic literature review of the evidence surrounding any health claims made by the products in the database. The PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) framework [14] will be used to direct the systematic review process and report the outcomes.

Figure 1. Flow diagram of study design. RCT: randomized controlled trial; GRADE: Grading of Recommendations, Assessment, Development and Evaluations; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis.



Scoping Review

Scoping Review Search Strategy to Identify Relevant Products

The scoping review of available functional foods, beverages, and supplements will be conducted in databases (ie, Medline, Embase, PsycINFO, and Web of Science) and search engines (ie, Google and Bing). Well-known publicly available travel catering gray literature (ie, PAX International, APEX, and Onboard Hospitality) that includes articles and advertisements of relevant functional foods, beverages, and supplements will also be searched. Search terms will include combinations, truncations, and synonyms of: "drinks", "beverages", "food", "snacks", "nutrition", or "supplements" combined with "airplane", "aviation", "deep vein thrombosis", "flight", "hydration", "jetlag", or "sleep".

Product Inclusion and Exclusion Criteria

Products identified in the scoping review will be included in the database if they meet any one of the following inclusion criteria.

1. The product is stocked or marketed to airlines, airports, or commercial cabin crews.
2. The product is claimed to be used or developed by commercial cabin crews.
3. There is a scientific publication performing trials of the product in a flight setting or flight simulation.
4. The product is specifically designed for or indicates it can be used in commercial flight settings.

Products will be excluded from the database if they were discontinued at the time of the search.

Product Database Formation

The following information will be transcribed into Microsoft Excel 2011 (Microsoft, Redmond, WA).

1. Product information including: brand, product name, flavor, serving size, product type, country of origin, parent company, location of procurement, nutrient reference range, website, date of initial product entry, and date of latest entry update
2. Health claims classified into one or more of the following categories: jetlag, fatigue, sleep, cognitive ability, immunity, hydration status, cardiovascular, protection against radiation, inflammation, anxiety, or gastrointestinal symptoms
3. Evidence provided by the manufacturer supporting any claims made will be categorized as: scientific article in flight setting; scientific article not in flight setting; trial of product; food authority; academic research institute, government agency, or nongovernment organization; customer testimonies; medical or academic professionals; generalized statements without evidence; or other
4. Advertised ingredients and full ingredients list
5. Price per serve (AUD) at time of entry
6. Recommended method of consumption
7. Nutritional Information per serve and per 100 g

Collating Ingredients of Products Within the Database

Active ingredients of functional foods and nutrients will be extracted and sorted according to the following categories: vitamins, minerals, macronutrients, consumption method, and other. Ingredients with possible beneficial effects on symptoms relating to flight will be further examined by a systematic literature review.

Systematic Literature Review

Search Terms

Search terms will be the ingredients of products within the database. These will be combined with synonyms and truncations of aviation terms such as air travel, aviation, cabin crew, and travel medicine. The Medline Thesaurus MeSH (Medical Subject Headings) term will be refined according to each database. The Scottish Intercollegiate Guidelines Network (SIGN) randomized controlled trial study filter [15] will be adapted to capture nonrandomized controlled trials and applied to searches conducted within Medline, Embase, and Cumulative Index to Nursing and Allied Health Literature (CINAHL).

Search Strategy

The databases CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Medline (including PreMedline), and PsycINFO will be searched from inception for studies. Any published scientific articles referenced by products in the database and the reference lists of included studies will be hand searched for additional citations.

Study Eligibility Criteria

Eligibility criteria for studies have been selected based on PICOS (participants, interventions, comparisons, outcomes, and study designs) standards.

Types of Participants

The target age group for included studies is adults aged 18 years or older. No animal studies will be included. Participants should be healthy with no pre-existing health conditions that could impact the primary outcome of intervention, such as hematological abnormalities. Studies that involve pregnant women or participants aged 18 years or younger are not eligible for inclusion. There will be no limitations placed on gender or ethnicity.

Types of Interventions

Intervention must involve administration of a functional food, beverage, or nutritional supplement to participants at any time before, during, or after a commercial flight or flight simulation that is intended to improve the well-being of the participant. No limitations will be placed on length of intervention or follow-up period. Studies that solely involve the use of pharmacological agents (with the exception of melatonin and caffeine) or nonpharmacological treatments other than nutrition such as physical activity will be excluded. Interventions that use a combination of nonpharmacological treatments but also test functional foods, beverages, or nutritional supplements will be eligible for inclusion if the effect of the functional or nutritional products can be isolated.

Types of Comparisons

Studies must make a comparison between those who received intervention and those who did not receive intervention or were given a placebo, and both groups must have undergone the same in-flight or flight simulation.

Types of Outcomes Measured

The primary outcome of this systematic literature review is to determine if there is an improvement in the physical or cognitive symptoms associated with air travel between participants that received intervention and the controls. This can be reported using valid qualitative and quantitative measures.

The secondary outcomes that will be investigated are the incidence of toxicity or negative effects within the intervention or control groups, study funding sources, and the prevalence of industry funding.

Types of Study Designs

Studies will be limited to randomized and nonrandomized controlled trials conducted using in-flight or flight simulation settings. All other study types and non-English studies will be excluded. Studies completed under space or military flight conditions will also be excluded, as the conditions of speed and altitude are not comparable to commercial air travel.

Study Selection

Bibliographic records for all papers will be exported into Endnote X9 reference management software (Clarivate Analytics, Philadelphia, PA). After duplicates are removed, the titles and abstracts of studies will be screened against the eligibility criteria and placed into two groups: further review or excluded. The full text of studies classified for further review will be obtained and reviewed again against the eligibility criteria. The reasons for exclusion of studies will be recorded in a PRISMA diagram. Two reviewers will independently complete each step of the process. Any disagreements between the two reviewers will be resolved through discussion. In the instance that a resolution cannot be reached, a third reviewer will be consulted to reach a final decision.

Data Extraction

The data extraction table will be designed using the principles of the PRISMA statement for reporting systematic reviews. The items to be extracted from the included papers are study details (ie, authors, year, country of publication, funding, and affiliations), participants (ie, characteristics, flight and simulation details, inclusion and exclusion criteria, attrition, and blinding), intervention and comparator details (ie, intervention, sample size, length of intervention and follow-up, and retention rate), and outcomes (ie, qualitative and quantitative measures of symptoms associated with flight and adverse effects).

Data Analysis

Reporting of Intervention Outcomes

A narrative synthesis of findings structured around the nutrients and herbal compounds investigated will be provided. Tests of heterogeneity between the studies will be conducted using the I^2 statistic. Meta-analysis by nutrients or supplements will be conducted using Stata software provided there is low heterogeneity (I^2 value <40%) between two or more studies [16]. The strength of evidence will be judged using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach [17].

Risk of Bias Assessment

Two review authors will independently assess the risk of bias of the included studies using the appropriate Cochrane Collaboration tool (Risk of Bias for Randomized Control Trials II or Robins I for Other Non-Randomized Interventions) [18,19]. The body of evidence from studies with a high risk of bias will be interpreted with caution.

Results

The scoping review of available functional foods, beverages, and supplements was conducted from March 6, 2019, to August 31, 2019. The systematic literature review commenced on October 1, 2019. The review is expected to be completed in 2020.

Discussion

There is a lack of valid scientific evidence for the use of foods and nutritional supplements to prevent and manage symptoms and medical conditions arising from long flights. This research employs a combination of both a scoping and traditional systematic literature review to identify the types of products available and examine the evidence surrounding their health claims.

These findings will inform the decision making of commercial airlines, retailers, commercial cabin crews, and the air travelling public around the use of functional foods, beverages, and supplements when flying.

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Authors' Contributions

Both authors MAF and VC contributed to design of study. VC is primary author and MAF provided revisions to manuscript.

Conflicts of Interest

MAF has been part of an airline project but has not received any funding for that work. MAF has received funding from NHMRC, ARC, NSW Health, and Cancer Council NSW.

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Abbreviations

CENTRAL: Cochrane Central Register of Controlled Trials
CINAHL: Cumulative Index to Nursing and Allied Health Literature
GRADE: Grading of Recommendations, Assessment, Development and Evaluations
MeSH: Medical Subject Headings
PICOS: participants, interventions, comparisons, outcomes, and study design
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis
SIGN: Scottish Intercollegiate Guidelines Network

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Protocol

Internet of Things–Enabled Technologies for Weight Management in Children and Adolescents: Protocol for a Systematic Review

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Abstract

Background: Childhood obesity is a serious global issue, leading to increased medical spending on obesity-related diseases such as cardiovascular diseases and diabetes. There is a need for health care services that link health behavior to risk factors, such as diet and physical activity, and that provide better advice and feedback to users, which Internet of Things–enabled technologies could facilitate.

Objective: The objective of the systematic review will be to identify available Internet of Things–enabled technologies for weight management of children and adolescents (users younger than 18 years). It will also aim to understand the use, effectiveness, and feasibility of these technologies.

Methods: We will search the Medline, PubMed, Web of Science, Scopus, ProQuest Central, and IEEE Xplore Digital Library databases for studies published after 2010, using a combination of keywords and subject headings related to health activity tracking, youth, and Internet of Things. In addition, a Google search to identify grey literature will be conducted. Two authors will independently screen the titles and abstracts identified from the search and accept or reject the studies according to the study inclusion criteria. Any discrepancies will then be discussed and resolved. The quality of the included studies will be assessed using the Critical Appraisal Skills Programme (CASP) checklists. Data from included studies will be extracted into a predesigned form to identify the types of devices or apps, Internet of Things applications, and health outcomes related to weight management.

Results: A preliminary search on Medline returned 484 results. The publication of the final systematic review is expected in mid-2020.

Conclusions: The effectiveness and feasibility of physical activity trackers and consumer wearables for different patient groups have been well reviewed, but there are currently no published reviews that look into these technologies in the wider Internet of Things context. This review aims to address this gap by examining Internet of Things–enabled technologies that are designed for youth weight management and thus inform further research and clinical studies to reduce childhood obesity.

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KEYWORDS

Internet of Things; IoT; childhood obesity; wearables; physical activity tracking

Introduction

Background

Childhood obesity and related costs are increasing worldwide [1-3]. It has been shown that the majority of children with obesity remained obese in adulthood, resulting in significant health care costs [4]. Promoting better diet and regular physical activities [5] can help prevent childhood obesity and thus reduce the occurrence of obesity-related metabolic and cardiovascular diseases [6], and in turn reduce health care costs.

Management of childhood obesity usually involves patient lifestyle counseling [7], but face-to-face counseling can be expensive and difficult for patients in rural areas [5]. There is a growing emphasis on patient-centered health care, where care extends beyond the hospital and is "respectful of and responsive to individual patient preferences, needs, values, and ensuring that patient values guide all clinical decisions"[8]. A promising solution for patient-centered care is the deployment of connected health technologies for remote diagnosis, monitoring, and treatment and patient self-care and support [9,10]. The tracking of physical activity has been studied extensively since the 2000s [11]. It is only in the previous 5 years that wearables, such as wristwatches with activity sensors, have become sophisticated enough to provide measures beyond steps, distance, calories, and sleep. For example, wearables can now measure activity minutes, heart rate, and goal and target-oriented designs [12]. These advances in wearables allow more accurate tracking of physical activities and provide greater insight into the type and form of physical activity undertaken by the user, such as exercise intensity and metabolic rate [13].

The use of these wearables can further be enhanced through integration with the Internet of Things (IoT) [14]. Since the advent of IoT in 1999 [15], IoT-enabled devices and networks have been applied to a range of applications including smart cities [16], virtual power plants [17], and health care [18,19]. In the health care setting, IoT-enabled devices—technologies that are connected to a network–can give accurate and real-time feedback that can generate health data to improve understanding of user behavior and personalize treatment regimes. Acampora et al [20] surveyed the applications of IoT in health care and identified six main applications in health care (Table 1).

Table 1. Summary applications of Internet of Things–enabled technologies in health care.

Application	Goal
Health monitoring, behavioral monitoring, emergency detection	Sensor networks for physiological measures (electrocardiogram, electroencephalogram, etc), health behaviors (such as physical activity) and hazard detection (such as falls)
Assisted living	Smart environments are created to support patients and older adults in their daily lives
Therapy and rehabilitation	Remote and autonomous rehabilitation service provision
Persuasive well-being	Motivate users to adopt a healthier lifestyle
Emotional well-being	Analyze emotions and improve mental well-being of users
Smart hospitals	Improve communication among hospitals

Technologies that track physical activity are widely used in health care applications. Previous studies have reviewed different applications of IoT and non-IoT physical activity trackers for various patient groups, including patients with rheumatic and musculoskeletal diseases [21], epilepsy, Parkinson, patients who have had a stroke [22], working-age women [23], people with serious mental illness [24], obese adults [25], and children [26,27]. These wearable activity trackers have generally shown significant effectiveness in increasing physical activity in the short-term [28], but there are still relatively few studies justifying their long term effectiveness [29]. Furthermore, long-term user adherence remains challenging [30].

Most systematic reviews on physical activity tracking and weight management in children were published several years ago. However, one recent review examined the feasibility and effectiveness of wearable activity trackers for young people (5-19 years old) [27]. Overall, they found that measures of effectiveness were mostly positive but nonsignificant. However, this review included any type of wearable activity tracker and did not focus on IoT.

With regard to user perspectives of mobile health interventions for weight management, it was found that user acceptance of trackers can vary greatly depending on their age group [31,32]. In addition, although the data from wearables can be a valuable source of data for diagnosis and patient monitoring, they are oftentimes not standardized or validated, which limits their clinical significance in supporting clinical decision making [22,33].

Objectives

There is a gap in the literature regarding children and adolescent's use of digital weight management technologies that are connected to a wider network. Currently, no studies focusing on the wider context of IoT-enabled technologies for weight management in children and adolescents have been published. Previously published reviews have focused on elements of this (ie, weight management in children and adolescents, the use of IoT in weight management technologies), but none have examined the intersection. This review will aim to understand how IoT-enabled technologies designed for youth, such as physical activity trackers and weight management apps, fit in the wider IoT context, how data obtained through these devices can improve health care delivery, and whether these address privacy concerns by considering regulations. Specifically, the review aims to answer the following questions:

1. What IoT-enabled solutions are used for weight management and physical activity encouragement in children and adolescents (<18 years old)?
2. How are the data collected with IoT-enabled solutions analyzed, and how do the technologies connect and contribute to the wider IoT ecosystem?
3. What are the ethical and regulatory barriers in implementing these technologies, especially with regard to data sharing and privacy?
4. What are the effectiveness measures used and reported by researchers?

Methods

Protocol

This protocol is developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement [34] and the systematic review to be executed based on this protocol will also be conducted in accordance with PRISMA.

Search

We will search Medline, Pubmed, Web of Science, Scopus, ProQuest Central, Engineering Village Compendex, and the IEEE Xplore Digital Library for studies published after 2010 using a combination of keywords and subject headings related to health activity tracking, youth, and IoT (Table 2). The search string will be constructed in this format: (Health activity tracking) AND (Youth) AND (IoT). Additionally, a Google search will be used to identify gray literature. A sample search conducted in Medline can be found in Multimedia Appendix 1.

Table 2. Search terms.

Theme	MeSH[a] terms[b]	Search terms
Health activity–tracking device	Fitness Trackers	electronic track* OR (electronic activ* AND track*) OR (electronic activ* AND monitor*) OR electronic fitness track* OR fitness track* OR (wearable AND track*) OR wearable OR sens*
Weight management	Weight Reduction, Body Mass Index	(Weight AND (manag* OR monitor* OR reduc* OR loss OR maint*)) OR (“body mass index” OR BMI) OR diet OR obes*
Youth	Pediatrics, Child, Adolescent	Child* OR teen* OR youth OR paed* OR ped* OR adolescent* OR young*
Internet of Things	N/A[c]	IoT OR Internet of things OR connected health OR digital health OR mobile health OR mhealth OR Bluetooth OR wireless OR application processing interface OR API

[a]MeSH: Medical Subject Headings.

[b]MeSH terms were included in the search terms and are only identified separately in this table to describe which search terms were MeSH terms.

[c]N/A: not applicable.

Eligibility Criteria

The study was defined as follows using the PICO (population, intervention, comparator, outcomes) model:

- Population: Children and adolescents younger than 18 who have interacted with IoT-enabled technologies for weight management, physical activity tracking, and encouragement of a healthy lifestyle.
- Intervention: Wearable IoT-enabled weight management and tracking technologies (eg, physical activity tracker, food tracker, sleep tracker) and other physical activity or dietary interventions designed to help young people lose or maintain weight.
- Comparator: Studies with and without a comparator will be included.
- Outcomes: This study will provide information on (1) the available weight management technologies and products for young people (designed for users below the age of 18), (2) the reported effectiveness of these technologies and the measures used to assess them, and (3) the benefits and limitations of each of these technologies reported by the studies.

The inclusion and exclusion criteria for the study can be found in Textbox 1.

Study Records

Data Management and Selection Process

All search results will be exported into a Mendeley library and duplicates will be removed. Two authors (CL and MM-I) will independently screen the titles and abstracts identified from the search and accept or reject the studies according to the study inclusion and exclusion criteria. Any discrepancies will then be discussed and resolved. The full texts will be downloaded for the selected studies and analyzed to determine eligibility. Where there is disagreement in either the screening or full-text analysis stages, a third reviewer will be consulted until consensus is reached.

Data Extraction

One reviewer will extract data from the included studies, which will be validated by a second reviewer. Data from eligible publications will be extracted into a predesigned form to identify the types of devices or apps, IoT architecture employed, effectiveness for youth weight management, and relevant ethics and regulations if mentioned (Textbox 2). The form was custom-built to reflect reported items identified in a preliminary search of the literature that were relevant to the stated research questions.

Textbox 1. Study inclusion and exclusion criteria.

Inclusion criteria

- English publications
- Studies published between 2010 (year of first published study identified by Ridgers et al for wearable activity trackers for youth [27]) and present
- Studies that describe a wearable device or mobile app for health activity tracking connected to a wider network (including internet and other networks beyond the standalone device)
- Health activity tracking and other weight management devices for young people that have data analysis functionalities connected to a network
- Studies that describes the data analysis process and how data is connected to the wider network

Exclusion criteria

- Studies that do not describe weight management intervention
- Studies that describe devices or mobile apps that are not connected to a wider network/platform for data analysis
- Health activity tracking devices that are not connected to a network beyond simple data storage
- Studies that are not focused on children or adolescents (below 18 years of age)

Textbox 2. Data extraction by theme.

Background information of study

- Year
- Country
- Target patient age group
- Test sample size
- Trial type
- Length of study
- Scientific theory

Sensing layer

- Product
- Type of device (eg, mobile app, wearable tracker)
- Sensor type
- Data collected (eg, activity, food intake, heart rate, sleep)

Networking layer

- Data transfer method

Service/interface layer

- What user needs does the product aim to satisfy
- Stakeholders (if identified)
- Data analysis methods

Effectiveness

- Researcher-reported effectiveness measures and outcomes (if any)

Ethics and governance

- Mention of ethics
- Mention of regulation

Data Analysis

As the number of studies are expected to be limited, the analysis will be qualitative, focusing on how existing technologies interact with IoT and connect to the wider internet.

Quality Appraisal

Two reviewers will independently review the identified randomized controlled trials using the risk of bias tool developed by the Cochrane Collaboration [35]. The quality of other included studies and systematic reviews will be assessed using relevant Critical Appraisal Skills Programme (CASP) checklists (eg, CASP checklist for randomized controlled trials, CASP checklist for systematic review) [36]. As we do not expect a large number of studies to meet the inclusion criteria, risk of bias and quality will be reported, but no studies will be removed.

Results

This study aims to identify the types of IoT-enabled technologies used for weight management of children and adolescents and identify the benefits, effectiveness, and limitations of each of these technologies. A sample search conducted on PubMed returned 592 results (search string and results can be found in Appendix 1). The results will inform future development of weight management technologies for children and adolescents to reduce the cost burden of childhood obesity on health care systems. Full results will be published mid-2020.

Discussion

Although wearables and apps for health activity management have been well-reviewed, their integration with the wider IoT network represents a gap in the knowledge for improving patient-centered health care. This systematic review will allow the health care and app development community to better understand how current technologies interact with the internet and provide insights for future IoT–enabled technology development for children and adolescents. The results of this work will inform future development of weight management technologies for young people. A potential limitation of this review is that studies of IoT devices might overrepresent children and adolescents from high socio-economic status, if the devices were preowned and not provided for the study.

This systematic review protocol will be executed within the next 12 months and the review will be published in a peer-reviewed journal to inform future developments in IoT-enabled childhood obesity management technologies.

Acknowledgments

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Authors' Contributions

CL and EM conceptualized and designed the review protocol. CL drafted and finalized the protocol with suggested revisions from MM-I, EM and MH.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Initial search results.
[DOCX File , 14 KB - resprot_v9i3e16930_app1.docx]

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Abbreviations

CASP: Critical Appraisal Skills Programme
IoT: Internet of Things
MeSH: Medical Subject Headings
PICO: population, intervention, comparator, outcomes
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols

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Protocol

Application of Internet of Things in Cell-Based Therapy Delivery: Protocol for a Systematic Review

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Abstract

Background: Internet of Things (IoT), or Industry 4.0, represents a smart shift to more interconnected manufacturing processes where individual entities within the supply chain communicate with each other to achieve greater flexibility and responsiveness in general manufacturing and leaner manufacturing to reduce the cost of production. IoT has become instrumental in driving leaner manufacturing and more efficient systems in other industries such as transportation and logistics. Cell-based therapeutic products could potentially transform various diseases; however, the delivery of these products is complex and challenging.

Objective: This study aims to understand the applicability of IoT in cell-based product supply chains and delivery.

Methods: We will search Medline, EMBASE (OvidSP), Web of Science, Cochrane Library & HEED, Scopus, ACM digital library, INSPEC, ScienceDirect, and the IEEE Xplore Digital Library for studies published after 2008 using a combination of keywords and subject headings related to IoT used in cell therapies. Additionally, a Google search to identify gray literature will be conducted. Two authors will independently screen the titles and abstracts identified from the search and accept or reject the studies according to the study inclusion criteria. Any discrepancies will then be discussed and resolved. The quality of the selected literature will be assessed using the Critical Appraisal Skills Programme systematic review checklist.

Results: Data from eligible publications will be abstracted into a predesigned form to map the current and future directions of the technologies, applications, benefits, and challenges in the implementation of IoT in regenerative medicine. This study will be published in a peer-reviewed journal in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. This systematic review will be executed by June 2020, and the completed review will be published in a peer-reviewed journal to inform future developments in IoT application for the delivery of cell-based therapies.

Conclusions: This review paper will provide an overview of all technologies available in the area and inspect the current IoT applications in cell-based therapies to identify the benefits, challenges, and future directions of using IoT to allow safe and cost-effective delivery of cell-based therapies.

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KEYWORDS

internet of things; IoT; childhood obesity; wearables; physical activity tracking

Introduction

Background

Internet of Things (IoT) is a concept first proposed by Ashton [1] at a presentation at Procter & Gamble (Cincinnati, Ohio) in 1999. By collecting data from individual things and using these data efficiently to facilitate the exchange of information within the network, material and product flows can be tracked to achieve more accurate and real time visibility of the supply chain, which improves communication between entities and streamlines the different steps in the supply chain.

Over the last two decades, IoT has been successfully implemented in various industries including aerospace, aviation, automotive, telecommunications, medicine and health care, independent living, pharmaceutical, retail, logistics and supply chains, manufacturing, process, environmental, transportation, agricultural and breeding, media and entertainment, recycling, and insurance [2,3]. Various benefits have been realized through the application of IoT. Constant monitoring and real-time data acquisition and analysis lead to benefits such as earlier detection of risks, faster response times, and cost savings. This has a wide range of usages from mine production safety [4] to home health care applications [5]. Usage of radio frequency identification (RFID), sensor technologies, and networking architecture, allows better perception and transmission of underground environment information, which leads to better and more timely decision making and safer mine production. Miniature wearable sensors are used to monitor older adults and patients with chronic conditions in order to allow monitoring beyond the boundaries of hospitals. This improves the standard of health care reducing labor costs by lowering the required amount of contact hours with medical staff. Interoperability from connecting information from one domain to others allows better use of resources [6]. One of the most significant applications is in smart highway systems where sensors and cameras are used to collect traffic information that then feeds into a real-time update of an indicator's operating rules on the highway such as speed limit [7].

A survey of the trends and topics in IoT research conducted by Whitmore et al [8] in 2015 looked into the evidence base available in the IoT research space and identified gaps in literature for specific applications and governance frameworks for the regulation of IoT. The implementation of IoT is generally divided into three layers—the sensing layer, the architecture layer, and the application layer [9]. In the context of cell therapies, which are therapies where whole living cells are administered to patients for treatment of diseases, Harrison et al [10] reviewed the application of fluorescent optical sensors on cell therapy manufacturing, and connecting real-time metabolic measurements to quality attributes of products, which could allow more scalable processes and better quality products. Outside of manufacturing, sensors can also be used for in vivo monitoring postadministration [11].

Technology platforms for facilitating information flow and exchange have been made available by industry and academic partnerships. Vitruvian Networks, for instance, is a partnership set up by GE Ventures (Menlo Park, California) and Mayo Clinic (Rochester, Minnesota) to make use of biomarkers, cell therapy processes, and clinical outcome data to guide therapy development [12]. IoT allows real-time control, more integrated maintenance, better adaptability to changing demands, better collaboration across the supply chain of cell therapies, better traceability, smarter products, and new business models for continuous improvement of products [13]. Frameworks for distributed manufacturing and service-oriented IoT deployments have been proposed and discussed in previous literature [9,14-17], but for highly regulated manufacturing environments such as for cell-based therapies, the interface between IoT architecture and Good Automated Manufacturing Practice [18] has not been documented. To allow successful implementation of IoT, the challenges specific to the area have to be identified. Issues such as privacy and security encountered in other IoT applications [19] have to be identified and considered in a manner specific to cell therapy manufacturing and delivery to inform a tailored IoT approach that facilitates translation and delivery of cell-based products.

This paper aims to systematically review all technologies available in the area, and inspect the current IoT application in cell-based therapies to identify the benefits, challenges, and future directions of using IoT to allow safe and cost-effective delivery of cell-based therapies.

Aims and Objectives

The aim of this review is to understand the current available technologies for IoT, the extent of implementation in cell-based therapy delivery, and the drivers and challenges for implementation of IoT. This will allow the gaps for IoT implementation to be identified and will inform future directions in cell therapy supply chain optimization.

Key Research Questions

Our research questions are as follows:

1. What is the current state of IoT implementation in cell-based therapy delivery? What companies and partnerships are engaged in IoT (especially for autologous therapies)?
2. What are the technologies available for IoT specific to cell-based therapy delivery?
3. What are the benefits of IoT in cell-based therapy delivery?
4. What are the challenges of implementing IoT on cell-based therapy delivery?

Methods

Study Design

This systematic review will be conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Multimedia Appendix 1) [20].

In accordance with the PRISMA-P (Protocols) checklist recommendation, the inclusion criteria of this protocol are in accordance with the PICO (Participant, Intervention, Comparator, and Outcomes) standards. Details of the PICO to be included in the review are described in Textbox 1.

Textbox 1. Participant, Intervention, Comparator, and Outcomes and study type review inclusion criteria.

Participant

- Patients receiving cell-based therapy

Intervention

- Any supply chain step using or interacting with the Internet of Things (IoT) technologies/networks in a cell-based therapy delivery process, from patient cell collection (if autologous) or cell sourcing (if allogeneic) to postadministration monitoring and follow-up

Comparator

- No intervention, standard practice, or any other type of intervention that is not IoT such as paper-based batch records

Outcomes

- Benefits and challenges of IoT implementation in tissue or cell-based therapy delivery

Study type

- Any study type (study type will not be subjected to any restrictions)
- Publications between 2008-2018
- English publications

Exclusion Criteria

The fields of both IoT and cell therapy are rapidly advancing; therefore, to ensure that studies found are up to date, only publications from 2008-2018 will be considered. Studies not published in the English language are excluded due to a language barrier. Studies relevant only to the discovery, research, and development phases of cell-based therapies are not in the scope of this review.

Search Strategy

The following databases will be searched: Medline, EMBASE (OvidSP), Web of Science, Cochrane Library & HEED, Scopus, ACM digital library, INSPEC, ScienceDirect, and the IEEE Xplore Digital Library. In addition, a search on Google to identify gray literature will be conducted. Table 1 shows the search concepts and keywords to be searched for this review. Search strings will be constructed using cell-based therapy keywords and keywords from other concepts. A sample search was conducted on the PubMed database, and the search strings used are described in Table 2.

Table 1. Search terms.

Concept	Keywords
Cell-based therapeutics	Cell* therapy
IoT[a]	Industry 4.0, smart factory, business intelligence, internet of things, IoT
IoT technologies	Sensor, biosensor, monitoring device, machine learning, barcode, RFID[b], Auto ID, WSN[c], Cloud computing, paperless
Communication	remote operation, automated workflow, data-driven, traceability, (network AND automat*)
Data security	Privacy, security, GAMP[d], data integrity
Data management	Data stor*, data analy*

[a]IoT: Internet of Things.

[b]RFID: radio frequency identification.

[c]WSN: wireless sensor network.

[d]GAMP: Good Automated Manufacturing Practice.

Table 2. Sample search conducted on the PubMed database.

Search string	Number of results
(“cell* therapy”) AND (IoT OR Industry 4.0 OR ”business intelligence“ OR ”internet of things“)	42
(”cell* therapy”) AND (sensor OR biosensor OR “monitoring device” OR “machine learning” OR “barcode” OR “RFID” OR “Auto ID” OR “WSN” OR “Cloud computing” OR “paperless”)	70
(“cell* therapy”) AND (“remote operation” OR “automated workflow” OR “data-driven” OR “traceability” OR (“network” AND automat*))	21
(”cell* therapy”) AND (Privacy OR security OR GAMP OR data integrity)	41
(“cell* therapy”) AND (”data stor*“ OR (data analy*))	74
Total results from PubMed search	248
Duplicates removed	170

Study Selection

EndNote X8 software will be used for the removal of duplicates. Textbox 1 describes the inclusion criteria of the review. Two independent reviewers will screen the titles and abstracts of papers to ensure no bias occurs. Papers that are ineligible will be eliminated, and the full text of those that appear to meet the review’s eligibility criteria will be obtained and read in full to ensure eligibility. Any contradictions or discrepancies between the reviewers that arise will be discussed until consensus is reached.

Quality Assessment and Risk of Bias

Two reviewers will independently check each article to minimize bias using the collaboration’s risk of bias tool as described in the Cochrane Handbook for Systematic Review of Interventions [21]. All selected articles will be judged for their quality based on the Critical Appraisal Skills Programme systematic review checklist [22] and data analysis.

Data Extraction

The eligible literature will then be described for its three-layer architecture of IoT proposed in various literature [9,23]. Any observed benefits and challenges of IoT in cell therapy delivery will be extracted and mapped against its status of implementation identified in the included studies. A sample data abstraction form can be found in Textbox 2. The data extracted will then be analyzed qualitatively.

Textbox 2. Sample data abstraction form.

Current practice/company and future directions for the items below

Sensing layer:

Sensing devices and technologies such as radio frequency identification tags

Network layer:

Service entities arrangement, virtual entity and information, resource modules

Application layer:

Functionalities of Internet of Things

Observed benefits (if any)

Observed challenges (if any)

Results

The study aims to provide a landscape of the application of IoT technologies in the cell therapy field and identify the gaps and challenges for IoT application. A sample search was conducted on the PubMed database, and the search strings used are described in Table 2. This systematic review will be executed by June 2020, and the completed review will be published in a peer-reviewed journal to inform future developments in IoT application for the delivery of cell-based therapies.

Discussion

This review paper will provide an overview of all technologies available in the area and inspect the current IoT application in cell-based therapies to identify the benefits, challenges, and future directions of using IoT to allow safe and cost-effective delivery of cell-based therapies.

Acknowledgments

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Authors' Contributions

CL conceptualized and wrote the manuscript. EM and MV provided systematic review expertise and assisted in the development of the protocol methodology. All authors read and approved the final manuscript. All authors completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 Checklist.
[DOCX File , 19 KB - resprot_v9i3e16935_app1.docx]

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Abbreviations

IoT: Internet of Things
P: protocol
PICO: Participant, Intervention, Comparator, Outcomes
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RFID: radio frequency identification

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Proposal

Thanatogenomic Investigation of the Hydroxymethylome and Mitochondrial Genome of Cadaveric Cardiomyocytes: Proposal for a Proof-of-Concept Study

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Abstract

Background: Cardiovascular disease (CVD) remains the leading cause of death in the United Arab Emirates (UAE). One of the common CVDs is hypertrophic cardiomyopathy (HCM). Recent studies conducted in heart cells of mice have shown that this condition involves a chemical modification called hydroxymethylation of the DNA of heart cells.

Objective: Objectives of the proposed research are to profile the distribution of 5-hydroxymethylation in the cardiomyocyte (CMC) genome of cadaveric cardiac tissue and cardiac biopsy specimens; to compare the hydroxymethylome of cadaveric CMCs with that of cardiac biopsy specimens from HCM patients and/or cardiac transplant patients (control) undergoing cardiac catheterization; to histologically appraise sarcomere distribution and mitochondrial morphology of CMCs in the presence of HCM; to correlate the mitochondrial genome with the HCM phenotype; and to integrate anatomy with biochemistry and genetics into the instructional design of HCM in the core medical curriculum at Mohammed Bin Rashid University of Medicine and Health Sciences (MBRU).

Methods: Normal and hypertrophic heart specimens will be obtained from 8 whole-body cadavers (2/8, 25% control and 6/8, 75% HCM). Myocardial biopsy specimens will be obtained from cardiothoracic and transplant units at the Cleveland Clinic in Abu Dhabi, UAE. As this is a proof-of-concept study, we plan to recruit 5 patients with HCM, where HCM has been diagnosed according to the guidelines of the 2014 European Society of Cardiology Guidelines. Patients with valvular heart disease, history of myocarditis, regular alcohol consumption, or cardiotoxic chemotherapy will be excluded. The control biopsy specimens will be obtained from patients who had received heart transplants. Three investigational approaches will then be employed: (1) gross anatomical evaluation, (2) histological analysis, and (3) profiling and analysis of the hydroxymethylome. These investigations will be pursued with minor modifications, if required, to the standard protocols and in accordance with institutional policy. The objective associated with the education of health professionals will be addressed through a strategy based on Graham's knowledge translation model.

Results: This study is at the protocol-development stage. The validated questionnaires have been identified in relation to the objectives. The MBRU and the Cleveland Clinic Abu Dhabi Institutional Review Board (IRB) are reviewing this study. Further clarification and information can be obtained from the MBRU IRB. There is funding in place for this study (MBRU-CM-RG2019-08). Currently, we are in the process of standardizing the protocols with respect to the various molecular techniques to be employed during the course of the study. The total duration of the proposed research is 24 months, with a provision for 6 months of a no-cost extension.

Conclusions: The spectrum of CVDs has recently received significant focus from the public health sector in the UAE. HCM is a common familial heart disease, contributing to the sudden increase in the mortality rate of young Emiratis in the UAE. Incorporating artificial intelligence into the identification of epigenetic risk factors associated with HCM will promote accurate diagnosis and lead to the development of improved management plans, hence, positive patient outcomes. Furthermore, integration of these findings into the instructional design of undergraduate, postgraduate, and continuous professional development medical curricula will further contribute to the body of knowledge regarding HCM.

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KEYWORDS

epigenomics; mitochondrial genome; hypertrophic cardiomyopathy; undergraduate medical education

Introduction

Background

Geographically, the Arab world is comprised of 22 countries from North Africa to Western Asia—Algeria, Egypt, Bahrain, Comoros, Djibouti, Iraq, Jordan, Saudi Arabia, Kuwait, Lebanon, Libya, Mauritania, Morocco, Oman, occupied Palestinian territory, Qatar, Yemen, Somalia, Sudan (including South Sudan), Syria, Tunisia, and the United Arab Emirates (UAE). These countries comprise the members of the League of Arab States. Each country has an inimitable set of historical, geopolitical, social, cultural, and economic characteristics, which define its public health systems and the burden of disease and injury. In 2014, Mokdad et al assessed the burden of disease and injuries in the 22 Arab countries in 1990, 2005, and 2010, employing data and methods from the Global Burden of Diseases, Injuries, and Risk Factors Study 2010 [1,2]. Interestingly, the study showed that since 1990, premature death and disability caused by communicable, newborn, nutritional, and maternal disorders, with the exception of HIV/AIDS, has decreased in the Arab world with a stark increase in ischemic heart disease, which contributed to 14.3% of deaths (see Figure 1) [1-3]. In addition, if one compares age-standardized mortality rates registered by the World Health Organization for specific countries in the region [4], a marked augmentation of cardiovascular deaths in most countries from the Middle East is observed, including in the UAE, when compared with data from comparator western countries (ie, the United Kingdom, Germany, and the United States); these deaths are predominantly from ischemic heart disease and hypertensive heart disease (see Figure 2).

Hence, with recent public health concerns focused on the high prevalence of cardiovascular diseases (CVDs) in the UAE, and with the sudden increase in deaths of relatively young Emiratis from CVD and associated disorders, the UAE National Service has implemented routine screening of all recruits for heart disease [5]. Interestingly, hypertrophic cardiomyopathy (HCM) has been identified as one of the four maladies contributing to the escalation in the mortality rate of young Emiratis, although the detailed statistics are still pending [5].

This necessitates that the molecular mechanism underlying HCM be elucidated, such that novel management and treatment strategies targeting the disorder can be identified and designed. Additionally, it is imperative that the concept of *genomics education of physicians* be integrated into the medical curriculum in the UAE, such that Emirati medical students can present findings based on correlation with known clinical information about the patients' diseases and traits.

This is pivotal in light of the revelation that HCM is the most common familial heart disease with vast genetic heterogeneity. Two decades of rigorous investigation have described the vast and intimidating heterogeneity of the HCM substrate. Early reports of seven mutations in one gene—the myosin heavy chain beta isoform (MYH7) [6,7]—have now expanded to 11 or more causative genes with over 1400 mutations, expressed primarily or exclusively in the heart. These genes encode thick and thin myofilament proteins of the sarcomere or contiguous Z-disc. Mutations in several additional sarcomere, or calcium-handling, genes have been proposed, but with less evidence supporting pathogenicity [8]. Also, HCMs show remarkable variability in their age of onset, phenotypic presentation, and clinical course [9], alluding to the fact that disease mechanisms must exist that modify the occurrence and progression of HCM, either by genetic or epigenetic factors that may interact with environmental stimuli and external influences. According to Frey et al [10], HCM develops in response to external influences—ischemia, valvular insufficiency and stenosis, fibrillation, and hypertension—and may eventually progress to heart failure [10]. Further, in the cardiovascular system, histone modifications and chromatin remodeling are believed to modulate adaptive, as well as maladaptive, molecular pathways in HCM and heart failure [11]; as well, methylation of DNA has been responsible for the hypermutability of specific cardiac genes [12]. Additionally, investigations by Jirtle and Skinner [13] as well as Herceg and Vaissiere [14] allude to the potential interplay between environmental factors and the disease phenotype by epigenetic mechanisms. This has been successfully demonstrated in HCM in animal model studies, especially those originating from the Condorelli group [15-17]. Also, studies from the Hein group indicate strict epigenetic regulation during prenatal development and postnatal maturation, as well as in diseased human cardiomyocytes (CMCs) [18-20]. However, the knowledge about the impact of epigenetic alterations on the disease phenotype, specifically in HCM in human patients, is still very limited. This can be attributed to the limited availability of study specimens, because cardiac biopsy is a delicate procedure requiring cardiac catheterization.

Figure 1. Top 25 causes of death in the Arab population in 1990 and 2010 (mean rank). A comparative analysis is provided. Solid blue lines indicate the elevation in rank for a condition or factor responsible for causing death in the Arab population from 1990 to 2010. Green dotted lines indicate a fall in rank of a condition or factor responsible causing death in the Arab population from 1990 to 2010. Red solid lines indicate the elevation or fall in rank of the factors contributing to cardiometabolic syndrome (CMS) in causing death from 1990 to 2010 (note: all the factors contributing to CMS are elevated in rank when compared between 1990 and 2010). Redrawn with modifications from Mokdad et al, 2014. COPD: chronic obstructive pulmonary disease; CV: cardiovascular.

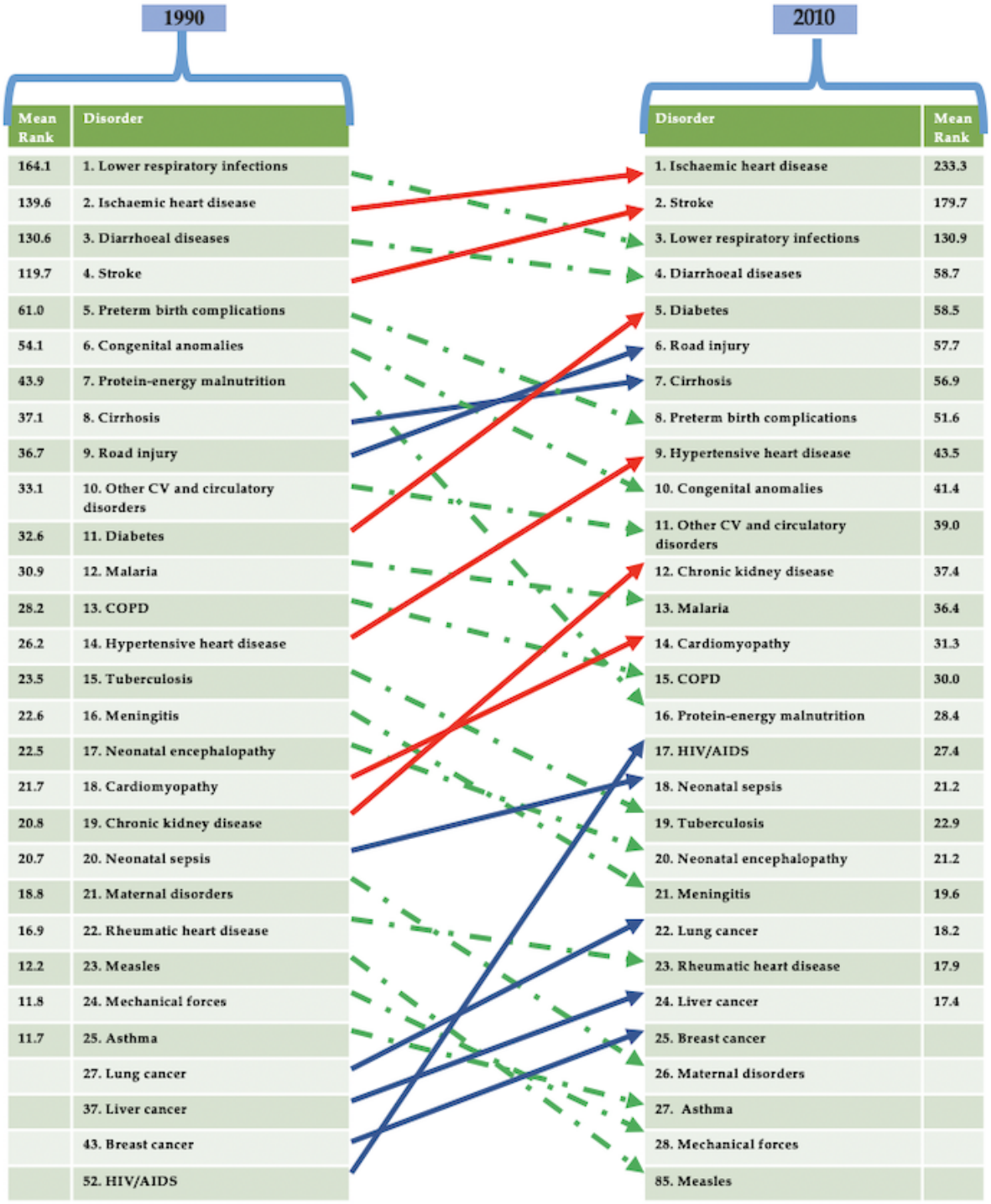
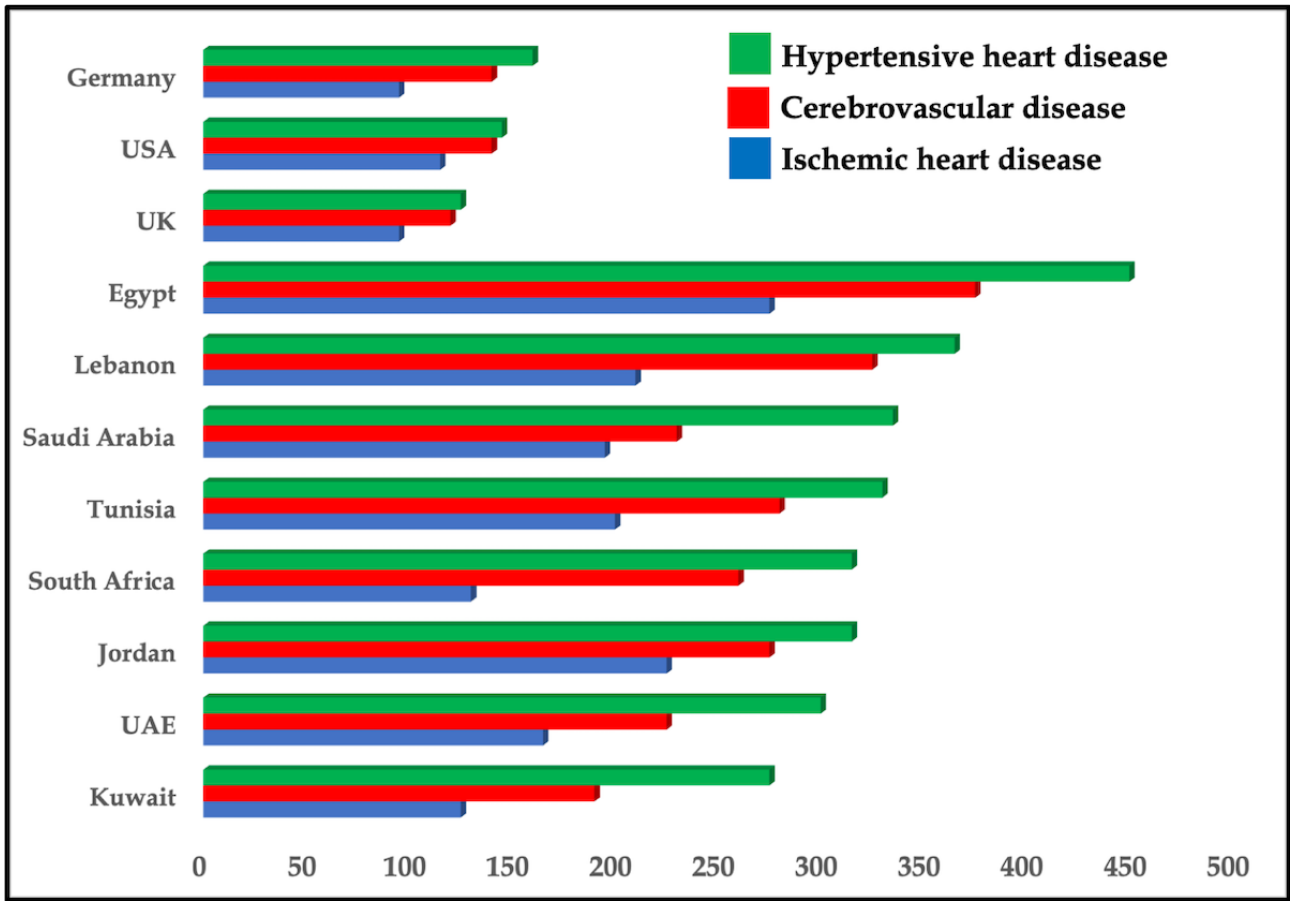


Figure 2. Death rates (ie, number of deaths per 100,000 people) from vascular diseases in selected countries in Africa and the Middle East compared to western countries. Drawn from data presented by the World Health Organization. UAE: United Arab Emirates.



Thanatology, which prioritizes the scientific study of death in the context of other fields of interest (ie, medicine, education, psychology, etc), has paved the way for genomic investigation of the pathological state; this is possible as formalin-fixed paraffin embedding of embalmed human cadavers preserves DNA, reduces the rate of decay, and promotes expansion of the available resource bank [21]. In fact, with the improvement in DNA isolation techniques, amplifiable DNA of high quality and quantity has been isolated from nonparaffin-embedded embalmed cadaver tissue [21].

This proposal is founded on the working hypothesis that the hydroxymethylome of cadaveric CMCs with HCM will exhibit epigenetic modification in the form of 5-hydroxymethylation of cytosine (5-hmC) in the genes, in line with observations from animal studies [19].

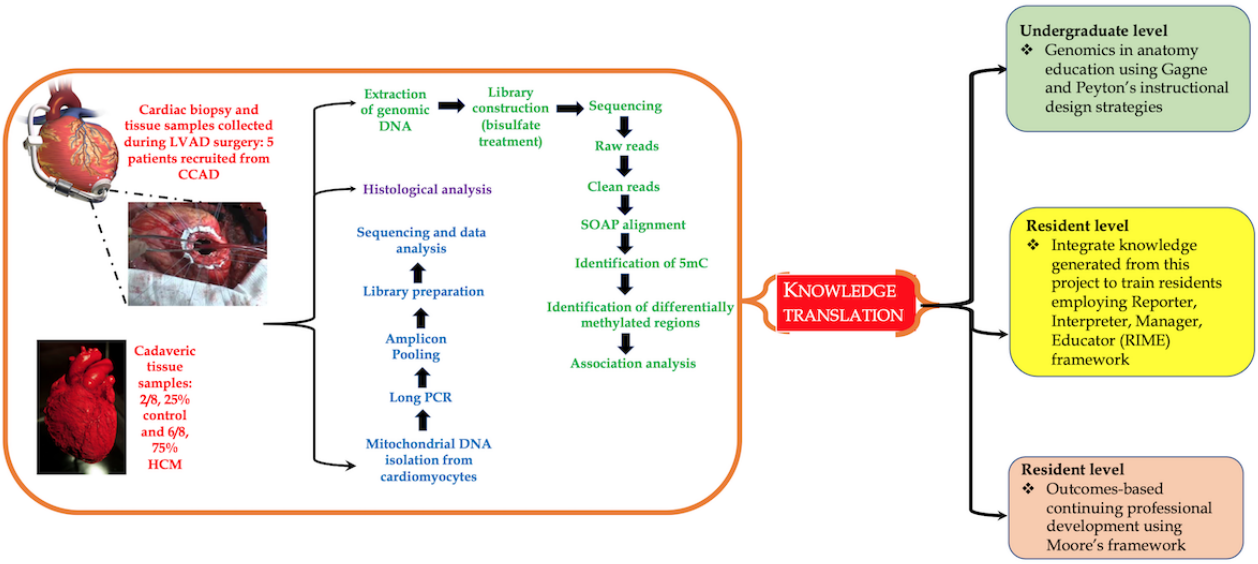
Study Aims

In line with our working hypothesis, the *primary objective* of this study involves profiling the distribution of 5-hmC in the CMC genome in cardiac tissue obtained from cadavers and comparing them with the hydroxymethylome of biopsy specimens obtained from the apical part of the free left ventricle (LV); these were collected during *left ventricular assist device* surgery from HCM patients or cardiac transplant patients (control) undergoing cardiac catheterization using a standardized protocol. Additionally, as HCM is attributable to mutations in the mitochondrial DNA [22], we will compare the mitochondrial genome of cadaveric CMCs with that of biopsy specimens from HCM patients or cardiac transplant patients (control) undergoing cardiac catheterization. A summary of the study is shown in Figure 3.

The *secondary objective* of this study aims to integrate genomics education into medical education, specifically *anatomy* education, whereby we will blend Graham's knowledge translation (KT) process [23] with instructional design models from Gagne and Peyton [24]. By doing so, we will strategize a lesson plan using the epigenetics of HCM as a case study to integrate *anatomy* with *genetics* and *biochemistry* into the core medical curriculum at Mohammed Bin Rashid University of Medicine and Health Sciences (MBRU).

In summary, this proposal aims to augment knowledge with regard to epigenetic regulation of HCM—one of the key cardiovascular concerns in the UAE—concomitantly strengthening medical education by integrating genomics education into *anatomy*. This will stimulate scientific inquiry among medical students, thereby providing KT, such that medical students can present new biomedical findings, correlating them with known clinical information about the patients' diseases and traits.

Figure 3. Summary of the proposed study; important steps are indicated (note: the results from this study will be used for competency-based medical education at different levels of training). 5mC: 5-methylation of cytosine; CCAD: Cleveland Clinic Abu Dhabi; HCM: hypertrophic cardiomyopathy; LVAD: left ventricular assist device; SOAP: short oligonucleotide alignment program.



Methods

In order to address the *primary objective*, the following methodology will be implemented.

Sample Collection

The total sample series will be obtained from two different types of tissue specimens, as follows: (1) cadaveric tissue and (2) biopsy specimens.

Cadaveric Series

Normal and hypertrophic heart specimens will be obtained from 8 whole-body cadavers (2/8, 25% control and 6/8, 75% HCM), which have been donated for the promotion of teaching and research to MBRU. As indicated in the cadaver records, 6 cadavers presented with a previous history of pathological conditions causing HCM. All cadavers were commercially embalmed according to standard protocols [25].

Dissection Protocol and Gross Anatomical Evaluation

The thickest heart slice will be selected and subjected to morphometric assessment. A digital caliper—Mitutoyo Digimatic Caliper, Model No. CD-8“ C (Mitutoyo Corporation)—will be used to measure the following parameters:

1. Thickness of the anterior, lateral, and posterior LV walls (ALV, LLV, and PLV, respectively).
2. Thickness of the anterior, lateral, and posterior right ventricle (RV) walls (ARV, LRV, and PRV, respectively).

Endocardial trabeculations, papillary muscles, and epicardial fat will be excluded from morphometric assessment.

In an effort to reduce intraobserver error, each parameter will be measured three times, from which a mean value will be determined. Clinical history with associated findings and demographic data (ie, age, race, sex, and nutritional status) pertaining to each cadaver will be documented. Ventricular wall thicknesses that exceeds 1.5 cm and 0.5 cm in the LV and RV, respectively, will be indicative of hypertrophy. These values will also be correlated with the weight of the heart and histological attributes of the CMCs to account for the effects of embalming, duration and method of storage, position of cadaver during storage, and rigor mortis. Heart specimens weighing more than 400 g will be described as hypertrophic.

Recruitment Criteria: Myocardial Biopsy Series

Myocardial biopsy specimens will be obtained from the cardiothoracic and transplant units at the Cleveland Clinic in Abu Dhabi, UAE. Collection will be in accordance with the principles of the Declaration of Helsinki. All participants of the study must provide written informed consent, and the study will be appraised and approved by the relevant ethics committees. HCM will be diagnosed according to the 2014 European Society of Cardiology Guidelines [26]. Patients with valvular heart disease, history of myocarditis, regular alcohol consumption, or cardiotoxic chemotherapy will be excluded. The control biopsy specimens will be obtained from patients who had received heart transplants. To be included in the control cohort, patients would have received successful cardiac transplants more than 6 months previously, with normal systolic and diastolic function and no evidence of relevant vasculopathy as judged by coronary angiography. Furthermore, all control patients will have to exhibit freedom from relevant acute or chronic organ rejection. Details regarding processing of ventricular biopsy specimens are described below.

Processing of Left Ventricle Biopsies

Tissue samples, measuring approximately 2 mm in length, will be extracted from the apical region of the LLV wall of 5 patients diagnosed with HCM and 3 cardiac transplant patients (control) undergoing cardiac catheterization, utilizing a standardized protocol used at the Cleveland Clinic in Abu Dhabi. Biopsies will be washed with NaCl (0.9%) and immediately transferred and stored in liquid nitrogen until DNA or RNA are extracted and histological analysis is pursued.

Histological Analysis

Tissue Preparation

Cadaveric and biopsy specimens will be fixed in an embedding medium. Each specimen will then be dehydrated in a series of alcohol solutions of increasing concentration up to 100% alcohol. Washing will occur for 6-18 hours to remove water. Alcohol will be removed by infiltration of xylene. The specimen will then be placed in a cassette containing liquid paraffin. Once the melted paraffin has cooled and hardened into a mold, it will be trimmed into a suitably sized block. The block will be mounted in a specimen holder of the microtome sectioning machine. By careful rotary movement of the hand wheel, the block will cut thin sections in the form of a ribbon. Individual sections will be partitioned from the ribbon and placed in a water bath of 40°C. They will then be mounted on glass slides with albumin and allowed to dry.

Staining

The glass slide will be placed in xylene before it is passed through a series of solutions of decreasing alcohol concentration. Each glass slide will undergo routine staining with hematoxylin and eosin. Lee's stain (ie, methylene blue and basic fuchsin) will then be employed to further highlight cytoplasmic organelles and enhance the contrast of the tissue.

The following connective tissue elements will be depicted: (1) nuclei in blue and (2) cytoplasm, mitochondria, and cilia in reddish-pink. The slide will then be passed through xylene to a nonaqueous mounting medium. A coverslip will be placed over the specimen on the slide to attain permanent preparation.

Semiquantitative Analysis

A total of three field areas per slide will be examined. Cross-sectional area, length, and width of CMCs will be quantified. In addition, organization of sarcomeres, mitochondrial size, and arrangement of cristae will be described.

Level of Significance

Statistical analysis will be performed using SPSS Statistics for Windows, version 24.0 (IBM Corp). The means and frequencies of the continuous and categorical variables, respectively, will be compared for difference or equivalence between parameters and demographically relevant factors.*P*P s of less than .05 will be considered statistically significant.

Profiling, Sequencing, and Analysis of the Hydroxymethylome

Extraction of DNA

DNA will be collected from cadaveric tissues according to the method of Gielda and Rigg, which involves modification of existing techniques of tissue disruption, combined with phenol-chloroform treatment [21]. For biopsy samples, we will use the protocol of Haas et al [27].

Total DNA will be extracted from CMCs from 6 cadaveric hearts diagnosed with HCM, 2 normal cadaveric hearts (control), and biopsy specimens obtained from the apical part of the free LV wall from 5 HCM patients. In addition, DNA will be extracted from the CMCs of 3 cardiac transplant patients (control) undergoing cardiac catheterization. DNA will be enriched for 5-hmC using a biotin-based streptavidin pull-down technique—Hydroxymethyl Collector, Active Motif (Epigenie)—originally described by Song et al [28,29]. The rationale behind employing Song's technique is that it has been successfully used in other studies [30,31].

Sequencing and Analysis of the Hydroxymethylome

Libraries will be prepared using 500 ng of 5-hmC-enriched DNA using the NEBNext Kit (New England Biolabs) and will be sequenced on the BGISEQ-500 platform (Beijing Genomics Institute, BGI), carried out by the BGI epigenetic sequencing service [32], where the corresponding author has collaborative projects.

The BGISEQ-500 generates approximately 500 Gb of sequence data per flow cell, or about 62 Gb per lane. Therefore, a single human genome library can be run across two lanes of the eight-lane flow cell to generate approximately 120 Gb of data per sample. Additional sequencing will be pursued for higher coverage.

Hydroxymethylation analysis will be performed using the Bismark online module for reading bisulfite sequence maps. In summary, FASTQ files will be quality filtered and adapter sequences will be trimmed using the Trimmomatic tool [33]. A bisulfite-converted human genome (HG19) reference genome file will be generated using Bowtie [34], and the EpiGnome (Epicentre) library sequence data will be aligned to the reference genome.

Hydroxymethylation information will be extracted from the output *.sam file, and genome tracks will be the output for visualization and reporting of downstream differential methylation calculations.

The hydroxymethylation extraction report should show minimal bias. A perfectly unbiased sequencing run would be a horizontal line. Visualization of hydroxymethylated sites of the genome will be performed using the Integrative Genomics Viewer (Broad Institute) [35].

To identify regions that gained or lost 5-hmC at specific differentially hydroxymethylated regions (DhMRs), the normal samples will be set as the control group and the HCM samples as the treated group, and the diffReps program [36] will be used with default settings. The diffReps program normalizes each sample by removing regions of low read counts and then calculates a normalization ratio for each sample based on the remaining reads. The medians of the ratios will then be used as normalization factors. To assess differential sites, diffReps uses a negative binomial test on sliding windows and the significant windows will be selected by a predefined cutoff (P<.001). The significant windows that overlap with each other will then be merged, and the differential sites will be used to perform the statistical tests again. The*P*P for each differential site and the best*P*P for the sliding window within each differential site will be documented and reported. Subsequently, DhMRs will be classified by diffReps into genomic locations and annotated using the human (HG19) reference genome.

Mitochondrial DNA Isolation

Mitochondrial DNA will be isolated from cadaveric and biopsy samples, for both HCM and control groups, employing the method of Quispe-Tintaya et al, as this technique exhibits an approximately 2000-fold enrichment of mitochondrial DNA in comparison to commercial kits and is also relatively cheaper [37]. Briefly, the process has two steps: (1) extraction of a mitochondrial DNA-enriched fraction employing a common plasmid miniprep kit and (2) additional purification of mitochondrial DNA using the Agencourt AMPure XP system (Beckman Coulter).

Library Preparation and Sequence Analysis of the Mitochondrial Genome

The CMC mitochondrial DNA will be amplified in two fragments using high-fidelity, long-distance polymerase chain reaction (PCR) with a proofreading polymerase—LA Taq DNA polymerase (TaKaRa)—as described by Tang et al [38]. The primers that will be used to amplify cardiac CMC mitochondrial DNA fragment 1 (9289 bp in length) and fragment 2 (7626 bp in length) are shown in Figure 4. The amplified fragments will be used for preparation and sequencing.

Figure 4. Sequence of primers that will be used to amplify cardiomyocyte (CMC) mitochondrial DNA fragment 1 (9289 bp in length) and fragment 2 (7626 bp in length). 18srRNA: 18S ribosomal RNA; MT-ND1: mitochondrial NADH-ubiquinone oxidoreductase chain 1.

Amplicon	Primer sequence
Fragment 1 forward	5′- AACCAAACCCCAAAGACACC – 3′
Fragment 1 reverse	5′- GCCAATAATGACGTGAAAGTCC – 3′
Fragment 2 forward	5′- TCCCACTCCTAAACACATCC – 3′
Fragment 2 reverse	5′- TTTATGGGGTGATGTGAGCC – 3′
MT-ND1 forward	5′- CCCTAAAACCCGCCACATCT – 3′
MT-ND1 reverse	5′- GAGCGATGGTGAGAGCTAAGGT – 3′
18srRNA forward	5′- TCAAGAACGAAAGTCGGAGG – 3′
18srRNA reverse	5′- GGACATCTAAGGGCATCACA – 3′

Complementary DNA (cDNA) libraries will be prepared with Nextera sample preparation kits (Illumina). These libraries will be quantified using a PicoGreen assay (Invitrogen) and a Kapa quantitative PCR (qPCR) library quantification kit (Kapa Biosystems). Size and quality of cDNA libraries will be confirmed using an Agilent Bioanalyzer 2100 DNA high-sensitivity chip. The cDNA libraries will then be pooled based on qPCR values. cDNA products will be sequenced in rapid mode using the BGISEQ-500 platform.

Paired-sequence reads will be demultiplexed using bcl2fastq, version 1.8.4 (Illumina). Reads will then be mapped to the reference mitochondrial genome—NC_012920.1 (version GI: 251831106)—and will undergo variant calling using the CLC Genomics Workbench, version 8.0.1 (QIAGEN), alignment tool. This will require a minimum coverage of 1000× and a minimum frequency of 1.00×10^{-6}. An average of 7.50 million reads will be mapped per sample. Sequencing data will then be compiled into Microsoft Excel spreadsheet form for analysis. Data in the form of mitochondrial DNA alterations—mutations in specific genes and single-nucleotide polymorphisms (SNPs) at specific loci—between the control and HCM samples will be analyzed using the chi-square test and the Fisher exact test.*P*Ps of less than .05 will be considered statistically significant.

Knowledge Translation

In order to address the *secondary objective*, we will employ Graham's KT process (see Figure 5). KT is a dynamic and iterative process that includes synthesis, dissemination, exchange, and ethically sound application of knowledge to improve the health of Emiratis, provide more effective health services and products, and strengthen the health care system [23].

In order to integrate *genomics* into *anatomy* education, we will use a blended approach where we will blend Gagne's approach with Peyton's approach [24]. A successful implementation of such KT using these approaches is explained using a scenario of familial hypercholesterolemia [39-41], which is the key research interest of the corresponding author. Here, data obtained from a project on familial hypercholesterolemia is used to augment knowledge regarding *bioinformatics* in undergraduate medical education. Data shown here are from an article by Tambi et al, published in JMIR Medical Education (see Figure 6) [24].

Figure 5. Graham's knowledge translation process (Straus et al, 2011). The central idea of this process is to create knowledge through diverse knowledge tools, which may be in the form of research, that could create new knowledge.

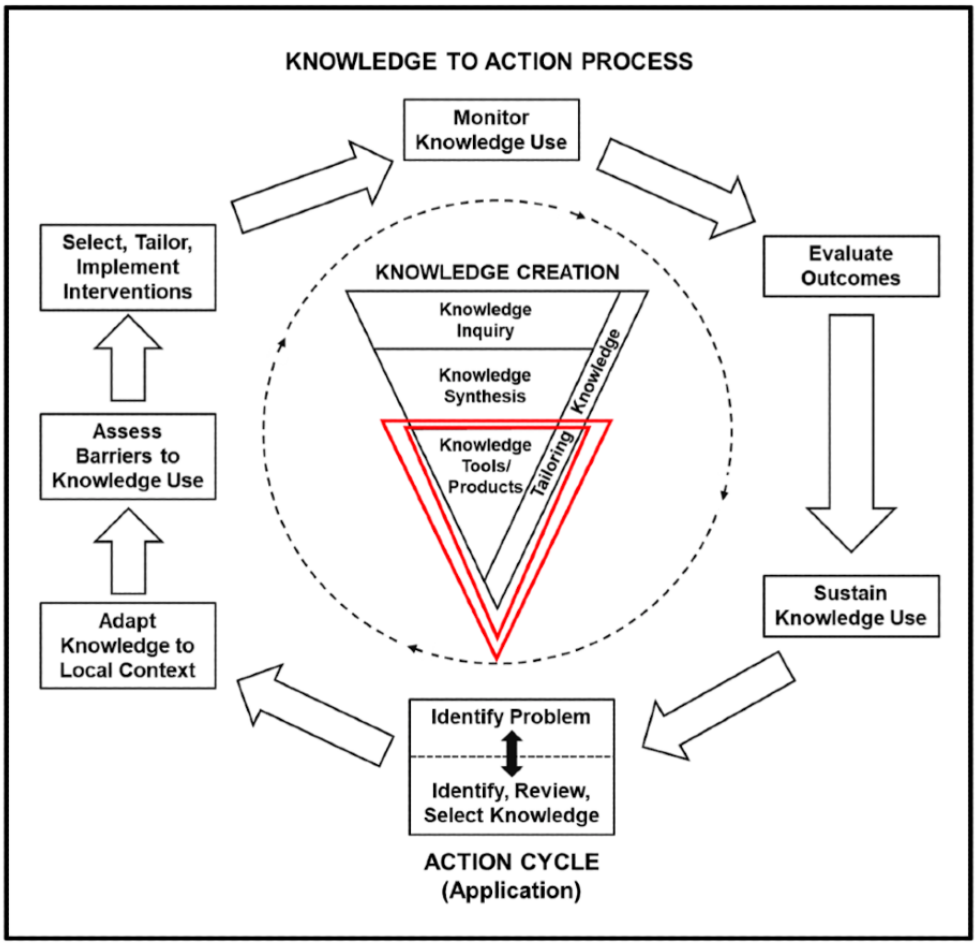
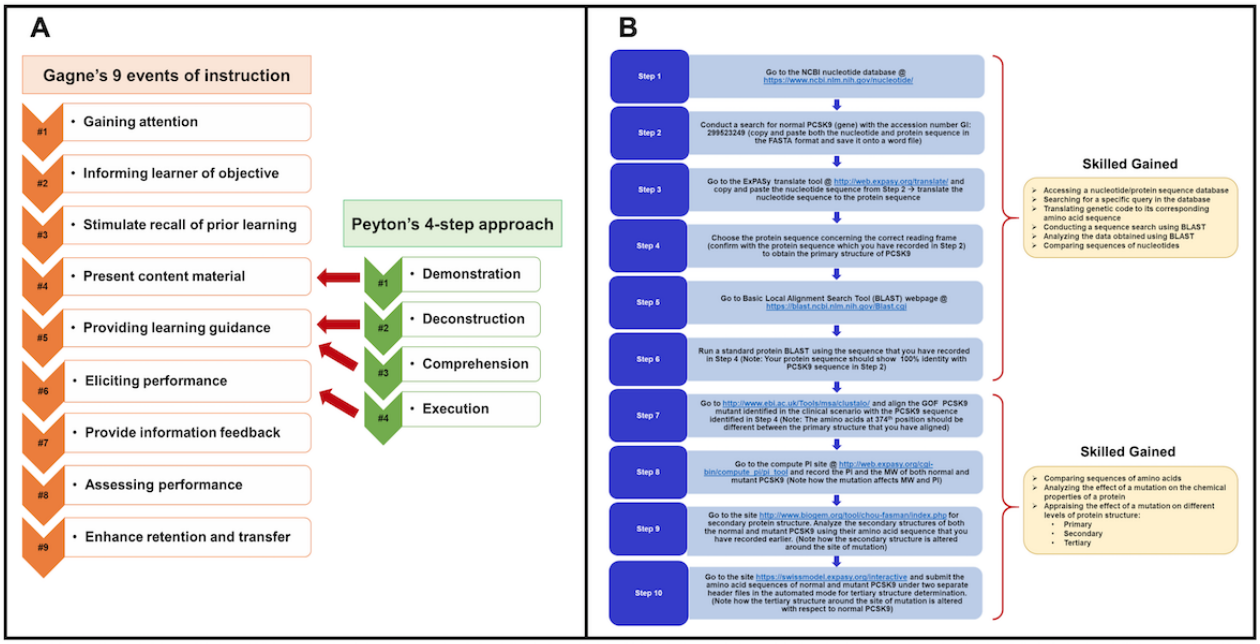


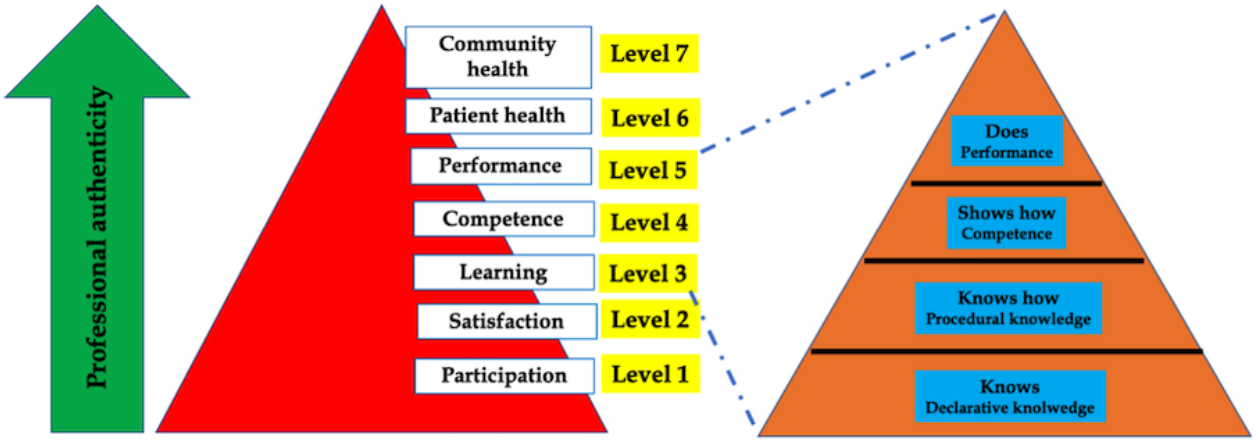
Figure 6. The framework for knowledge translation to be implemented in this study, elaborated using a vignette of autosomal dominant familial hypercholesterolemia. A. Description of the blended lesson plan: Gagne's events of instruction and Peyton's approach. B. The sequential steps of the lesson plan and skills gained. ExPASy: Expert Protein-Analysis System of the Swiss Institute of Bioinformatics; GOF: gain of function; NCBI: National Center for Biotechnology Information; PCSK9: proprotein convertase subtilisin/kexin type 9; PI: isoelectric point; MW: molecular weight.



The proposed research will generate new knowledge with regard to HCM. We aim to add this to the existing knowledge available in the literature and adapt it to suit the needs of medical education in the UAE by assessing barriers to knowledge use (see Figure 5). We will do this via the following proposed KT strategies:

1. At the *undergraduate medical student* level, integration of *genomics* into anatomy education will be pursued by the implementation of instructional design strategies, specifically by blending Gagne's and Peyton's approaches (see Figure 6) [24].
2. At the *resident* level, KT will involve Pangaro's *Reporter, Interpreter, Manager, Educator* (RIME) framework [42], as this model has particular merit for providing feedback to residents.
3. At the *practicing physician* level (noncardiologists), KT will be facilitated through outcomes-based continuing professional development devised by Moore (see Figure 7) [43,44].

Figure 7. Framework for outcomes-based continuing professional development (CPD) to be used in the proposed research.



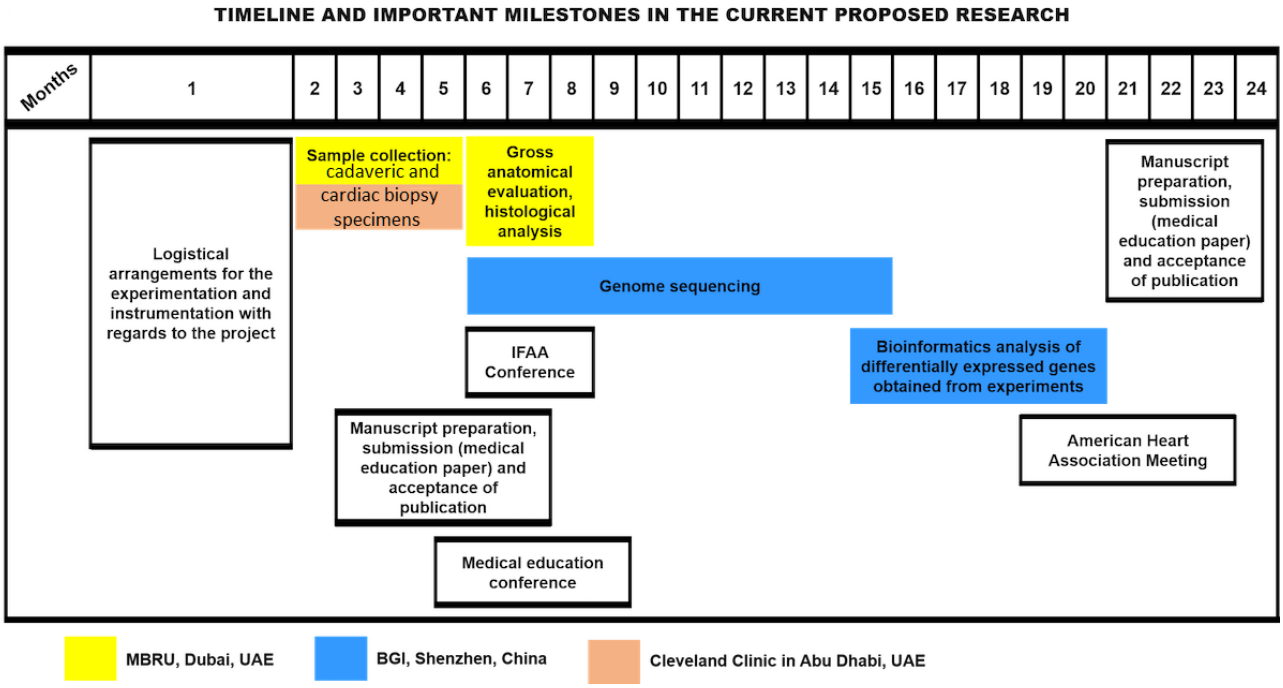
Outcomes framework of Moore

CPD framework	Description	Data source
Level 1 – participation	Number of physicians and health care professionals who participated in the CPD activity	Attendance records
Level 2 – satisfaction	The degree to which the setting and delivery of the CPD activity met the participants' expectations	Questionnaires completed by attendees following the CPD activity
Level 3a – learning: declarative knowledge	The degree to which participants can articulate what the CPD activity intended to convey	Objective: pre- and post-test knowledge Subjective: self-report of knowledge gain
Level 3b – learning: procedural knowledge	The degree to which participants state how to do what the CPD activity intended for them to do	Objective: pre- and post-test knowledge Subjective: self-report of knowledge gain
Level 4 – competence	The degree to which participants demonstrate/show in an educational setting how to do what the CPD activity intended them to be able to do	Objective: observation in an education setting Subjective: self-report of competence, intention to change
Level 5 – performance	The degree to which participants do what the CPD activity intended them to be able to do in practice	Objective: observation of performance in patient care setting, patient charts, administrative databases Subjective: self-reports of performance
Level 6 – patient health	The degree to which the health status of a community of patients changes in response to changes in the practice behaviour of CPD participants	Objective: health status measures recorded in patient charts or administrative databases Subjective: patient self-report of health status
Level 7 – community	The degree to which the health status of a community of patients changes in response to changes in the practice behaviour of CPD participants	Objective: epidemiological data reports Subjective: community self-report

Results

This study is at the protocol-development stage. The validated questionnaires have been identified in relation to the objectives. The MBRU and the Cleveland Clinic Abu Dhabi Institutional Review Boards (IRB) are reviewing this study. Further clarification and information can be obtained from the MBRU IRB. There is funding in place for this study (MBRU-CM-RG2019-08). Currently, we are in the process of standardizing the protocols with respect to the various molecular techniques to be employed during the course of the study. The total duration of the proposed research is 24 months, with a provision for 6 months of a no-cost extension. Key project milestones and the timeline are shown in Figure 8.

Figure 8. Timeline and key milestones for the study; the sites where the research will be conducted are also indicated. BGI: Beijing Genomics Institute; IFAA: International Federation of Associations of Anatomists; MBRU: Mohammed Bin Rashid University of Medicine and Health Sciences; UAE: United Arab Emirates.



Discussion

Overview

To the best of our knowledge, this is the first study exploring the correlation between the HCM phenotype and alterations in mitochondrial DNA. If a correlation is observed, then a study in a larger HCM cohort is warranted.

Additionally, we believe that specific adjustments will be required in the protocol by Quispe-Tintaya et al [37] when isolating mitochondrial DNA from cadaveric samples. This will provide a standardized protocol for such a procedure, benefitting medicine as well as forensic research.

The problem of nuclear copies of mitochondrial DNA (NUMTs) is often encountered while sequencing mitochondrial DNA. Double bands in PCR results or double peaks in mitochondrial DNA sequences indicate NUMTs, however, the case of mitochondrial DNA heteroplasmy has to be ruled out first. In order to avoid NUMTs, we are using mitochondrial DNA-specific primers and a rigorous mitochondrial DNA purification process. Furthermore, this work will be pursued at BGI [45], where the protocol for the required experimentation is standardized [38].

For the *secondary objective*, data will be collected through semistructured interviews regarding participants' use of genomics in their understanding of HCM, as well as the ability of different frameworks to raise awareness regarding the importance of HCM with regard to the Emirati population.

We believe that successful implementation of KT frameworks will support the *primary objective*, as increased participation in these frameworks will ensure successful dissemination of sequence analysis—in the form of undergraduate students participating in the process—and obtainment of specimens—in the form of resident and physician participation.

Conclusions

The spectrum of CVDs has recently received significant focus from the public health sector in the UAE. While HCM is a common familial heart disease, it is now considered to be one of four CVDs contributing to the sudden increase in the mortality rate of young Emiratis in the UAE. Incorporating artificial intelligence to identify the epigenetic risk factors associated with HCM will promote accurate diagnosis and lead to the development of improved management plans, hence, positive patient outcomes. Furthermore, integration of these findings into the instructional design of undergraduate, postgraduate, and continuous professional development medical curricula will further contribute to the body of knowledge regarding HCM. In summary, this proposal aims to augment knowledge with regard to epigenetic regulation of HCM. This concomitantly strengthens medical education by integrating *genomics* education into *anatomy* to stimulate scientific inquiry among medical students. KT is thereby provided, such that medical students can present new biomedical findings, correlating them with known clinical information about patients' diseases and traits.

Firstly, while this study will include a small cohort of specimens due to tissue accessibility, it will begin to answer the question, "Is there a correlation between epigenetic modification of the genome and HCM phenotype?" and will allude to whether mitochondrial DNA alterations have detrimental consequences with regard to CMC structure and function. If the investigational approaches employed in this study hint toward a positive correlation, future study of the hydroxymethylome in a larger cohort of HCM patients will be warranted.

Secondly, as cadaver and patient records will provide information regarding other comorbidities (eg, diabetes, metabolic syndrome, and dyslipidemia), the underlying effect of these conditions on the severity of HCM may be elucidated, which, like above, will require confirmation in a larger cohort of patients with HCM. This study will also pave the way to design the strategy of integrating genomics education into anatomy teaching, as well as KT through different frameworks at different levels and competence of medical training. The success of this integration may be evaluated via different models of feedback, such as that of Pendleton [46], and structured questionnaires.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from MBRU College of Medicine.
[PDF File (Adobe PDF File), 89 KB - resprot_v9i3e17241_app1.pdf]

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Abbreviations

5-hmC: 5-hydroxymethylation of cytosine
ALV: anterior left ventricle
ARV: anterior right ventricle
BGI: Beijing Genomics Institute
cDNA: complementary DNA
CMC: cardiomyocyte
CVD: cardiovascular disease
DhMR: differentially hydroxymethylated region
HCM: hypertrophic cardiomyopathy
IRB: Institutional Review Board
KT: knowledge translation
LLV: lateral left ventricle
LRV: lateral right ventricle
LV: left ventricle
MBRU: Mohammed Bin Rashid University of Medicine and Health Sciences
MYH7: myosin heavy chain beta isoform
NUMT: nuclear copy of mitochondrial DNA
PCR: polymerase chain reaction
PLV: posterior left ventricle
PRV: posterior right ventricle
qPCR: quantitative polymerase chain reaction
RIME: Reporter, Interpreter, Manager, Educator
RV: right ventricle
SNP: single-nucleotide polymorphism
UAE: United Arab Emirates

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Protocol

Youth Experiences With Referrals to Mental Health Services in Canada: Protocol for a Web-Based Cross-Sectional Survey Study

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Abstract

Background: Youth mental health is an important public health concern affecting low-, middle-, and high-income countries, and many young people in need of mental health services do not receive the care they need when they need it. An early step in accessing mental health care is the referral process, yet most of the research done on pathways to care has focused on clinical populations (eg, first-episode psychosis) recruited from mental health care settings. There has been limited research attention on the experiences of referral to mental health services from the perspectives of youth recruited from the general population who may or may not have received the services they need.

Objective: This study aims to investigate the experiences that youth between the ages of 17 and 30 years have with referrals to mental health services and to better understand their perspectives on the use of technology to facilitate referrals.

Methods: This study will use a cross-sectional, Web-based survey design. A convenience sample of 400 participants from 3 Canadian provinces (Quebec, Ontario, and British Columbia), between the ages of 17 and 30 years, will be recruited via Facebook and will be invited to complete a Web-based survey anonymously. A questionnaire including a series of quantitative and qualitative questions will ask participants about their sociodemographic characteristics, past experiences with referral and access to mental health services, and opinions about using technology to facilitate the referral process.

Results: Participant recruitment is planned to be initiated by early January 2020 and is estimated to be completed by May 2020. Data will be analyzed using descriptive statistics and logistic regression or chi-square tests for quantitative data, and descriptive content analysis will be used for the qualitative data.

Conclusions: The results of this study can help inform the improvement of referral policies and procedures in youth mental health service delivery. A better understanding of young people's perspectives on referral processes and their opinions on how these processes can be improved are essential to providing appropriate and timely access to mental health care.

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KEYWORDS

mental disorders; health care quality, access, and evaluation; mental health; psychology; telemedicine; young adult; health services accessibility; technology; referral and consultation

Introduction

Background

Mental health disorders are among the leading causes of morbidity and mortality in young people aged between 10 and 24 years and are major contributors to the global burden of disease [1]. Most mental health disorders will emerge by the age of 24 years [2], and one in every four to five individuals aged 12 to 24 years will experience at least one mental illness in any given year [3]. The prevalence of mental health disorders in young people combined with poor access to timely and appropriate care is an issue affecting low-, middle-, and high-income countries [4]. For example, in Canada, research has shown that youth aged 15 to 24 years have higher rates of mental illness than any other age group, with approximately 8% of youth experiencing a mood disorder and approximately 12% experiencing a substance use disorder [5]. Despite such high rates of mental illness, a Canadian Community Health Survey showed that only 12% of Canadians aged between 15 and 24 years reported consulting mental health professionals about emotional, mental, or substance use problems within the previous 12 months [6]. In addition, only about half of youth living with a mental health disorder consulted professional services (eg, psychologists, psychiatrists, nurses, and social workers) within the last 12 months, indicating the possibility of unmet mental health needs among young Canadians [6]. Moreover, the pathways for those who attempt to seek help but do not receive it are unclear.

Accessing Mental Health Services

The barriers that youth face when trying to access mental health services relate to the individual, the society, and the mental health care system. Common help-seeking barriers reported in the literature include stigma, lack of confidentiality and trust, lack of knowledge regarding symptoms and service options, and self-reliance [7-15]. Even when the help-seeking process has been initiated by a young person and/or their caregivers, there can be several challenges in accessing services [7], such as long wait lists. In a Canadian survey of agencies providing youth mental health care 91.3% (106/116) of agencies reported a waiting list for one or more of the services they offered [16]. Only 63.7% (65/102) of these agencies were mostly or always able to meet the Canadian Psychiatric Association wait time benchmarks for provision of urgent care within 2 weeks, and only 31.4% (32/102) were mostly or always able to meet the 1-month benchmark for scheduled care [16].

According to the Fraser Institute's 2018 national waiting list survey conducted in Canada, the median wait time from referral by a general practitioner to a psychiatrist is 20.8 weeks, which is slightly higher than the weighted median wait time of 19.8 weeks across medical specialties and higher than the wait time for other specialties such as general surgery (12.9 weeks), nonurgent (elective) cardiovascular surgery (9.9 weeks), internal medicine (13.3 weeks), radiation oncology (4.0 weeks), and medical oncology (3.8 weeks) [17]. It should also be noted that response rates for psychiatric wait times (186/4099, 4.54%) were much lower compared with response rates for wait times for other medical services (1718/10,209, 16.82%), and there is, therefore, a potential for bias within the results because of the low response rates for psychiatric services [17].

Certain demographic factors, such as gender, race and ethnicity, housing stability, immigration status, employment and education status, and location, have also been noted in the literature to be associated with access to mental health care. For example, barriers faced by rural youth are a particular concern in Canada; about 10 million or one-third of Canadians live in rural communities [18]. Parents of youth with mental illnesses living in rural areas in Canada have highlighted the lack of resources and services, funding issues, long waiting lists, and distance to services as major barriers to accessing appropriate mental health care for their children [19].

In addition, research has shown that immigrants, refugees, and members of visible minority and ethnocultural groups have limited access to mental health services. For example, a 2007 survey of the catchment area of a comprehensive community clinic located in Montréal found that ethnocultural minority immigrant groups born in the Caribbean, Vietnam, or the Philippines were significantly less likely than their Canadian-born peers to use mental health services, despite using medical services for physical health issues at similar rates [20]. Importantly, the lower rates of mental health service use among immigrant groups could not be attributed to other sociodemographic differences (ie, differences between groups in sex, age, marital status, employment status, and citizenship status), differences in physical or psychological symptoms or distress, length of stay in Canada, or use of alternative resources [20]. Limited knowledge about symptoms of mental illness and the services available, cultural and language barriers, and discrimination are some examples of obstacles faced by immigrants who require mental health care [21]. The barriers that young people, especially those in certain demographic groups, experience when seeking help for mental health concerns can influence their pathways to care and the delays associated with this process.

Pathways to care are defined by the help-seeking behavior of the individual, the sequence of contacts the individual has with mental health services, and how those services respond to the needs of the individual, for example, through referrals to appropriate mental health care services [22,23]. For youth, getting a professional referral to appropriate mental health services can be a harrowing process. For example, within the studies that reported total contacts before receiving specific health services, the number of contacts ranged from 0 to 15 contacts (with a pooled mean of 2.9 contacts) per participant and included medical and nonmedical professionals, friends and family, health care institutions, the justice system, traditional healers, and electronic mental (e-mental) health contacts [24].

The mean duration of untreated psychosis (DUP) for youth experiencing first-episode psychosis ranged from 1.5 to 102 weeks (with the median ranging from 8 to 70 weeks) across 23 studies [24]. Duration of untreated illness (DUI) for youth experiencing a variety of mental health problems ranged from 1 week to 45 years across 15 studies (pooled mean or median were not specified in this review) [24]. Importantly, among the studies that differentiated between referral delays and help seeking delays, the majority reported that referral delays were longer than delays related to help seeking behavior within both DUP and DUI [24].

Various solutions have been implemented to improve pathways to mental health care, for example, the use of open referral systems that provide access to services through any sources of referral, including the individual themselves, family, or other sources [25]. However, the use of open referral systems in youth mental health care have traditionally relied on paper-based methods with limited technology-enabled systems in place to triage, track, and monitor referrals over time. For example, in Canada, the Prevention and Early Intervention Psychosis Program-Montréal offers an open referral approach in which anyone (eg, the individual experiencing mental health–related issues, their families, teachers, and emergency departments) can contact the clinic in person, by phone, or by email [26,27]. However, despite this approach, most referrals to the clinic still come from formal health services [27], indicating that barriers to self-referral exist within open referral systems that use traditional methods of referral (eg, phone, paper, and fax).

More recently, information and communication technologies have been leveraged to improve the efficiency of the referral process to mental health services. Kim et al [28] evaluated the implementation of a Web-based self-referral system in a mental health clinic for adults. In this study, 30% of new adult patients to the clinic were introduced by the Web-based self-referral tool; 80% (45/56) of the clients were satisfied with the Web-based tool, 93% (53/57) said the response to their self-referral was timely, 89% (50/56) felt comfortable using the system, 51% (29/57) said the system improved the quality of health care received, and 89% (50/56) would use a similar Web-based referral system if available [28]. After the trial, the tool was successfully adopted by the clinic [28]. In another recent study, the use of an electronic referral form connected to an electronic health record was implemented to facilitate care coordination among a multidisciplinary team providing mental health services to youth [29]. However, the implementation of Web-based referral services that directly connect youth to public mental health care services is still limited, and to the authors' knowledge, no studies have focused on youth's perspectives in relation to the potential use of technology to complete a self-referral process (eg, perceived benefits, concerns, and suggestions). Such knowledge is important to ascertain, given that research has shown that although youth are open to the idea of using technology in the context of mental health care [30-34], there is variation in terms of the types of Web-based services to which they are receptive [32,33].

In addition, although previous studies have explored the pathways that youth take to access mental health services, the majority of this research has either focused on pathways pertaining to specific mental health concerns (eg, first-episode psychosis), has only recruited clinical populations from within mental health care settings, or has not reported the referral sources within these pathways [24]. Regarding the latter, only 22 of the 45 pathways to care studies included in the review by Macdonald et al [24] examined and reported on referral sources. The referral pathways of youth in the general population who do not successfully access services have been largely ignored. In addition, although several studies have reported on the length of time between the first contact and the reception of mental health services [35-45], little attention has been paid to the actual process of referral. Moreover, further research is needed to have a more complete understanding of the experiences that youth in the general population have with the process of referral to mental health care.

This Study

This study investigates the experiences that Canadian youth between the ages of 17 and 30 years have with being referred to mental health services. The study will examine the following subquestions: (1) What mental health concerns do youth report seeking services for in Canada? (2) What are the pathways and processes that youth experience when trying to access mental health services? (3) What are the barriers and obstacles that youth face in the process of referral to mental health services? (4) What, if any, sociodemographic factors (eg, age and gender) are associated with access to mental health services and mental health service referrals? and (5) What are the views of youth on the use of technology to facilitate self-referrals to mental health services?

Methods

Design

This study will be conducted using a cross-sectional research design. The main method of data collection will be an anonymous Web-based survey that includes open and closed questions. The ability to gather precise numerical data, study large populations, and have generalizability are all important benefits of collecting quantitative data [46]. However, the experiences that youth have with accessing and being referred to mental health care services vary largely, and the restricted nature of quantitative questions may lead to important information being overlooked. Thus, we will also collect qualitative data in conjunction with the quantitative methods to allow for a deeper understanding of young people's referral experiences [46].

Study Population and Inclusion and Exclusion Criteria

To be included in the study, participants must be between the ages of 17 and 30 years; have reported accessing or trying to access mental health services in Quebec, Ontario, or British Columbia within the past 5 years; be able to complete the survey in English or French; and give online consent to participate in the study. Participants will be excluded from the study if they do not provide online consent for participation or if the participant does not click on the submit button at the end of the survey.

The definition of youth varies between contexts but commonly includes the period between the ages of 12 and 25 years [47,48]. This study will focus on interviewing individuals aged between 17 and 30 years to ensure that the experiences reported in the survey occurred when participants were within the age range (ie, 12-25 years) considered youth.

Sampling, Sample Size, Recruitment, and Endpoint

Sampling Method

A convenience sampling method will be used for this study. Convenience sampling involves sampling participants who are available to approach at the time of recruitment, for example, recruiting participants from a specific university course or club [49]. It is a useful method to recruit broad target populations and has the additional advantages of being inexpensive and time efficient [49]. Previous research has used convenience sampling with Web-based surveys to better understand youth experiences with mental health care or mental health, specifically within the context of e-mental health [13,34,50], including a recent Canadian study conducted using a Web-based survey with youth aged 17 to 24 years recruited from the general population on their experiences with Web-based and traditional mental health resources [33].

Sample Size and Endpoint

The estimated sample size is 400. This was estimated using Cochran's sample size formula for a single population proportion for large population using a 95% CI, a margin of error of 5%, and an estimate of the sample proportion of 50% [51,52]. The CI and margin of error were selected based on standard values used for research. The sample proportion is an estimate of the proportion of the population that has an attribute we want to measure. A sample proportion of 50% was chosen because this value provides the largest sample size estimate [51-53]. A sample size of 400 will also allow us to compare reported use and satisfaction with mental health services between demographic groups. For example, if we wanted to detect a 20% difference in reported satisfaction (satisfied vs unsatisfied) between females and males using a power of 80% and a margin of error of 0.05, we would need to have about 80 participants in each gender group. Furthermore, we plan to perform regression analyses to explore any potential associations between 12 sociodemographic variables and reported use and satisfaction with mental health services. Given the rule of thumb N>104+m, in which N is the number of participants and m is the number of variables in the regression, our sample size of 400 should be sufficient for such analyses [54]. The end point of the study will occur when the desired sample size of 400 is reached. On the basis of previous studies using similar methodologies and recruitment methods, this is estimated to take approximately 4 months [13,33], but the timeline will be adjusted to reflect the actual rate of recruitment.

Recruitment

Participants will be recruited through Facebook advertisements on pages targeted toward youth living in Quebec, Ontario, and British Columbia between the ages of 17 and 30 years. This includes the Facebook pages of relevant groups or organizations on university, high school, and Collège d'enseignement général et professionnel (CEGEP) campuses; community mental health organizations; and general Facebook pages accessed by youth. We will initially target university- and community-based Facebook pages that the research team has access to. To maximize the representativeness of our sample population, we will also randomly select universities, high schools, CEGEPs, and youth-focused organizations from comprehensive provincial lists of these institutions and identify whether the selected institutions have Facebook pages where we could potentially post our flyer. We will contact the selected Facebook pages of these groups via private message on Facebook and invite them to post the study advertisement with the link to the survey on their pages.

Facebook recruitment was chosen because of the large proportion of Canadian youth who report using Facebook. For example, a recent Web-based survey study of 1500 participants showed that 95% of Canadians between the ages of 18 and 24 years and 94% of Canadians between the ages of 24 and 34 years have a Facebook account, with 88% and 82% being monthly active users, respectively [55]. Facebook use is high (above 75%) across income levels, education levels, and employment levels [55]. In addition, previous studies have found that participants recruited through Facebook were representative of the populations from which they were sampled [56-58]. Notably, Fenner et al [56] reported that the proportions of foreign-born and indigenous participants recruited through Facebook were similar to the proportions of foreign-born and indigenous individuals in the target population (46/276, 16.7% vs 19.8% were foreign born and 3/278, 1.1% vs 0.9% were indigenous in the study and target populations, respectively). Importantly, in our study, to conserve the anonymity of participants, Facebook accounts will not be linked to the questionnaire.

Questionnaire Development

The questionnaire was developed using the Research and Electronic Data Capture (REDCap) (Vanderbilt University) tool hosted internally at the Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM), which will also be used to deploy and manage the questionnaire. REDCap is a secure application that provides an interface for data entry, audit trails for tracking data export and analysis, automated data export to various statistical software, and the ability to import data from outside sources [59]. All data will be collected anonymously using the REDCap tool, and answers will not be attributed to any individual.

The questionnaire was developed based on a previous, brief consultation questionnaire that the principal investigator (PI) had developed on the subject of youth experiences of being referred to mental health services in Canada and their point of view on the use of a Web-based self-referral tool for mental health services before obtaining funds for this project. Building on this consultation questionnaire, the current version of the questionnaire was further developed through a literature review and discussion between the research team (research assistant, PI, and a research coordinator in the PI's laboratory). Following this, a more systematic process was used to elicit feedback from 5 reviewers, including research staff and student interns, of

whom 3 were individuals with disclosed lived experience accessing mental health care in Canada. Each reviewer provided individual feedback using a standardized feedback form that was used to revise the questionnaire.

The questions, introduction, and consent form subsequently underwent an extensive translation process from English to French, including forward and back translation involving 4 bilingual members of the research team, of whom 2 are native French speakers and 2 are native English speakers. The questionnaire was then piloted in English and in French with 2 additional members from the PI's laboratory (who are also individuals within the target age range of the population being recruited), and feedback was obtained to enhance readability and the content of the questionnaire, before being finalized. During this pilot study, the questionnaire took between 10 and 15 min, on average, to complete.

Description of the Questionnaire

The questionnaire collects data on demographic information, past experiences accessing mental health service referrals in Canada, and opinions on using technology to facilitate referral to mental health services (see Multimedia Appendices 1 and 2). The questionnaire includes a total of 51 questions; 8 questions are open ended and 43 are closed questions (including 4 with Likert attribute responses and 39 with multiple choice options). To ease the burden of participation, the questionnaire includes skip logic to ensure participants only answer questions that are relevant to their experiences. The questionnaire includes the following structure: screening questions, consent form, demographic questions, past experiences with mental health referrals, and views on a Web-based self-referral tool described in further detail below.

Screening Questions

The questionnaire includes 3 screening questions to assess participants' eligibility to participate in the study. The questions ask about age and whether the individual has accessed or tried to access mental health services in Ontario, Quebec, or British Columbia (see Figure 1).

Figure 1. Questionnaire introduction and screening questions.

Consent Form

Once participants are deemed eligible to participate, a consent form appears that explains the purpose of the study, what the data will be used for, how the data will be stored, requirements of the participant, and any potential benefits or risks incurred by participating, and that consent for participation can be withdrawn at any point before submission of the questionnaire. Owing to the anonymous nature of the questionnaire, participant

information cannot be withdrawn after a participant submits their data, as the researchers will not know which data belong to each participant. Participants are informed of this in the consent form.

Demographic Questions

A total of 15 demographic questions (3 open ended and 12 close ended) are included in the questionnaire. A series of 7 questions ask participants about their age, gender, level of education, transgender status, immigration status, and ethnicity. Age is asked at the beginning of the questionnaire to determine eligibility to participate in the study. Owing to the complex nature of the topic, the question about ethnicity is a close-ended question followed by an open-ended option that invites participants to self-report their ethnic identity. A series of 7 questions ask participants about their age, location, vocational status, living situation, annual household income, and length of stay in Canada (if not born in Canada). These questions are asked in relation to their status when participants first accessed or tried to access mental health services in the past 5 years.

Past Experiences With Mental Health Referrals

A total of 28 questions (3 open ended, 3 Likert, and 22 close ended) ask participants about past experiences accessing mental health services and referrals. Questions ask about the first-time participants accessed or tried to access mental health services in the past 5 years, including the type of mental health concern that prompted help seeking, the first person they approached for help, and whether mental health services were actually received for the concern or not. If participants received mental health services they are then asked for information about their experiences with the first mental health service provider they contacted, including questions about the setting of the service, the role of the professional contacted (ie, doctor and psychologist), the type of service received, who recommended the first contact to the participant, the steps the participant took to access the first contact, the method of contact (including forms), wait times, obstacles, satisfaction with the referral process, and whether an additional referral to a second mental health service provider (second contact) was provided. If a referral to a second contact was provided, participants are then asked for similar information as above, up to a maximum of 2 contacts. Finally, participants will be asked for information about their overall pathway to receiving appropriate mental health services, including number of contacts, length of time, and overall satisfaction. Participants who sought help but did not actually receive mental health services will only be asked about the obstacles that kept them from receiving mental health services.

Perspectives on Using Technology to Facilitate Referral to Mental Health Services

The last section of the questionnaire includes a series of 4 questions (3 open ended and 1 Likert) that ask participants about their perspectives on using technology to facilitate referral to mental health services. Questions cover topics such as receptivity to using technology to facilitate referral, including potential benefits and concerns and recommendations related to this approach.

Follow-Up and Compensation

Collection of Personal Information

After completing the questionnaire, participants will have the option to provide their contact information, including their first name, email address, and phone number. If participants choose to provide contact information, it will be used to update participants on the results of this study and invite them to future studies and activities. Participants will also have the option to be entered into a lottery to win one of three Can $100 (US $74.96) gift cards on completion of the questionnaire. Participants do not have to agree to receive updates or agree to be invited to participate in future studies to enter the gift card draw. Contact information will be collected using a separate form, so any personal information cannot be linked to the data provided in the Web-based questionnaire.

Concern for Welfare

Mental health can be a sensitive topic, and our questionnaire has the potential to trigger emotional reactions. In the informed consent section of the questionnaire, we will mitigate this risk by warning participants that the questions might be of a sensitive nature, and participants will be assured that they can skip any question that they do not feel comfortable answering. We will also provide resources for free online supports, and a list of resources will be offered at the end of the questionnaire for any participant who may feel the need to speak with someone on completion of the questionnaire.

Data Storage

All data will be stored on secure internal servers at the CRCHUM and will be directly downloaded from the REDCap tool and stored on a password-protected computer in a locked room at the CRCHUM. Data will be stored for 10 years at the CRCHUM before they are destroyed. The 10 principles outlined in the Personal Information Protection and Electronics Document Act were considered throughout the development of the methodology to ensure the proper handling of the personal information collected in the study [60].

Results

Current Progress

This study has been approved by the ethics review board at the University of Montréal Hospital Research Centre (project #18.255) and additionally received approval from the ethics review board at McGill University (project A04-B19-19B). The recruitment and data collection phases are estimated to be initiated in January 2020 and to be completed by May 2020.

Data Analysis Plan

Data will be analyzed and summarized in a final report of the findings but will remain anonymous and nonidentifiable. Quantitative data will be analyzed using R statistical software (Lucent Technologies, Murray Hill, NJ). R is a free statistical computing language developed at Lucent Technologies (formerly AT&T and Bell laboratories) [61]. Simple descriptive statistics (eg, mean, standard deviation, and frequencies) will be used to analyze demographic data and data from close-ended

and Likert questions. For example, we will report on the number and percentage of the total participants who identify their gender as each of the following: *Male*, *Female*, *Non-Binary*, *Other*, and *Prefer not to say*. Open-ended questions will be analyzed using descriptive content analysis. Specifically, a manifest analysis methodology with an inductive coding system will be used to identify and categorize qualitative data from open-ended questions [62]. In manifest analyses, researchers describe reported answers, often staying close to and using words given in the original text [62]. A manifest analysis was chosen because of the anonymous nature of the questionnaire, as it would be difficult for the researchers to interpret and ascribe meaning to the given answers without certain contextual clues that might be present in other qualitative data collection methods (eg, vocal tone in interviews or focus groups). Using inductive coding, we will create codes for the categorization of data during analysis, as opposed to using predetermined codes [62]. The flexible and data-driven nature of inductive coding is preferable, considering the heterogeneity of the survey sample and the potential for unanticipated themes to arise in the data. At least three members of the research team will be involved in the content analysis process. We also plan to quantify key topics identified by participants, for example, in the form of frequencies expressed as percentages. Themes identified in the descriptive content analysis will be used to supplement and support quantitative data regarding young people's experiences of referral pathways and views on the use of Web-based technology to facilitate referrals. Logistic regression or chi-square tests will be used to explore whether any sociodemographic differences exist in mental health service use, and satisfaction with mental health care services depending on the nature of the data collected. For example, we will analyze whether there are any significant differences between genders ($P<.05$) in the number of participants that indicate they accessed mental health care services for their concerns.

Discussion

Principal Findings

The results of this survey will help expand knowledge about the accessibility of mental health services in Canada. Specifically, the results will provide insights into the referral processes and pathways experienced by youth, including those who may not yet have received appropriate assessment and care. This study will build on previous pathways to youth mental health services research that has primarily focused on youth experiencing first episode psychosis [10,24,35,36,63-68]. Our results will help create a more comprehensive understanding of the mental health referral experiences of young Canadians.

In addition, although previous research has indicated that youth who self-refer are likely to meet diagnostic thresholds for mental illnesses [69] and that electronic referral systems can increase the use of appropriate mental health services in youth-centered settings [29], limited research exists on the perspectives of youth in using technology to facilitate the process of referral to mental health services. Their views on this topic are important to ascertain, especially given that research has shown that the level of receptivity young people have with using technology in relation to mental health care varies depending on the type of service that is being proposed to be delivered via technology [32,33]. In addition, studies show that youth have reported hesitations or challenges with Web-based mental health services, including limited knowledge about internet search strategies, concerns about the way information is presented online (particularly the validity or quality of information and comprehension of the information), lack of interest, lack of time, cost of internet access, the need for more information on e-mental health services, and concerns about privacy online [31,70]. However, these studies address e-mental health services more generally or cover other types of e-mental health interventions, and thus, there remains a need for research on youth concerns specific to the use of technology to facilitate referrals.

Implications for Improving Services

The knowledge gained from this study will help inform the improvement of the referral process for Canadian mental health services. Information collected regarding the mental health concerns that youth report seeking help for, the pathways and processes that youth experience when seeking help, and the barriers that youth commonly face during the referral process can be used by mental health services to help improve their accessibility for young people. In addition, if the results of this study reveal important sociodemographic differences in satisfaction with referral pathways and access to appropriate services, such information can be used by mental health services and Canadian public health agencies to prioritize addressing such determinants to reduce the barriers that certain youth may face in accessing mental health care. If youth further indicate that they are open to and likely to use a Web-based system to facilitate referrals to mental health services, health services and programs can work toward incorporating technology in their referral process.

Implications for Future Research

Although this study includes some qualitative questions about the mental health referral experience for youth, more in-depth opportunities to explore the topic of referral may be warranted through interviews and focus groups. In particular, if this study identifies common themes among answers to qualitative questions after analysis, these themes may be identified as essential topics to explore in greater detail through qualitative methodology.

Strengths and Limitations

This study benefits from the data collection instrument, participant eligibility criteria, and recruitment method. We chose a Web-based survey design because of the benefits that this survey method offers, especially for data collection on sensitive and stigmatized topics such as mental health [71]. Owing to the high levels of stigma that surround mental illness, some individuals may be more comfortable sharing their experiences using an anonymous tool such as a Web-based questionnaire [14,71,72]. Confidentiality and privacy are always concerns in an online environment, especially for sensitive information such as personal mental health experiences [73]. The anonymous nature of the Web-based questionnaire instrument minimizes

the risks related to privacy and confidentiality for participants. Although there is always the possibility of interference from third parties in online environments, hosting the questionnaire on a secure server minimizes the risk of such interference.

In addition, past studies related to pathways to mental health care have primarily sampled from clinical populations who have successfully accessed services [24]. Our inclusive eligibility criteria ensure that we will be able to gather information from individuals who do and do not successfully access mental health services to better understand the experiences and obstacles faced by a broader range of youth. Finally, given the ubiquitous nature of Facebook use among young people [55], recruiting participants via Facebook allows us to access portions of the target population who we might not be able to access using other recruitment methods such as email listservs. Importantly, many of the targeted recruitment pages on Facebook (ie, university, high school, and CEGEP groups; community mental health organizations; and general youth-oriented pages) are publicly available, meaning individuals do not need to have personal Facebook accounts to access the posts on these pages. The public nature of these pages additionally increases our ability to access hard to reach portions of the target population.

There are various limitations to our study. Sampling bias is a concern with using convenience sampling methods. It is possible that the sample we collect will be systematically different than the general population of Canadian youth, which may cause our study to be biased and will limit the generalizability of our results. We will monitor this throughout the recruitment process and adjust our study advertising strategy accordingly. For example, given that immigrants, refugees, and members of visible minority and ethnocultural groups often face accessibility issues when it comes to mental health services, we want to ensure that we are appropriately sampling from these groups. Previous research has found that targeted Facebook advertisements have been successful in recruiting significantly greater proportions of foreign-born participants than general advertisements [59]. Therefore, we will target recruitment through Facebook pages that are geared toward these groups (eg, Facebook pages intended for international students on university campuses and cultural groups). Furthermore, we will only be sampling from 3 provinces in Canada. As health care is managed at the provincial level, there might be some important differences in the pathways to mental health care between provinces. The results from our study, therefore, might not reflect the experiences and perspectives of youth living in other provinces in the country. In addition, social desirability bias, in which participants answer questions in a way that they believe are socially acceptable, rather than telling the truth, is also a concern in survey studies and could limit the validity of our results [74]. Low response rates are another common concern with Web-based survey studies, and there is the potential that we will have slow or low response rates for our questionnaire. We will mitigate this possibility by increasing our selection of Facebook pages over time or by using alternative advertisement strategies (eg, paid Facebook advertisements) to meet our desired sample size.

Conclusions

Overall, this study will contribute to the knowledge of youth experiences of referrals to mental health services in Canada. Our results will expand on previous studies of pathways to care and can be used to inform the improvement of referral policies and procedures in youth mental health service delivery. A better understanding of young people's perspectives on referral processes and their opinions on how these processes can be improved are essential to providing appropriate and timely access to mental health care.

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Authors' Contributions

SL conceived the original idea for the study including the overall objectives, methodology, and the first draft of the questionnaire. SL and DS drafted the study protocol and the manuscript; RF contributed to the study methodology, the development of the questionnaire, and the drafting of the manuscript. All authors reviewed and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Web-based questionnaire samples.
[DOCX File , 309 KB - resprot_v9i3e16945_app1.docx]

Multimedia Appendix 2
Questionnaire.
[DOCX File , 80 KB - resprot_v9i3e16945_app2.docx]

Multimedia Appendix 3
Peer review reports from Mitacs Accelerate.
[PDF File (Adobe PDF File), 241 KB - resprot_v9i3e16945_app3.pdf]

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Abbreviations

CEGEP: Collège d'enseignement général et professionnel
CRCHUM: Centre de Recherche du Centre Hospitalier de l'Université de Montréal
DUI: duration of untreated illness
DUP: duration of untreated psychosis
e-mental: electronic mental
PI: principal investigator
REDCap: Research and Electronic Data Capture

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Protocol

A Mobile App for Thyroid Cancer Patients Aiming to Enhance Their Quality of Life: Protocol for a Quasiexperimental Interventional Pilot Study

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Abstract

Background: Thyroid cancer (TC) is one of the fastest growing cancers all over the world. Differentiated thyroid cancer (DTC) is the most frequent subtype of TC. When appropriate treatment is given, the prognosis for the patient is generally excellent. Despite the generally good prognosis of thyroid carcinomas, the symptoms may range from emotional to physical discomfort, depending on the thyroid hormone status, which can severely affect the patient. Moreover, the diagnostic and therapeutic procedures that DTC patients have to undergo, such as thyroidectomy and radioiodine therapy, significantly affect their mental and physical well-being. Often, the physician only addresses the favorable prognosis of DTC compared with other cancer types and neglects to assess issues related to the quality of life (QoL) of the patient; this was the reason we decided to design a mobile app for DTC patients and their caregivers.

Objective: The aim of this study is to research the feasibility and applicability of an mHealth app tailored to DTC patients, as reflected in their QoL. The main features of the developed app offer access to useful information about thyroid cancer, diagnostic tests, and the appropriate therapy administered to DTC patients.

Methods: Based on the existing literature, we created an up-to-date information platform regarding TC and especially DTC. In order to develop an effective app that can be implemented in current health care, we designed a section where the patient and physician can keep a medical record in an effort to enable access to such information at any time. Finally, we designed a user-friendly notification program, including pill prescription, follow-up tests, and doctor visit reminders in order to equally facilitate the lives of the patient and physician.

Results: Having developed this mobile app, we aim to conduct a pilot quasiexperimental interventional trial. Our intention is to enroll at least 30 TC patients and assign them to intervention or control groups. Both groups will receive standard care for treating and monitoring TC, and the intervention group will also receive and use the DTC app. TC patients' QoL will be assessed for both control and intervention groups in order to examine the effectiveness of the DTC app. QoL will be assessed through the QoL core questionnaire European Organisation for Research and Treatment of Cancer (EORTC) QLQ-THY34 in combination with the EORTC QLQ-C30 questionnaire through quantitative statistical analysis.

Conclusions: The use of mHealth apps can play a significant role in patient education, disease self-management, remote monitoring of patients, and QoL improvement. However, the main limitation of the majority of existing studies has been the lack of assessing their usefulness as well as the absence of specific instruments to carry out this assessment. In light of those considerations, we developed a mobile app tailored to the needs of DTC patients. Furthermore, we evaluated its contribution to the QoL of the patients by using the EORTC QLQ-THY34 questionnaire, an accurate and safe instrument for the evaluation of the QoL in TC patients, while supporting future planned endeavors in the field.

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KEYWORDS

mhealth; thyroid cancer; application; quality of life; patient-centered medicine; patient education

Introduction

Although thyroid cancer (TC) is a relatively rare neoplasm, accounting for approximately 1% to 5% of all cancers in females and less than 2% in males, it is the most common endocrine malignancy [1]. Furthermore, despite recent observations by Shi et al [2] that TC incidence rates for both sexes have declined since 2009, numerous other studies establish that thyroid gland neoplasms have shown the fastest increasing incidence of all malignancies over the past decades. This epidemiological trend, mostly attributed to overdiagnosis, has also been associated with several environmental factors [3]. According to the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, it is estimated that by the end of 2018 the number of new cases of TC will be 53,990 (3.1% of all cancers), and approximately 2060 patients will die of the disease [4]. Differentiated thyroid cancer (DTC) is the most frequent subtype of TC and includes papillary and follicular types and their variants [5]. When appropriate treatment is given, the prognosis of the disease is generally excellent. Taking into consideration that DTC epidemiological trends and favorable prognosis present a high 5-year survival rate (up to 98.2%) and an unimpaired life expectancy in most patients, it is crucial to ensure the quality of life (QoL) of the patient [6].

Surgery is the primary and most effective therapeutic approach for TC patients. Near total or total thyroidectomy with or without lymph node neck dissection is followed by radioiodine administration where appropriate. Thyroid stimulating hormone (TSH)-suppressive doses of thyroid hormone are administrated. This therapeutic management minimizes the risk of disease recurrence and metastatic spread while enabling accurate long-term surveillance. Systematic and targeted therapy is considered only for a small fragment of TC patients [7-10]. These therapeutic interventions, their preparation, possible complications or adverse events as well as the series of diagnostic and follow-up tests patients have to undergo may severely affect their QoL. TC patients often have difficulty in realizing the ways in which the disease will affect their everyday lives including, among other things, daily levothyroxine administration and frequent appointments with their doctors for diagnostic, therapeutic, and follow-up procedures. These procedures can be quiet stressful resulting in aggravating their mental health, especially in periods of hypothyroidism [11,12]. Moreover, the lack of proper information regarding the type of symptoms the patients will face, diagnostic and therapeutic procedures to which they are about to be submitted, and their impact on their physical and mental health accentuates feelings of isolation, fear, and anxiety [13,14]. Finally, caregivers play a crucial and demanding role regarding the care of TC patients, since they do not only exchange medical information with health care providers but also closely experience the disease of their loved ones to such an extent that they are often considered as a unit of care and may themselves experience mood disturbances and psychological impairment [15,16].

Proper patient education is of great importance as it ensures that the patient understands the potential side effects of their treatment. A patient who is informed and aware of all the side effects of the respective treatment is likely to be more tolerant of the treatment than an uniformed one [17]. It is also crucial for them to understand the seriousness of the potential side effects in order to comply with physician recommendations to help prevent or minimize radiation-induced sequelae. Educational programs are required to adequately prepare not only patients but also health care professionals for future care. In particular, recognition of the totality of the cancer experience and the need for both staff and patient education were illustrated by Stajduhar et al [18]. If health care professionals were providing comprehensive cancer care, psychosocial and physical needs would be equally addressed. Fulfilling these needs requires a collaborative approach among patients and health care professionals, and more modern approaches such as mobile health (mHealth) are also of great assistance [18].

The use of mobile phones and mHealth apps is constantly proliferating [19]. The increasing use of health apps has been documented among health care professionals, younger and higher educated patients, and the general public. Apps can play a significant role in patient education, disease self-management, remote monitoring of patients, improving patient and caregivers QoL [20]. There have been many papers and reviews on the topic of mHealth. Even in cases of chronic diseases, such as cancer, patients expressed their preference regarding the use of apps. In a recent editorial for a relevant special issue, Coughlin [21] outlined the proliferation of mHealth by exploring institutional guidelines for smartphone development in the United States and other countries [22,23]. Previously, Bender et al [24] found 1314 potentially relevant apps, out of which 309 met the selection criteria for their systematic review on smartphone apps for the prevention, detection, and management of cancer. Eleven apps provided tools to support the management of cancer. The majority of these apps (n=7) were

not specific to a particular cancer type, and none of them was tailored for TC. These apps offered a combination of tools to assist the management of medical appointments, self-monitoring of symptoms, or medication consumption. The authors concluded that despite the existence of hundreds of cancer-focused apps, there is a lack of evidence regarding their utility, effectiveness, and safety [24]. Seiler et al [25] concluded, in a rather rigorous systematic review and meta-analysis, that very few mHealth apps targeted fatigued cancer survivors, however they revealed some rather interesting incidental results. First, most of the apps targeted healthy lifestyle maintenance, emphasizing dietary and physical activity goals; second, it was assessed that in most cases results were positive toward these goals [26-29]. Furthermore, in a systematic review/position paper, Nasi et al [30] succinctly outlined the mHealth environment. In short, they summarized the core feature that makes mHealth prolific, namely the flexibility of information availability in a wireless network. This was made apparent by the truism "a wireless network may be not mobile, but a mobile network must be wireless" [31]. Furthermore, this work managed to defined the key direction for mHealth apps which is not treatment itself but empowerment, information, and improvement in QoL for the patient [30]. In this study, it was also made clear that most of the literature in mHealth provided positive results and focused in chronic diseases and specifically cancer. More than a third of the surveyed literature (14/38, 37%) comprised cancer subtopics such as chronic cardiovascular, pulmonary, and metabolic diseases (diabetes, asthma, obesity). Given adequately established interest in the field, a 4-dimensional framework for mHealth performance was introduced: efficiency, effectiveness, clinical effectiveness, and QoL [30]. Based on this framework, the aforementioned literature, and the fact that TC is a disease that is radically treated within a relatively short treatment time, our focus in this study was the fourth dimension, QoL. In this context, we designed and developed the first iteration of DTC, an mHealth app dedicated to DTC patients; in this study we aim to examine its effectiveness in patient QoL. Since the main limitation of most research is the lack of validated instruments for the evaluation of mHealth apps utility and effectiveness, the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-THY34 questionnaire was used in order to yield accurate conclusions regarding the effectiveness of our intervention.

Methods

Study Aims

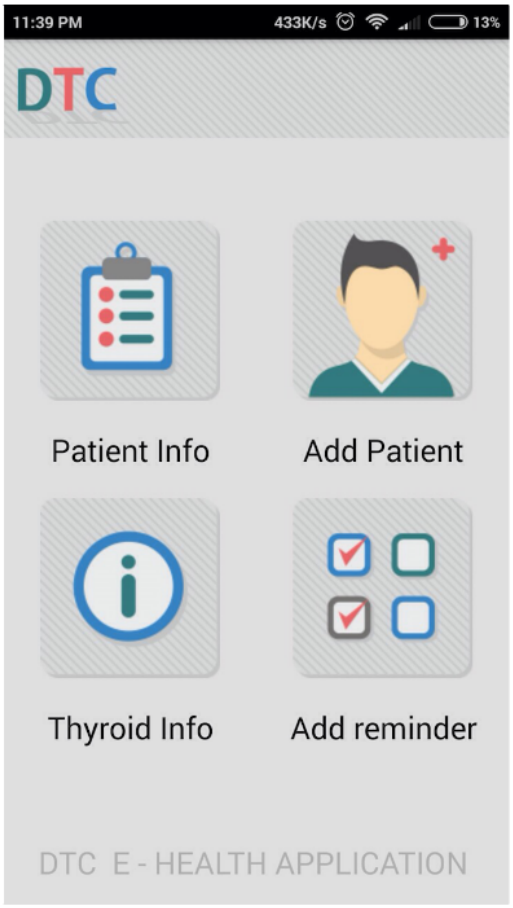
The primary objective of our study is to evaluate the design and implementation of an mHealth app tailored to DTC. This app aims to assist patients undergoing treatment for the management of malignant thyroid neoplasms by educating and motivating both them and their caregivers, facilitating maintenance of their medical record, and organizing their medication and appointments with their doctors. In order to examine the effectiveness of our intervention, we intend to conduct a quasiexperimental study assessing impact of the intervention on patient QoL as recorded in the EORTC QLQ-THY34 and EORTC QLQ-C30 questionnaires to reach accurate conclusions regarding the effectiveness of our app.

App Development

Content of the App

Our intention is to create an easy-to-use, accessible, and credible DTC app for patient QoL (Figure 1). We incorporated 4 different sections, with a specified function for each one of them. These included the core, informative Thyroid Info section which contains information regarding the thyroid gland and TC, especially DTC. The Add Patient and Patient Info sections enable both the doctor and patient to enter or view demographics and clinical data in order to keep an accessible medical record. Finally, the Add Reminder section includes an appointment organizer and pill reminder. The latter serves as an assistive tool to remind the patient to take daily levothyroxine and get properly prepared by undergoing thyroid hormone withdrawal or administering recombinant (rh)-TSH for diagnostic or therapeutic purposes.

Figure 1. Screenshot of the DTC app home screen showing features Thyroid Info, Add Patient, Patient Info, and Add Reminder.



The importance of proper information and education on TC patients' effective disease management and therefore their prognosis, psychological status, and QoL is undisputed [17,18]. Given the amount of mostly nonvalidated and at times erroneous online information on thyroid malignancies, the majority of TC patients are rather misinformed and confused regarding their disease's progress and the diagnostic and therapeutic procedures they must undergo. In this context, we intend to create and provide an educational tool for our patients, available any time through their mobile device (phones, tablets, etc). After reviewing the literature, focused mainly on guidelines for the management of TC, we developed an up-to-date, accessible, and easily understood information section, Thyroid Info, in clear and plain language (Figures 2 to 4). We conducted a literature search between September 2015 and July 2016 to review all aspects of thyroid function and neoplasms and their management from diagnosis to treatment and follow-up using the following electronic databases: PubMed, Highwire, and Google Scholar. The keywords and terms used in the literature research were: "hormones," "thyroid gland," "thyroid cancer," "epidemiology," "risk factors," "management," "diagnosis," "treatment," "radioiodine," "adverse effects," "guidelines," "TC," and "pregnancy." These terms were used individually and in combination with the following links: or, and. Additional articles and reports were accessed via citations in reviewed papers that appeared in the original research. Our final database contains 71 publications. Our app is directed toward Greek patients, therefore we chose to use Greek in the app's text. Thyroid Info consists of chapters on hormones and endocrine glands, thyroid gland, thyroid gland nodules, malignant neoplasms of the thyroid gland, management of TC, radioiodine treatment of DTC, follow-up of TC, TC and pregnancy, and the references we used. We structured Thyroid Info taking into consideration the respective literature and the disease issues that affect our patients. Each chapter is divided into several questions, allowing the patient to select the question that best matches their needs. Our text contains figures and tables rendering access to information easier and more targeted.

Figure 2. Thyroid Info feature comprises 8 chapters and references. Each chapter contains several questions so the patient can have the option to choose the topic they are interested in each time.

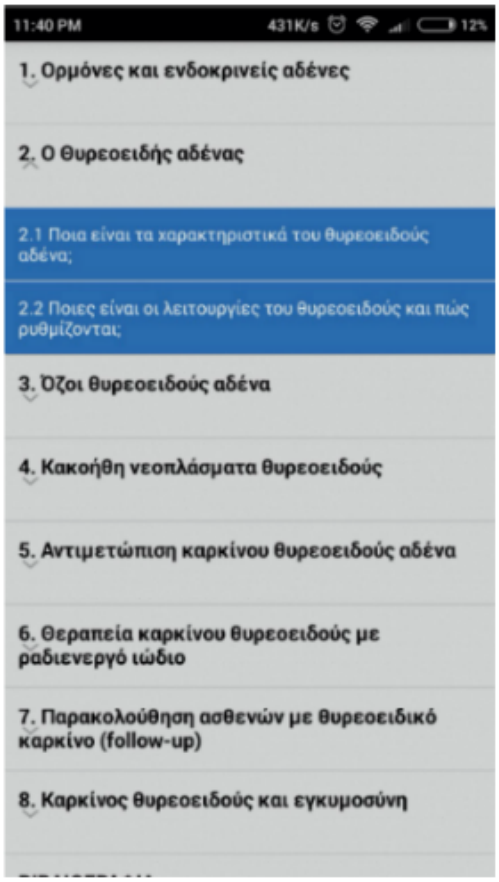


Figure 3. Screenshot of Thyroid Info feature content.

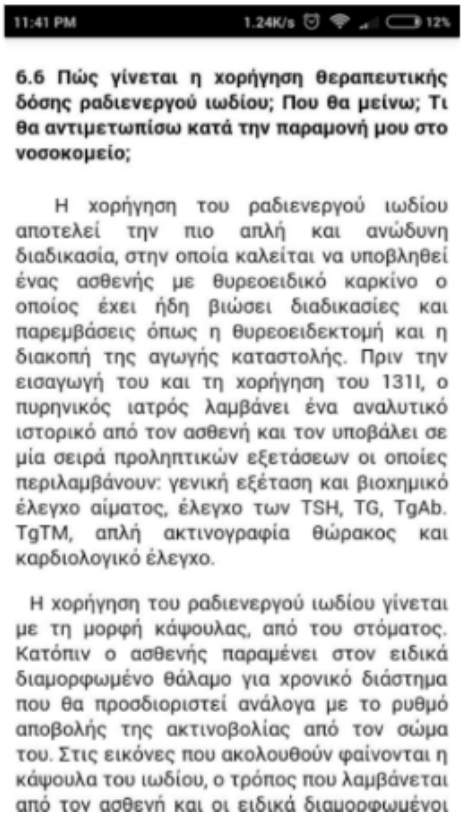
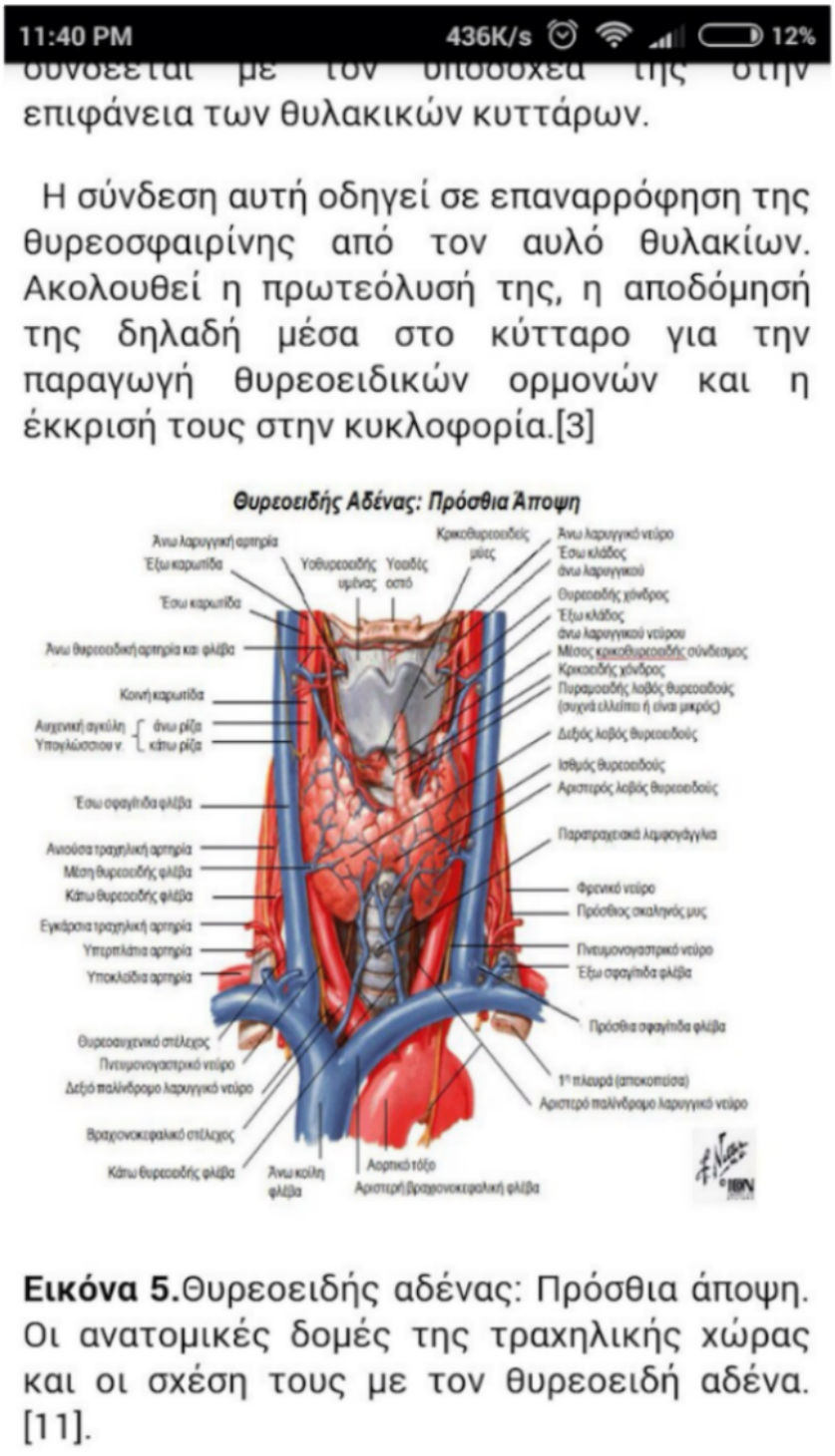
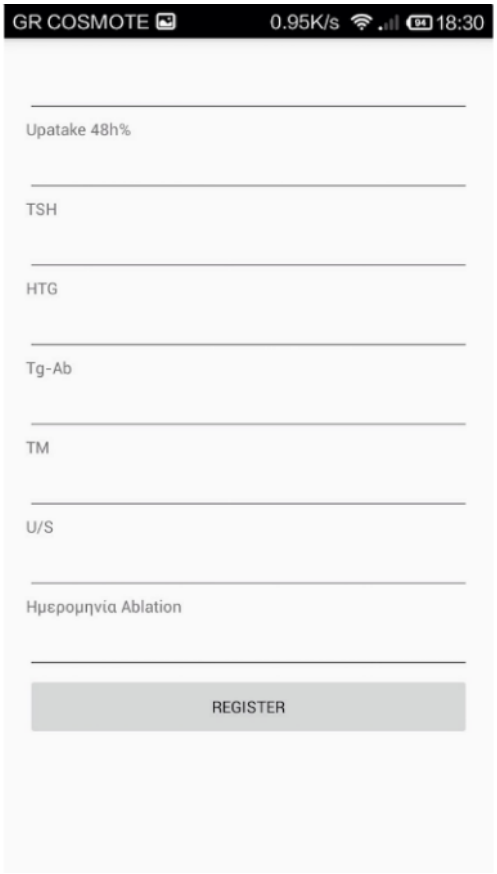


Figure 4. Screenshot of Thyroid Info feature content.



In the Add Patient panel, the patient or physician can add relevant demographic and clinical information and the results of any follow-up tests (Figure 5). Information includes registration number, name, surname, username, password, email, code, phone number, address, gender, date of birth, age at diagnosis, date of surgery, name of surgeon, histology, maximum diameter of the largest TC foci, number of foci, thyroid gland lobe that TC was detected, invasion, number of excised lymph nodes, number of excised lymph nodes with metastases, stage, date of postsurgical remnant thyroid gland scintigraphy, date of radioiodine ablation, days between surgery and radioiodine ablation, preparation (thyroid hormone withdrawal or rh-TSH administration), I-131 scintigraphy, 24 hour uptake of I-131, neck-thyroid bed ultrasound, and levels of TSH, thyroglobulin, thyroglobulin antibodies, and thyroperoxidase antibodies. The Patient Info platform will serve as a medical record, containing patients' registered data, available with the use of username and password set by the patient (Figure 5). The doctor or administrator has the option of adding new patients and their data from their personal computer.

Figure 5. Screenshot of an Add Patient page. Registration can be done either in English or Greek.



The Add Reminder panel includes appointment organizer or reminder. This section was designed to serve as an appointment reminder and levothyroxine administration alert, enabling proper preparation for diagnostic and therapeutic procedures. The reminder will inform patient regarding when to withdraw thyroid hormone medication or rh-TSH injections in order to receive radioiodine for diagnostic or therapeutic purposes. Given that the volume of notifications received by users can be significant, we decided to use only a small number of notifications. When a patient visits the doctor, they can jointly arrange the next visit and prescribed medication and store this information in the app. In this context, we used Google's Calendar API (application programming interface) to enable an organized display of the patient's appointments and medication plans. The patient receives notifications for appointments a few days before the appointment and on the very day of the appointment. Regarding the medications, notifications are also used as a reminder. To best accommodate the needs of each patient, notifications can be edited.

App Design

The app was designed and developed in the Android Studio Development environment. The architecture used in this specific research study is a basic mobile architecture based on easy-to-use interface, system security, and data integrity. The app is easily deployable on any Android mobile platform, and plans are underway for the development of an iOS app. This app aims to provide a simple and intuitive interface, access to medical information (written by specialist doctors), and the ability to enable, store, and retrieve patient data (demographic and medical) in and from the cloud. The app also provides information to the user through notifications.

It is well known that the health care sector is extremely sensitive and has specific data protection requirements. Designing and developing a mobile app that contains sensitive patient data requires adherence to strict rules necessary to prevent unauthorized access to private information or personal data on the patient. It is also important to maintain updated log records for system failures. In view of the above, security has been one of our major concerns when designing and developing the DTC app. Data confidentiality and integrity has been ensured, while user and app authentication have been verified. This is the reason why we opted for cloud storage. Every data structure we store to the cloud is cryptographed. Tools such as hash functions, digital signatures, and symmetric and asymmetric keys are needed to achieve these features. Apart from that, we work on integrating the HL7 standards for the transfer of clinical and administrative data between software apps used by various health care providers.

Generally, the app design was geared to support the patient during treatment and management of DTC by informing and educating them. Furthermore, it was designed to empower them by keeping an up-to-date and easily accessible medical record while respecting their privacy, and providing reminders for medication and doctor appointments. Overall, the DTC mHealth app aims to become a key component in contributing to the improvement of patient QoL.

Results

Study Design

For this interventional study, we chose a quasiexperimental design to examine DTC patients' QoL. The quasiexperimental approach was selected instead of the more rigorous randomized controlled trial (RCT) for two reasons. The first was the exploratory nature of this research since it is aiming to scope the features of such an app specifically pertaining to TC. The second is the necessity for credible but rapid results in order to iterate on the app itself. An RCT type of study is planned for a future iteration of the DTC app.

The main weaknesses of most of the previous studies regarding mHealth are the lack of assessment of the feasibility, usefulness, and effectiveness of mHealth apps and the lack of specific instruments for this assessment. As far as thyroid-related problems and functioning are concerned, only a few thyroid-specific QoL questionnaires have been developed. Moreover, we are informed assessments have been done largely using generic instruments. The EORTC created a TC-specific module to be used as a supplement to the QoL core questionnaire EORTC QLQ-C30 (phase I and II of the EORTC module development process) [32,33]. In these previous phases, items were derived from a longer list of QoL issues that could be relevant for TC patients. Phase III of the instrument development, according to the EORTC module development guidelines published in 2017, resulted in the EORTC QoL module for TC (EORTC QLQ-THY34) currently at the final phase IV validation which will be used in our study [34]. We acknowledge that using the not-yet-validated version of the EORTC THY34 is both a strong and a weak point of our study. By using the EORTC QLQ-THY34 questionnaire in combination with EORTC QLQ-C30 questionnaire, our intention is to reach safe and accurate conclusions given that both the app and questionnaire are tailored for TC [35].

Participant Recruitment

Patients will be recruited at the 3rd nuclear medicine department of Papageorgiou Hospital, Aristotle University of Thessaloniki, Greece, and the nuclear medicine department of Theagenio Cancer Hospital, Thessaloniki, Greece. A formal protocol of the study has been submitted and approved by the ethics committee of the Aristotle University of Thessaloniki (no 398/11.12.2017) that shall include written consent from the patients to use their pseudonymized data in a statistically aggregate manner while respecting their privacy. We aim to enroll at least 30 patients into two groups without randomization. The first group will be given the DTC app, while the rest of the patients will receive oral instructions and informative printed material. Both groups will undergo standard diagnostic and therapeutic procedures the DTC patients receive. The inclusion criteria for patient participation in the intervention group are having undergone thyroidectomy, diagnosis of DTC, radioiodine treatment medically indicated, possession of mobile phone or tablet supporting Android software, and the ability to use Android apps. The control group will have similar demographic and clinical characteristics.

Data Collection

For both groups there will be recorded demographic and clinical characteristics. As far as the intervention group is concerned, the data will be recorded by the nuclear medicine physician either via the DTC app on the patient's mobile device or the physician's personal computer. Following that, data will be exported in Excel (Microsoft Corp) files and stored in SPSS Statistics 25.0.0.0 (IBM Corp). Control group data will be recorded in Excel files and then stored in SPSS Statistics 25.0.0.0. Patients of both groups will be given the EORTC QLQ-THY34 and EORTC QLQ-C30 questionnaires to examine their QoL. This is the only instrument in the native language of the patients, developed by the EORTC QoL Group. The EORTC QoL module for TC consists of 34 items and is currently being pilot-tested for the final international field validation in phase IV. It will be available in the following languages: Arabic, Chinese, Dutch, English, French, German, Greek, Hebrew, Hindi, Japanese, Italian, Polish, Portuguese, and Tamil [32]. The module has been developed according to the EORTC guidelines and approved after formal review. The EORTC QLQ-THY34 is still under development and is thus being shared only with those groups willing to provide data relevant to evaluating its psychometric properties. In this framework, we received authorization to use the EORTC QLQ-THY34 questionnaire, assuring our compliance with the EORTC's rules. Considering that the EORTC QLQ-THY34 questionnaire is formally translated and validated in Greek, it is appropriate to argue that it constitutes the most accurate and safe instrument to evaluate QoL in TC patients, thus ensuring the validity of our results on the effectiveness of the DTC app.

Data Analysis

All data will be downloaded and stored in SPSS Statistics. Descriptive statistics will be used to characterize the overall sample, each condition, and study acceptability and demand. To examine preliminary differences in feasibility, we will use chi-square tests, Fisher exact tests, and nonparametric Mann-Whitney *U* tests for nonnormal data at the level of significance of $P<.05$ as appropriate.

Clinical evolution questions and diagnostic markers shall be checked for possible psychological effects of better information (eg, question 34: Have you experienced any throat ache?). However, the respective analysis shall focus on questions describing both the emotional disposition of the patient (eg, Did you feel distressed or irritated?) and their perceptions about the quality of care provided (eg, Did you feel well supported by your doctors?). The hypothesized scales assessed for our patients through the questionnaires are anxiety, body image, cramps, discomfort in the head and neck, dry mouth, fatigue, hair, impact on job or education, joint paint, neuropathological problems, restlessness, shoulder functioning, social support, swallowing, temperature tolerance, voice, and worries about important others.

Discussion

Mobile Health in the Service of Thyroid Cancer Patients

TC is a malignant neoplasm with excellent prognosis in cases where appropriate treatment is given. The standard therapeutic interventions, their preparation, possible complications or adverse events, and numerous diagnostic and follow-up tests that TC patients must undergo may severely affect their QoL. Evidence-based medicine, a more personalized patient approach, novel management strategies such as the use of rh-TSH, and proper patient education are intended to ensure QoL. The use of mHealth apps—currently proliferating—can play a significant role in patient education, disease self-management, and remote monitoring of patients, thus resulting in an improvement in their QoL. There have been already several papers and reviews on the topic of mHealth addressed in conjunction with chronic diseases and, more specifically, with cancer. However, the key weakness of most of the studies to date has been the lack of assessing their usefulness and specific instruments used in the assessment. In this context, we attempted to develop a mobile app tailored to DTC patients and evaluate its contribution to patient QoL by using the EORTC QLQ-THY34 questionnaire. To the best of our knowledge, the QLQ-THY34 questionnaire is the most accurate and safe instrument to evaluate QoL in TC patients and is also under validation and translated in Greek, which ensures the validity of our results on the effectiveness of the DTC app.

The work described here is a precursor to a planned RCT endeavor on the impact of such solutions on the overall QoL aspect of cancer survivorship, an active and open research endeavor. This work aims to assess how effective the app is regarding the improvement of QoL of these patients (soon to be considered as productive and healthy individuals), evaluate the DTC mHealth solution regarding the patient's access to medical information, and provide moral support during and after treatment. This shall be achieved with validated evaluation instruments through accepted common practices at two of the largest hospitals in Greece. This quasiexperimental study shall provide evidence-based feedback for the iterative refinement of this mHealth solution and support future planned endeavors and research in the field.

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Conflicts of Interest

None declared.

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Abbreviations

API: application programming interface
DTC: differentiated thyroid cancer
EORTC: European Organisation for Research and Treatment of Cancer
mHealth: mobile health
QoL: quality of life
RCT: randomized controlled trial
rh-TSH: recombinant thyroid stimulating hormone
TC: thyroid cancer
TSH: thyroid stimulating hormone

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Protocol

Evaluating Mobile Apps and Biosensing Devices to Monitor Physical Activity and Respiratory Function in Smokers With and Without Respiratory Symptoms or Chronic Obstructive Pulmonary Disease: Protocol for a Proof-of-Concept, Open-Label, Feasibility Study

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a global public health problem, and continuous monitoring is essential for both its management as well as the management of other chronic diseases. Telemonitoring using mobile health (mHealth) devices has the potential to promote self-management, improve control, increase quality of life, and prevent hospital admissions.

Objective: This study aims to demonstrate whether a large-scale study assessing the use of mHealth devices to improve the treatment, assessment, compliance, and outcomes of chronic diseases, particularly COPD and cardio-metabolic syndrome, is feasible. This will allow our team to select the appropriate design and characteristics for our large-scale study.

Methods: A total of 3 cohorts, with 9 participants in each, will use mHealth devices for 90 days while undergoing the current standard of care. These groups are: 9 “non-COPD,” otherwise healthy, smokers; 9 “grey zone” smokers (forced expiratory volume in 1 second/ forced vital capacity ≥0.70 after bronchodilator treatment; COPD Assessment Test ≥10); and 9 smokers diagnosed with Stage 1-3 COPD. Rates of recruitment, retention, and adherence will be measured. Overall, two mHealth devices will be utilized in the study: the AnaMed Original Equipment Manufacturer device (measures distance, energy expenditure, heart rate, and heart rate variability) and the Air Next mobile spirometry device. The mHealth devices will be compared against industry standards. Additionally, a questionnaire will be administered to assess the participants’ perceptions of the mHealth technologies used.

Results: The inclusion of participants started in June 2019. Study results will be published in peer-reviewed scientific journals.

Conclusions: This study will demonstrate whether a large-scale study to assess the use of mHealth devices to improve the treatment, assessment, compliance, and outcomes of chronic diseases, particularly COPD and cardio-metabolic syndrome, is feasible. It will also allow the research team to select the appropriate design and characteristics for the large-scale study.

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KEYWORDS

COPD; mobile health apps; mHealth; smokers; feasibility study

Introduction

Chronic obstructive pulmonary disease (COPD) accounted for 3.2 million deaths globally in 2015 [1] and is the fourth leading cause of death both worldwide and in Kazakhstan [2]. COPD is a heterogeneous condition, with a variety of disease-related phenotypes [3,4], and its main risk factor is cigarette smoking [5]. The chronic airflow limitation that characterizes COPD is caused by obstructive bronchiolitis and parenchymal destruction (emphysema). Pulmonary emphysema is a form of COPD; however, pulmonary emphysema without airway obstruction is common in smokers [6,7]. Smokers with symptoms suggestive of COPD who do not qualify for a diagnosis of COPD based on spirometry are referred to as "grey zone" COPD patients. They have preserved pulmonary function (forced expired volume in 1 second/forced vital capacity [FEV_1/FVC] of at least 0.70 after bronchodilator and FVC ≥80% of the expected value) and respiratory symptoms (COPD assessment test [CAT] ≥10).

Continuous monitoring is vital for the management of COPD. Implementing telemedicine and mobile health (mHealth) innovations has allowed clinicians to intervene in COPD earlier and prevent complications. However, there remain challenges in the form of alarm frequency and response, both of which need to be implemented into the existing workflow [8]. Data flow and workflow processes need to be designed with precision at the outset if telemedicine is to be applied in clinical practice. Telemonitoring using mHealth devices has the potential to promote self-management, improve control, increase quality of life, and prevent hospital admissions [9-13]. Technological advances in mHealth home telemonitoring (electronic health [eHealth]) programs and systems can affect care for patients with COPD [12,14-17]. mHealth devices are an emerging opportunity in clinical studies, and their utility (ie, sensitivity, accuracy, and reproducibility) has previously been assessed for telemonitoring for COPD [14].

Telemonitoring is a promising alternative or adjunct to the provision of traditional health care services in COPD [18]. Although some studies have shown that telemonitoring may improve some clinical outcomes and reduce health care costs [19,20], the effects of telehealth interventions on emergency department attendance, hospital admissions, duration of admissions, health-related quality of life, costs, and mortality remain less certain [18,21-25].

In a recent study of telemedicine in the home setting using multiple activity sensor monitoring equipment in COPD patients, the augmentation of traditional telemedicine methods with motion sensing, spirometry, and symptom diaries appeared feasible [26]. In a literature review (141 randomized trials; n=37,695) of studies of eHealth practices, such as telemetry, telephone calls, or home visits by nurse specialists, most studies were relatively short term (<6 months) and did not yield strong evidence for telemedicine use in the management of chronic diseases [27]. However, the comparison of outcomes in studies using telehealth applications is difficult due to advances in monitoring and communications technology and heterogeneity in the type of monitoring, the disease entity and severity, and the variations in the process of care brought about by the telemedicine intervention [12].

Although peak flow monitoring has been used for at-home detection of asthma exacerbations, and studies in the past have monitored vital signs and symptoms in patients with COPD [28], few studies have attempted to deploy spirometry for home monitoring of COPD [29]. With technical advances, spirometry is increasingly being used to track the progress of COPD over time and to identify acute exacerbations [30-34].

While the number of COPD mHealth devices is rapidly increasing, most have not been validated as clinically effective tools for the management of the disease. In addition to empowering patients and facilitating disease self-management, mHealth offers promising aid to COPD researchers to help them personalize treatments based on patient-specific profiles and integrate symptom occurrence and medication usage with environmental and genomic data. An integrated and targeted practice-managed approach that uses mHealth technologies in primary care settings will be most effective for the early identification, monitoring, and management of chronic diseases, particularly COPD and cardio-metabolic syndrome (ie, combined diabetes mellitus, systemic arterial hypertension, central obesity, and hyperlipidemia). Health information technologies are revolutionizing health care by assisting patients in self-monitoring and decision-making, driving a shift toward a care model increasingly centered on personal use of digital and web-based tools [35-37]. Because there is a dearth of evidence that direct-to-consumer mHealth tools are effective or that they provide accurate disease recommendations, they are not yet widely used in clinical practice. Nonetheless, the preponderance of mHealth is gradually increasing in health care, industry, and as a subject of research [38].

This study aims to investigate the feasibility and utility of using mHealth devices to improve the treatment, assessment, compliance, and outcomes of smokers with and without respiratory symptoms/COPD. It namely means to assess the feasibility of mHealth devices in current smokers with and without respiratory symptoms or COPD by monitoring physical activity, vital signs, and respiratory function, and aims to assess the validity of mHealth devices in detecting vitality parameters as compared to industry standards.

After demonstrating proof of concept in this study, its purpose will be to incorporate mHealth devices into an ongoing 5-year longitudinal cohort observational study to monitor selected vitality parameters and other comorbidities [39]. Specifically, depending on the outcomes of the study, the AnaMed Original Equipment Manufacturer (OEM) device and the Air Next mobile spirometer will be introduced to record data from a randomized subsample of participants in an observational cohort study, including smokers of combustible cigarettes and users of IQOS with HeatSticks.

Methods

Study Design

This is a proof-of-concept, open-label, three-arm, observational, single-center feasibility study. A total of 27 participants in three

cohorts will use the mHealth devices for 90 days while undergoing the current standard of care based on their smoking disease state or lack of disease state. The groups are made up of nine "non-COPD," otherwise healthy, smokers, nine "grey zone" smokers (ie, FEV_1/FVC ≥0.70 after bronchodilator treatment, CAT ≥10; six-minute walk test [6MWT]<450 meters), and nine smokers diagnosed with Stage 1-3 COPD.

In each group, nine participants will be randomly assigned to three types of reminders: three participants will be reminded every morning by text message or phone call and contacted every evening by phone or chat services (eg, Skype, WhatsApp, Viber, texting) to share their experiences and feedback on mHealth device usage; three participants will receive only morning reminders; and three participants will receive neither morning reminders nor evening communication/feedback.

Study Devices and Assessments

Two mHealth devices will be utilized in the study: the AnaMed OEM device (measures step counts, energy expenditure, heart rate, and heart rate variability) and the Air Next mobile spirometry device (Nuvoair AB, Stockholm, Sweden) (measures FEV_1, FVC, and forced expiratory flow).

At the Kazakhstan Academy of Preventive Medicine COPD Center, standard spirometry data are collected by using the BTL-08 SPIRO (BTL Industries Limited, United Kingdom) spirometry system. The spirometer used in this study is tested and continuously standardized with a 3-liter syringe. Quality assessments will be performed throughout the study. The Vive Precision DMD 1003 pulse oximeter is used to get peripheral capillary oxygen saturation (SpO2) and pulse readings at the Kazakhstan Academy of Preventive Medicine COPD center and will be used for comparison to the results produced by the AnaMed OEM device.

Outcome Measures

Safety and tolerability will be evaluated through adverse events (AEs), lung function tests, vital signs, and supportive care medications. Primary measures are defined as rates of recruitment, retention, and adherence as well as safety of the intervention that are common for feasibility studies [40]. Recruitment is defined as the number of potential participants screened for study eligibility versus the number of people who enrolled in the study. Retention is defined as the proportion of participants enrolled who completed the intervention and all study measures. Adherence to the study protocol is determined as the proportion of participants enrolled who had all their mHealth parameters registered every day.

The mHealth devices will be compared to the industry standards. Additionally, a questionnaire will be administered to assess the participants' perceptions of the mHealth technologies used.

Inclusion and Exclusion Criteria

Inclusion Criteria

Participants should meet the following criteria to be eligible to enroll in the study:

- 40-59 years of age
- Current smokers who are smoking conventional cigarettes with a minimum of a ten pack-year smoking history (calculated by taking the average number of cigarettes smoked per day divided by 20 and multiplied by the number of years smoked):
  - Asymptomatic current smokers: no symptoms (CAT<10, 6MWT≥450 meters) and preserved pulmonary function based on spirometry (FEV_1/FVC of at least 0.70 after bronchodilation treatment and FVC ≥80% of the expected value) and respiratory symptoms (CAT ≥10); OR
  - "Grey zone" current smokers: initially preserved pulmonary function based on spirometry, but with clinical symptoms based on CAT (>10) and 6MWT (<450); OR
  - Current smokers with a confirmed diagnosis of COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage I-III).
- Able to use and willing to be trained to use mHealth devices.
- Provide written, informed consent to participate in the study.

Participants will undergo the current standard of care based on their smoking disease states or lack of disease state.

Exclusion Criteria

Participants meeting any of the following exclusion criteria are not eligible to enroll in the study:

- Smokers with COPD exacerbation (defined as a change in symptoms requiring increased doses of current medicines or the prescription of new medicines, such as corticosteroids or antibiotics) that has not resolved at least 28 days before screening. Smokers with COPD exacerbations occurring after screening but before the first study visit should also be excluded.
- Smokers with pneumonia or other respiratory tract infections that have not resolved at least 14 days before screening. Any participant that experiences pneumonia occurring after screening but before the first study visit should also be excluded.
- Smokers with other active respiratory disorders: tuberculosis, lung cancer, significant bronchiectasis, sarcoidosis, bronchial asthma, lung fibrosis, pulmonary hypertension, interstitial lung diseases, or other active pulmonary diseases.
- Any comorbid medical condition that, in the opinion of the investigator, would make participation in the study unsafe or unfeasible. This includes conditions that prohibit completion of exercise testing, such as orthopedic, neurological, cardiovascular, or other conditions that significantly impair standard biomechanical movement patterns and limit the ability to walk/cycle, as judged by the investigator.
- Use of supplemental oxygen therapy.
- Inability to abstain from smoking during the period in which the participant is admitted to the Kazakhstan Academy of Preventive Medicine COPD Center.
- A history of allergies or hypersensitivity to metal, particularly stainless steel.

- Any vital sign indicator, such as hypertension or tachycardia at rest that, at the discretion of the investigator, would make participation in the study unsafe or unfeasible.
- Women who test positive for pregnancy during screening, lactating women, or women planning to become pregnant during the study.
- Participants using assistive devices like walking aids, as these are likely to interfere with physical activity.
- Other patients who are considered ineligible for the study by the investigator.

Sample Size Calculation

The primary endpoints of the study are rates of recruitment, adherence, and retention. To assess the feasibility of the intervention, we plan to recruit 27 participants, which should be enough to get estimates with a sufficient degree of uncertainty. We conservatively predict that 30% of the people invited to participate will be recruited to the study, with a 95% CI of 13-47%. We also assume the dropout rate will be 15%. The accuracy of the estimated retention rate will be at least ±13%. Further, we believe that 70% of participants will adhere to the use of mHealth devices. In this case, the accuracy of the estimate will be at least 17%. All calculations are based on two-way 95% confidence intervals.

Study Procedures

Overview

The study will last 90 days and has two stages. The first stage includes the initial period of using the mHealth devices (Days 1-21) to evaluate the validity of collecting vitality parameters (eg, heart rate, blood oxygenation, steps/motion) on mHealth devices. The main period of use for the mHealth devices (Days 22-90) is the second stage, which aims to evaluate the feasibility of participants using these devices. The schedule of enrollment and data collection is shown in Table 1.

For Table 1, spirometry was performed to diagnose and monitor COPD. Providing of mHealth devices involved the provision of the AnaMed OEM device, the Air Next mobile spirometer, and instructions/review of how to use these tools (print and verbal instructions). For the assessment of the AnaMed OEM device, the participants' SpO2 will be measured at each visit using industry-standard pulse oximetry devices, and for the assessment of the Air Next spirometer, participants will host the mobile spirometer at home for once daily measurements. Measurements will be validated at Study Center visits using an industry-standard device before and after the use of a bronchodilator.

Table 1. Schedule of study activities.

		Device assessment period			Clinical feasibility study period			
	Screening	Baseline visit	Interim visit	Final visit	Interim visits			Final visit
Visit	1	2	3	4	5	6	7	8
Days	1	7	14	21	28	35	56	90
Informed consent process	✓							
Study eligibility and smoking status	✓							
Reviewing medical history (including physical examination and BMI[a] measurement)	✓	✓	✓	✓	✓	✓	✓	✓
COPD[b] assessment test	✓	✓	✓	✓	✓	✓	✓	✓
Spirometry	✓	✓	✓	✓	✓	✓	✓	✓
6-minute walk test	✓	✓	✓	✓	✓	✓	✓	✓
Providing the study requirements handout and explaining the study/visit requirements	✓	✓	✓	✓	✓	✓	✓	✓
Dichotomous questionnaire for visit readiness	✓							
Providing mHealth[c] devices	✓							
Assessment of AnaMed OEM[d] device		Continuous monitoring						
Assessment of Air Next mobile spirometer against standard		Continuous monitoring						

[a]BMI: body mass index.

[b]COPD: chronic obstructive pulmonary disease.

[c]mHealth: mobile health.

[d]OEM: original equipment manufacturer.

Participant Recruitment and Registration

We will employ various nonprobability sampling techniques, including quota and snowball sampling methods, to recruit study participants. The Kazakhstan Academy of Preventive Medicine research team will register patients for each mHealth device. Installation and user guides for each technology used include labeled photographs and written instructions to be used by all

teams and patients during setup. All equipment has been tested before deployment. Training is provided on setup, installation, and use as well as individual checklists, decision trees, and troubleshooting information. The break for charging is at a standard time (20:00) across arms. In addition to direct phone communication, WhatsApp, texting, and other types of messaging systems are used for sharing daily experiences each evening to assist with assessing the level of comfort and address issues with wearing the AnaMed OEM device and using the Air Next mobile spirometer.

Data Collection

Participants will synchronize their wearable device (AnaMed OEM device) and the Air Next mobile spirometry device by signing into their account. Data are stored in a local cloud system. The entire process of data ingestion and storage has been audited, according to ALCOA (attributable, legible, contemporaneously recorded, original, accurate) standards [41]. Whenever a participant synchronizes new activity data to their device cloud, those data would be ingested, processed, and archived, and then aggregated and summarized in JSON data format by summarization services.

Mobile Health Apps

Participants will be provided with a smartphone (iPhone) to perform and visualize measurements and are expected to keep smartphones after the study completion, which will serve as compensation for participation. This is reflected in the Informed Consent Form.

Participants will be guided to assess their health status using the Symptomaster application (HealthCity, Kazakhstan) and zdrav.kz database, which will both also act as tools to determine any potential AEs. The SmartHealth technology Symptomaster helps patients to establish the probable causes of the symptoms of diseases without assistance from a healthcare professional. Using a smartphone, a participant inputs his/her symptoms into the system, which then produces the most likely preliminary diagnosis. After receiving the diagnosis, a patient can refer to zdrav.kz, an online library that contains information about the 1000 most common diseases and their causes and symptoms, in addition to ways to prevent and treat them. These technologies allow a participant to make an informed decision about whether they should seek immediate medical assistance by calling an ambulance or if they should consult a doctor on their next routine visit.

Physical Examination

Physical examinations will be conducted during each visit based on the Stanford Medicine 25 comprehensive clinical assessment to identify clinical signs of abnormalities. This will be in addition to standard anthropometric measurements and vital sign assessments (pulse rate, blood oxygenation, and blood pressure).

Spirometry

The Air Next mobile spirometer will be used by patients to assess respiratory function. To use it, patients must hold their hands on tubular grips or use wrist clamps. Subsequent respiratory efforts allow the determination of inspiratory capacity and FEV_1. Participants are categorized for analysis using the GOLD staging system according to their spirometry, which will be performed before and after two inhalations of salbutamol (0.1 µg per inhalation). Among the criteria needed to make a diagnosis of COPD are deficits in the rate at which one can forcefully exhale. Most experts consider a low ratio (<0.70) of the FEV_1 to the FVC after bronchodilator use to be a key diagnostic criterion. Bronchodilator responsiveness will be considered positive if the participant has a ≥12% change in FEV_1 or FVC above prebronchodilator measurements.

Six-Minute Walk Test

This test measures the distance that a patient can quickly walk on a flat, hard surface in 6 minutes. A 100-feet hallway is needed, and no exercise equipment or advanced training for technicians is required.

Physical Activity

Study participants will measure their pedometer-determined physical activity using the AnaMed OEM wearable devices. While performing the six-minute walk test, participants will simultaneously use the AnaMed OEM and Garmin Vivo (Garmin Ltd, Olathe, Kansas, United States) devices to compare step counts from both devices.

Chronic Obstructive Pulmonary Disease Assessment Test

The CAT is used as an add-on test with existing assessments in COPD (eg, with FEV_1). It is a simple and reliable measure of health status in COPD as it assists patients and their physicians in quantifying the impact of COPD on the patient's health. The CAT is a validated, short (8-item) questionnaire to be completed by patients.

User Experience Questionnaire

Participants will be administered questionnaires to assess their mHealth device use experience. One questionnaire is administered for each device. The questions will address comfort levels and ease of daily vital measurements. The interviews will be conducted by clinical investigators not involved with the quantitative monitoring or analysis to reduce the possibility of bias.

Data Management

All study data will be stored in the information technology Unit of the Kazakhstan Academy of Preventive Medicine. Verification of eligibility was completed via a web questionnaire after participants signed the consent form, and participants will be tracked for the completion of all the study data. If a participant is excluded or discontinues use during or after the study procedures, the specific exclusion or discontinuation reason will be recorded in the database.

All electronic files are encoded using a 128-bit advanced encryption standard and are password protected on a computer with both hardware and software firewalls. The locator form and any documents with identifying information are kept in a separate folder and kept locked in filing cabinets.

Statistical Analysis

For this proof-of-concept phase, access to device-derived data will be enabled via a cloud-to-cloud solution. Graphical and statistical comparisons will be made between the mobile biosensing device–derived data and the data derived from the clinical standards, and between the three different study groups. Descriptive statistics will be used to summarize required qualitative and quantitative study elements (eg, proportion, mean, standard error, median, interquartile range, 95% confidence interval).

The exploratory graphical analysis will be done before the numerical analysis. Histograms and two-dimensional scatterplots of raw data will provide information on the univariate and bivariate distributions of the variables, focusing on the distribution of variables and relationships between the variables (whether there is a linear or nonlinear relationship). Additionally, preliminary graphs will be used to screen raw data by highlighting obvious data errors. Tabulations will be produced for appropriate disposition, demographics, baseline, safety, and clinical parameters.

Statistical comparisons will be made between the mobile biosensing device–derived data and the data derived from the standard diagnostic equipment and methods. Agreement analysis will be performed for both binary and quantitative measures. For binary variables, percent of agreement (overall, positive, and negative agreement) as well as Kappa coefficient, *P* value, and 95% confidence interval will be calculated. For two quantitative measures of a parameter, we will use the Bland-Altman method (Bland-Altman plot and limits of agreement). The Bland-Altman plot analysis will allow us to evaluate a bias between the mean differences and to estimate an agreement interval, within which 95% of the differences between two quantitative methods of measurement are included. Correlation analysis will also be run so that Pearson's correlation coefficient and the 95% confidence interval will be calculated.

The agreement analysis will be done for baseline, 7-day, 14-day, 21-day, 28-day, 56-day, and 90-day visits separately and for the data pooled from all measurements. Within-Subject study design will be accounted for to assess accuracy and precision for a single mobile device. All statistical analyses will be done for all participants and by study group. Additionally, we will compare trends of binary and quantitative outcomes from three study groups wearing mobile devices.

The analysis will be performed using R Statistical Software (R Foundation for Statistical Computing, Vienna, Austria).

Ethics Approval

The Ethics Committee of the Academy of Preventive Medicine approved this study on June 3, 2019. The study has been registered at ClinicalTrials.gov (NCT04081961).

Results

The inclusion of the participants started in June 2019. Study results will be published in peer-reviewed scientific journals.

Discussion

Principal Considerations

The proposed study is the first step in a series of studies aiming to investigate the effect of using mHealth devices to improve the treatment, assessment, compliance, and outcomes of smokers with and without respiratory symptoms/COPD. The results from this proof-of-concept, open-label, device feasibility study will be used to finalize the protocol for a randomized, open-label, placebo-controlled, single-center, two-arm, 12-month study designed to assess clinical feasibility and the effect of this intervention.

Limitations

This study is a small-scale, exploratory, pilot study which is looking to answer questions about whether a larger trial is feasible or not and seeks to get estimates of parameters required for the calculation of the sample size of the main study. The results of this study cannot be used to estimate the effect size of using mHealth devices because the sample size is too small.

Conclusion

Many studies have shown that mHealth tools are effective or that they provide accurate disease recommendations. This study will demonstrate whether a large-scale study to assess the use of mHealth devices to improve the treatment, assessment, compliance, and outcomes of chronic diseases, particularly COPD and cardio-metabolic syndrome, is feasible, and will also allow for the selection of an appropriate design and characteristics for the later large-scale study.

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Authors' Contributions

The study was designed by AS, BZ, DS, IK. AS and BZ drafted the manuscript. All authors critically revised the manuscript and then read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

6MWT: six-minute walk test
AE: adverse event
CAT: Chronic Obstructive Pulmonary Disease Assessment Test
COPD: chronic obstructive pulmonary disease
eHealth: electronic health
FEV_1: forced expiratory volume in 1 second
FVC: forced vital capacity
GOLD: Global Initiative for Chronic Obstructive Lung Disease
mHealth: mobile health
OEM: original equipment manufacturer
SpO2: peripheral capillary oxygen saturation

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Protocol

Brief Intervention to Prevent Sexually Transmitted Infections and Unintended Pregnancies: Protocol of a Mixed Methods Feasibility Study

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Abstract

Background: Sexual well-being is fundamental to physical and emotional health, and the ability to achieve it depends on access to comprehensive sexuality information and high-quality sexual health care from evidence-informed, nonjudgmental providers. Adequate and timely delivery of these components to individuals who are at high risk for sexually transmitted infections (STIs), including HIV, and unintended pregnancies promotes sexual health and mitigates consequences arising from risky sexual behavior. Brief interventions that allow health care providers to improve the information available to clients and motivate and help them to develop risk-reduction skills are seen as efficient ways to improve knowledge, change client behavior, and reduce provider stigma regarding sexual health.

Objective: The aim of the study is to evaluate five aspects of feasibility (acceptability, willingness, safety, satisfaction, and process) of a brief sexuality-related communication (BSC) intervention based on motivational interviewing and behavior change techniques in primary health care settings in low- and middle-income countries (LMICs).

Methods: This protocol outlines a multisite, multiphase study of feasibility of a BSC intervention in primary health care settings in LMICs that will be examined across four phases of the study. Phases I through III involve the collection of formative, qualitative data to examine provider and client perceptions of the feasibility of the intervention, adaptation of the intervention guide, and training providers on how to implement the final version of the BSC intervention. During phase IV, the feasibility of the intervention will be tested in a nonrandomized pre-post test trial where providers and clients will be followed for 6 months and participate in multiphase data collection.

Results: Phase I is currently underway in Moldova, and phases I and II were completed in Peru in late 2019. Results are expected for the feasibility study in 2021.

Conclusions: This feasibility study will determine whether the implementation of brief intervention programs aimed at improving sexual health outcomes is possible in the constraints of LMIC health systems and will add to our understanding of factors shaping clinical practice among primary care providers.

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KEYWORDS

brief interventions; brief sexuality-related communication; sexual health; risky sexual behavior; STIs; unintended pregnancy

Introduction

Sexual health is fundamental to the physical and emotional health of individuals, couples, and families and the social and economic development of communities and countries [1,2]. Sexual health encompasses the human rights of all persons to have the knowledge and opportunity to pursue a safe and pleasurable sexual life [2]. The ability to achieve sexual well-being depends on access to comprehensive sexuality information (knowledge about the risks and benefits and vulnerability to unintended consequences of sexual behavior) and high-quality sexual health care from evidence-informed, nonjudgmental providers [2-4]. The confluence of these components promotes sexual health and may avert two consequences that arise from risky sexual behavior: acquiring sexually transmitted infections (STIs), including HIV, and unintended pregnancies [1].

Brief interventions are seen as efficient ways to improve knowledge, change behavior [5-12], and reduce provider stigma regarding sexual health [13,14]. When built on evidence-based behavioral change techniques [15] and delivered using brief sexuality-related communication (BSC) [3] tools, brief interventions address client-driven sexual health goals in a single session (less than 25 minutes) between clients and their health care provider. Brief interventions often use techniques based on motivational interviewing (MI). This client-centered approach enhances intrinsic motivation to change by exploring and resolving ambivalence and allows health care providers to improve the information available to clients, motivate clients, and help clients develop the concrete skills necessary to change risk behaviors [5,8,11].

However, much of the evidence on brief interventions comes from countries with highly developed health care systems [11,16]. There is little known about how brief interventions can be tailored to improve sexual health in LMICs. There is also little literature on how providers in LMICs view their ability to embed such an intervention in their practice settings and health system environments. Characterized by competing demands for limited resources and a shortage of many types of primary health care providers [17-19], the health systems of many LMICs may be initially ill-equipped to widely implement the proposed intervention, thus requiring important alterations to any brief intervention. Likewise, the degree to which a brief intervention should be tailored to populations with specific sexual health needs (eg, sex workers, men who have sex with men [MSM]) versus standardized across populations to ease implementation and reduce provider burden is unknown in these settings.

To address the limitations of the literature, we propose a multisite, multiphase feasibility study of a brief intervention designed to improve sexual health in various settings. The feasibility study is grounded in the information-motivation-behavioral skills (IMB) model [20]. This model borrows from established behavior change theories [20] such as the theory of reasoned action [21] and the concept of self-efficacy [22] and has received considerable attention in HIV prevention and antiretroviral medication adherence [23-31].

Information is a necessary but insufficient precursor to preventive behavior and risk reduction [20,30]. It can include specific facts about the consequences of the risk behavior in question that serve as a guide for personal preventive actions and cognitive processes that significantly influence performance of preventive behavior [27]. Just as important as factual information, however, is misinformation regarding the risk behavior in question [23]. Inaccurate information regarding prevention of and care for STIs, HIV, and unintended pregnancies can negatively influence this component of the IMB model, reducing the chances of a successful change in preventive behavior [23,32].

Motivation is a function of two components that influence incentive to practice preventive behaviors: behavioral intention and subjective norms [21]. These components reflect the degree to which personal motivation (ie, feelings about the preventive action in the context of competing life demands) and social motivation (ie, social support, level of stigma associated with the preventive action, or the consequences of inaction) facilitate the adoption of a preventive behavior [23]. The development of behavioral skills is an additional step that aids in behavior change. It involves the objective ability and perceived self-efficacy concerning performance of the behavior [20]. The ability to obtain behavioral skills is not limited to individuals themselves (ie, knowledge of how to effectively use condoms) but can involve structural elements as well (ie, access to condoms or social norms that discourage condom use in marriage) [33].

The IMB model stipulates that information and motivation work primarily through behavioral skills to influence behavior. Associations between information and motivation theoretically lead directly to behavior change, although these pathways are less robust in structural equation modeling analysis than the indirect pathways via behavioral skills [20].

The BSC intervention itself is based on techniques of MI. Developed by Miller and Rollnick [34], MI is defined as a "directive, client-centered counseling style for eliciting behavior change by helping clients to explore and resolve ambivalence"

[35,36] and aims to increase clients' intrinsic motivation to stimulate change from within rather than being imposed externally [35]. In a single 20- to 25-minute session, providers will move through a series of steps designed to elicit clients' life goals and current sexual risk behaviors. These will be used to fashion an individualized concrete action plan to reduce risk behaviors in service to their larger life goals. In addition to reducing client sexual risk behavior, the intervention aims to change how providers communicate with clients regarding their sexual health in an empathic, respectful, and nonjudgmental manner. By altering client-provider communication to be less didactic and more individualized, providers may increase clients' intrinsic motivation for behavior change.

The aim of the study is to evaluate 5 aspects of feasibility (acceptability, willingness, safety, satisfaction, and process) of a BSC intervention based on MI and behavior change techniques in primary health care settings in LMICs.

This document is a generalized protocol, applicable to all potential study sites. Study locations will be chosen at a later date in consultation with in-country researchers and providers. This will lead to the creation of country-specific protocols developed over a series of 2-day site meetings with officials from the national, regional, and local Ministries of Health to clearly delineate roles, responsibilities, and alterations to the general protocol that may be necessary in each selected study community. This paper outlines the master protocol: the overall research approach that will be used to determine the feasibility of the BSC. The protocol will be adapted accordingly for individual countries.

Methods

Testing the Feasibility of a Brief Sexuality-Related Communication Intervention

The purpose of this study is to test the feasibility of a BSC intervention. Feasibility in this study will be guided by 5 technical principles: acceptability, willingness, safety, satisfaction, and process (study logistics). These aspects of feasibility will be examined across all phases of the study. This study was approved by the Ethics Review Committee (ERC) of the World Health Organization (WHO).

The feasibility study will follow a 4-phase, iterative design. These phases are structured to refine the intervention for optimal implementation with providers and clients in primary care settings. Phases I through III will involve the collection of formative, qualitative data to examine provider and client perceptions of the feasibility of the intervention and their attitudes toward sexual health and perceived sexual health information needs. Data will be collected using an iterative approach, with data from the previous phase being analyzed and the study refined before beginning the subsequent phase. After phase III, providers will be trained on how to implement the final version of the BSC intervention. After the final phase of formative, qualitative work (phase III), the feasibility of the intervention will be tested in a nonrandomized pretest-posttest trial of the BSC intervention (phase IV).

Study Sites

The feasibility study will be implemented across multiple countries and multiple study communities within each country. For the purposes of this protocol, the term study site refers to an individual primary health care center. Study populations in each study country will be selected according to national sexual health priorities within the bounds of the proposed client population and sexual health outcomes. All research, training, and intervention documents will be translated from English to the appropriate local languages by local research teams and then backtranslated to English and compared for accuracy.

Participants

Participants will include key informants in phase I and health care providers and clients across all 4 study phases. Key informants include stakeholders at local, regional, and national levels. Stakeholders will include decision makers and experts at health facilities and clinics, health departments, and other sexual and reproductive health organizations. In accordance with WHO guidelines on BSC [3], participating health care professionals will include those at the first point of client contact. This definition includes physicians, nurses, nurse practitioners, and other providers (eg, HIV testing counselors, family planning counselors) who offer primary health care. The aim of the intervention is to improve sexual health by reducing the burden of STIs and unwanted pregnancies. Client populations will vary by country but will include specific populations in each country who experience a high burden of STIs and/or HIV or want to prevent pregnancy. For example, key client populations experiencing high levels of STI/HIV may include sex workers, MSM, and people seeking treatment for STIs. Clients experiencing high levels of unwanted pregnancy will be women (including adolescent women) seeking family planning services (who may also be targeted for STI prevention). The intervention is standardized to populations of interest for each country based on conversations with key stakeholders, with minor differences in language and content depending on the specific client population and country. These differences in language and content are designed to promote cultural sensitivity, address unique issues of stigma in each location, and tailor the intervention to the specific sexual health issues facing each population.

Recruitment

Key informants will be recruited using existing contacts of the in-country key stakeholders and study staff who, in turn, will reach out to possible key informants on local, regional, and national levels to invite them to share their expertise. Clients and providers will be recruited at each phase of the feasibility study. That is, while clients and providers will not be prevented from participating in more than one phase, additional clients and providers will be recruited at each stage of the feasibility study. Recruitment of providers and clients will occur through primary health care sites and organizations. To avoid the potential coercion that may occur with the unequal power balance between provider and client, providers will not recruit their own clients into the study.

Recruitment sites may include those that address the specific needs of the selected study populations, such as general primary care clinics, health care clinics, organizations addressing issues of STIs and unintended pregnancy, pharmacies, and mobile outreach clinics. Recruitment of providers and clients in these sites will occur with the assistance of a key stakeholder at each site; recruitment of clients will also be facilitated by study staff. Potential provider participants will be approached by study staff and brought to a room at the health care site with audio and video privacy to explain the study, establish eligibility, and provide informed consent if the participant agrees to participate.

For recruitment of clients, the key stakeholder will assist by identifying appropriate times to approach potential client participants with study recruitment materials in the waiting areas of the primary health care sites. Study staff will be stationed in these waiting areas and, using a predetermined protocol, will approach every fourth person who enters the waiting area. Study staff will take the potential participant to a space in the same building with audio and visual privacy to screen the participant for eligibility, explain the study, and provide informed consent should the potential participant agree join the study.

All participants (including providers and client populations) will receive locally appropriate reimbursements for their time and effort participating in research activities; reimbursements are not meant to be a motivating factor for enrollment in the study.

Sample Size

Sample sizes are approximate and will differ by study country, study community, and study site. As the goals of this study are to inform the feasibility, willingness, and acceptability of the BSC protocol among providers and clients, sampling is not intended to maximize external validity or provide data that are generalizable. However, it is important that the feasibility data are reflective of a diverse range of opinions and lived experiences. In sampling for the feasibility study, a diverse sample will be sought in terms of age and locally specific race/ethnicity in order to gather a range of opinions regarding both the formative qualitative (phases I to III) and quantitative (phase IV) portions.

Procedures

The study will be jointly implemented by an international team of researchers, key stakeholders in each study country already known to the international research team, and in-country study staff who have specific knowledge of the study populations and health care system in each study community. This implementation strategy will occur across all phases of the study.

Phase I

During the first phase of the study, 3 study activities will take place: key informant interviews with stakeholders in each study community, individual in-depth interviews with health care providers, and focus group discussions with client populations.

Key informant interviews are in-depth, qualitative interviews used to better understand the contexts in which the intervention will be implemented: to address the appropriateness and safety of the intervention in facility settings, perceived usefulness of the intervention, special considerations for adaptations to study communities, and barriers and facilitators for implementing the intervention. Key informant interviews will be conducted by the national research team with approximately 10 local, regional, and federal stakeholders in each community for about 30 minutes. Interviewers will use a semistructured interview guide that will be identical across study sites but adapted based on the stakeholder level (local, regional, federal).

Individual in-depth interviews will address provider perceptions around participating in the research study, participating in the intervention training, and providing the intervention. In-depth interviews will assess attitudes toward providing sexual health information to clients and providers' perceived sexual health needs of their clients and their comfort in working with vulnerable populations (eg, MSM). In-depth interviews will be stratified by study site and provider type (doctor, nurse, and lay counselor), with approximately 15 in-depth interviews for each study site (5 per group). Interviews will be conducted using semistructured interview guides, occur in locations with audio and visual privacy, and last approximately 45 to 60 minutes. Addressing all key domains of feasibility (acceptability, willingness, safety, satisfaction, and process), the interviews will examine: (1) overall attitudes about the intervention, (2) willingness and motivation to participate in the research study and implement the intervention, (3) logistics of implementation, (4) ability to implement the intervention, and (5) attitudes about providing sexual health services.

Focus group discussions with clients will be used to increase understanding of clients' general perceptions about the intervention. Three focus group discussions will be conducted in each study community with approximately 24 to 30 clients seeking to alleviate concerns regarding stigmatization and discrimination that may occur in some study communities (eg, MSM, sex workers) and explore similarities in sexual risk behavior and sexual health needs. Focus group discussions lasting approximately 60 to 90 minutes will be conducted by trained moderators (one from each of the local research teams) using a semistructured focus group discussion guide. Guides will be the same across study communities and translated into the local language. During focus group discussions, the moderator will describe the process of the BSC intervention and illustrate how the intervention works by conducting a short role play with an example of the intervention. Participants will then be asked about their reactions to the process and logistics of the research study, the intervention, and the general content of the intervention. Participants will be asked to rate specific aspects of the intervention based on its perceived importance and usefulness, comfort with the intervention, perceived safety of the intervention, and willingness to participate in the intervention. Participants will also discuss their perceived sexual health information needs and their comfort in talking about sexual health with their providers.

Phase II

Phase II uses cognitive interviewing, in which feedback is sought regarding the language, phrasing, and delivery of the BSC guide to each of the study populations [37]. The aim of

the cognitive interviews is not to generate substantive data on attitudes or perceptions but to test comprehension of language used in the intervention. Cognitive interviews will be conducted among providers (n≈4) and clients (n≈8) in each study community for approximately 30 minutes. The number of proposed cognitive interviews is a suggestion and may be adapted for each country depending on the degree of heterogeneity identified in comprehension of the intervention language. The number of cognitive interviews may also need to be expanded for countries with multiple languages. Cognitive interviews differ from traditional interviews in that key passages of the BSC guide will be read to the interviewee with the intent of ensuring the message of the passage comes across as intended. The goal of these interviews is not to collect data from participant responses but rather information on how they respond and why. This will help to elicit information on the validity of the language in the guide as translated and improve cultural sensitivity of the intervention by including site-specific terminology. To avoid repetitiveness and conditioning a social desirability bias [38,39] and to mitigate task burden on the part of interviewers, only selected modules from the BSC guide will be reviewed during the cognitive interview. These will be selected in advance by the research team to give a broad view of the types of words, phrases, and language used in the intervention.

Phase III

Phase III consists of theater testing commonly used to gauge participant responses to an intervention session [40] and will be performed among providers and clients for approximately 60 to 90 minutes. The aim of this phase is to obtain an assessment of willingness and acceptability of participants to take part in the intervention. During theater testing, in-country study staff will demonstrate a mock BSC session (via a video recorded BSC session). The participants, who will be selected to represent potential study participants, will provide feedback on the content, delivery, and materials used in the BSC intervention and engage in group dialogue surrounding potential improvements to the guide.

Four to six providers per study community will participate in theater testing. For clients, groups will be stratified based on the population of interest. There will be three separate groups per study community (n≈8-10 participants per group), with one group for each study population. During these client theater testing sessions, the standardized client persona in the mock BSC session will be matched to the population of that particular focus group.

Intervention Training

After revisions to the intervention based on phases I to III are complete, training will take place at each study site with recruited providers. The training package consists of 12 modules delivered over three days, covering the burden of STIs in the local context, the WHO sexual health framework [2] and BSC principles [3], importance of creating nonjudgmental clinical spaces, client confidentiality, ways to reduce implicit and explicit biases in delivering sexual health care, and finally, how to conduct the BSC intervention. Training will be a combination of didactic learning and role playing: trainees will have the opportunity to role play through a number of scenarios (eg, different sexual health needs and/or different client groups [eg, MSM]).

Phase IV: Testing the Intervention

Phase IV will test the feasibility of the intervention. During phase IV, trained providers will deliver the intervention as revised in phases I to III as part of regularly scheduled consultations with clients in one of the study populations. To test the feasibility of the intervention during this phase, providers and clients will be followed for 6 months and participate in a variety of study activities. Providers will participate in knowledge, attitude, and practice (KAP) surveys, and a subset will participate in intervention observations. Intervention observations are intended to assess the fidelity to the intervention. Clients will participate in pre-post surveys and exit interviews upon completion of an intervention session. Separate measures are used to elicit data on the intervention from providers and clients (eg, willingness to participate in the intervention).

Knowledge, Attitude, and Practice Surveys for Providers

Prior to beginning training, providers will complete KAP surveys that will serve as the pretest for the intervention. Follow-up KAP surveys will be administered to providers at 3 and 6 months posttraining in order to examine changes in the measures of interest. A 6-month follow-up period was chosen to facilitate measurement of short-term gains in MI techniques and identify changes in attitudes and perceptions about providing sexual health services to client populations. The surveys will cover 6 domains of the provider experience with the intervention, provider-client interaction, and the providers' perceived utility of the intervention to both the provider and the client, including sociodemographic information, provider skills, efficacy and autonomy, competency and capacity, implementation, and attitudes. Provider intervention measures include indicators such as willingness to deliver the intervention and comfort with MI techniques (willingness), perceptions of the intervention's impact on client behavior (satisfaction), perceptions of the intervention's fit with the facility's culture and clinical requirements (acceptability), and ability for the study site to continue delivering the intervention after the research study concludes (intervention logistics).

Intervention Observations

During phase IV, in-country study staff will observe 10% of BSC sessions to independently assess provider knowledge, practice, and fidelity to the BSC protocol as written. The goal of the intervention observations is to assess the degree to which providers retain fidelity to the study protocol and provide nonjudgmental care consistent with the technical principles of MI. In-country study staff will use a standardized checklist to determine fidelity to the BSC guide. The checklist will include all the behavior skills taught in the training and the expected steps of the BSC session. During the observations, staff will be positioned so as not to interfere with the client-provider interaction, and the client will be asked if they consent to having the study staff member present. Intervention observations will

collect quantitative data regarding provider ability to deliver the intervention protocol as written. Staff will check off skills as they are observed and record whether the steps of the BSC intervention are followed and are followed in order. At least two intervention observations per client type will be performed at each study site. Any issues regarding cultural sensitivity for key populations will be noted by study staff during the intervention observations. Providers who consistently demonstrate nonadherence to the intervention will be offered a 1-day refresher training for the intervention.

Pre-Post Surveys With Clients

A convenience sample of clients from each study community will be recruited, and pre-post surveys will be administered prior to participation in the intervention (at baseline) and at 3 and 6 months postintervention. Adaptive, computer-assisted self-interviewing software with audioenabled playback will be used to address language barriers and issues of client literacy. The survey will take approximately 20 minutes to complete and include questions that assess (1) client sociodemographics and willingness, satisfaction, safety, and acceptability of the intervention (domains 1 to 5) and (2) client sexual health, including sexual competency and sexual behaviors (domain 6). Approximately 90% of questions will be the same across the key populations of clients; however, there will be some differences in questions regarding sexual behaviors depending on whether the outcome of interest is prevention of STIs, unintended pregnancy, or both.

Exit Interviews

Exit interviews will qualitatively assess client reactions to the intervention and the research study. Interviews will be completed upon receiving the intervention in order for clients to discuss their immediate feelings and attitudes toward the intervention. Approximately 24 interviews lasting 45 to 60 minutes will be conducted per study community, approximately 6 per key client population, by a member of the local research team. Interviewers will use an identical semistructured interview guide translated into the local language. Exit interviews will address client satisfaction with and willingness to use the intervention and client perception of intervention acceptability and safety.

Study Documentation

Data will be collected regarding the recruitment and retention of clients and providers. These data will be collected by in-country study staff at each site using standardized checklists that track the number of clients and providers approached, number of those who agree to participate in the study, number who refuse, and the main reason for refusal. Participant contact information will be collected in order to provide reminders for the follow-up surveys. During the follow-up period, client and provider subject identification numbers will remain consistent in order to track retention through the 6-month follow-up period. In case of attrition, an attempt will be made to collect data on the reasons for discontinuing the study.

Ethics and Consent to Participate

The core BSC protocol was first submitted to the WHO Research Project Review Panel; after its technical approval in 2016, WHO ERC was consulted for a special evaluation of the ethical components, with the following approval in 2017: prior to participation in any study activities, all participants (providers, clients, and key informants) will provide written informed consent at all stages (phases I to IV) of the study. The informed consent forms are explained in detail, and participants are asked to read them in full before agreeing to sign. If the individual chooses to participate, they sign the informed consent form and are offered a copy of the signed form. They can choose to decline taking a copy of the form if there is any concern that this would create additional risks.

Results

Phase I is currently underway in Moldova, and phases I and II were completed in Peru in late 2019. Results are expected for the feasibility study in 2021.

Analysis of Phases I and III

All focus group discussions and in-depth interviews will be audiorecorded, transcribed verbatim, and deidentified. For the focus group discussions, a notetaker will be present and will indicate the order of speakers and the first few words that each speaker says in order for the transcriber to be able to differentiate between speakers. For all activities in phases I and III with the exception of cognitive interviewing, a thematic analysis of these transcripts will be completed, using elements of grounded theory [41] and building on the IMB model. This will include the systematic and consistent application of deductive and inductive codes to the text. Inductive codes will include themes that are explicit domains present in the interview and focus group discussion guides, and deductive codes will include salient themes that arise more organically in the data. Additionally, all inductive themes and codes will be grouped according to the constructs in the IMB model, including information, motivation, and behavioral skills.

A preliminary codebook will be developed with provisional definitions for each code. A team of 2 to 5 data analysts will apply the provisional codebook to a single transcript, and the coded transcripts will be merged for comparison. Analysts will examine and discuss discrepancies in coding, and the code definitions will be revised based on an examination of coding disagreement. The process will be repeated with the revised codebook until consistent agreement among coders is attained. This process will occur with transcripts from all data collection activities using the same codebook for transcripts across all data collection activities. Once the final codebook is established, codes will be applied to all transcripts, with at least 2 analysts coding each transcript.

Based on systematic close readings of coded text, analysts will create thick descriptions for each theme. These descriptions will identify common concepts, patterns, and unique statements that appear in the transcripts. Specific themes arising in phases I to III regarding content and delivery of the intervention will be used by the research team to further refine the intervention for phase IV, determine the best way to present content, and better understand provider/client attitudes and willingness to participate. While small changes will be site-specific in order

to promote cultural sensitivity, larger changes will be implemented universally across study sites.

Analysis of Phase II

Analysis of phase II will be completed separately from the in-depth interviews and focus group discussions. For each interview, interviewer notes will be synthesized and grouped into themes based on the content of the participant feedback. These themes will be used for making recommendations to improve the intervention. Specifically, these recommendations will involve possible changes to the phrasing and language of the intervention, with the goal of improving comprehension and acceptability of the intervention among providers and clients. While small changes in the language, phrasing, and delivery of the intervention will be site-specific in order to promote cultural sensitivity, larger changes will be implemented universally across study sites to maintain protocol fidelity.

Analysis of Quantitative Data From the Pre-Post Surveys and Exit Interviews

Data (client and KAP surveys and client exit interviews) will be deidentified and entered into the study database at each time point (0, 3, and 6 months). At each time point, descriptive statistics will be computed, and 3- and 6-month follow-up data will be compared with previous survey data. Appropriate tests of comparison (ie, *t* tests, chi-square tests, analyses of variance) will be used to determine differences in the primary (feasibility) and secondary (sexual health) outcome measures between time points. Although this phase is not powered to detect statistically significant differences in the sexual health outcomes, this analysis will provide information on whether the intervention is associated with differences in these outcomes from baseline to 3- and 6-month follow-up. Once collected by in-country study staff, the quantitative data from the intervention observations will be deidentified and entered into the study database.

Discussion

Feasibility Study Implications

Brief interventions provide an opportunity to train providers on the topic of sexual health for different populations, including marginalized populations for which they may have received little to no training. By training providers to improve their communication with these populations, providers may be able to work with clients to create plans of action that reduce risk behaviors in service to the clients' larger life goals. However, the scale and novelty of this project in LMICs requires a feasibility study to determine if the implementation of wider brief intervention programs is possible given the constraints of LMIC health systems and the demands already placed on primary care providers. This protocol, therefore, lays out an innovative approach to refining existing methods for implementing brief interventions for use in more resource-constrained settings. By taking an iterative approach, this feasibility study allows for the alteration of the protocol to best fit the needs of the target populations, both client and provider.

Limitations

Despite these strengths, the feasibility study does have limitations. Reliance on existing health care resources in the study communities may show that there is a demand among clients but a lack of feasibility among health systems and providers. This would require a different approach altogether—one outside of the health system. The ability to recruit and retain providers and participants may also be challenging given the multiple follow-up time points. The study only follows clients and providers for 6 months: this shorter follow-up period is expected to increase retention but will preclude the ability to identify longer term changes in provider's skills and attitudes. While this remains a potential limitation, the research team will work closely with the in-country study team to fashion reimbursements and contact methods to maximize retention throughout the study period.

Conclusions

Using brief interventions to reduce provider stigma and sexual risk behaviors among marginalized populations has the potential to be a cost-effective approach to improve sexual health in resource-constrained settings. The collection of formative, qualitative data that directly inform the content and delivery of the brief intervention may increase our understanding of how brief interventions can be delivered by health care providers in resource-limited health systems and different sociocultural contexts. Testing of the feasibility of the BSC in multiple settings and across multiple population groups will provide vital information on best practices for implementing brief interventions that are culturally sensitive and meet the needs of a range of vulnerable groups (eg, MSM or adolescent women). The data will also highlight factors shaping clinical practice among primary care providers and allow for the creation of more concrete, effective action plans designed to reduce sexual risk behaviors.

This feasibility study will determine whether the implementation of brief intervention programs aimed at improving sexual health outcomes is possible in the constraints of LMIC health systems. Understanding the ability of primary health care providers to deliver brief interventions and factors shaping clinical practice that will be investigated in this study is an important step in the improving the quality of sexual health services in resource-limited settings. While both provider and client perceptions of the feasibility of the intervention will be examined, adaptation of the intervention guide based on the feedback of the study populations and training providers on how to implement the final version of the BSC intervention will be performed during the study. However, careful attention will also be needed to the sustainability of the intervention. The current protocol will establish whether the integration of a BSC into routine patient visits is feasible. If proven feasible, strategies will need to be in place for sustainability, including routine trainings, training refreshers for providers, and close collaboration with key stakeholders (eg, ministries of health). Brief interventions will allow health care providers to improve the information available to clients, motivate and help them to develop risk-reduction skills that are seen as efficient ways to

improve knowledge, change clients' behavior, and reduce provider stigma regarding sexual health.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Approval of the study master-protocol by the Research Proposal Review Panel (RP2) of the World Health Organization's Department of Reproductive Health and Research (RHR; included two independent reviewers). RP2 approval is a condition sin qua non to continue a project within RHR and RP2 was also responsible for approving the proposed budget for the study.
[PDF File (Adobe PDF File), 855 KB - resprot_v9i3e15569_app1.pdf]

Multimedia Appendix 2
RP2 approval of the site-specific Protocol for Peru.
[PDF File (Adobe PDF File), 427 KB - resprot_v9i3e15569_app2.pdf]

Multimedia Appendix 3
Approval of the core protocol by World Health Organization Research Ethics Review Committee.
[PDF File (Adobe PDF File), 331 KB - resprot_v9i3e15569_app3.pdf]

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Abbreviations

BSC: brief sexuality-related communication
ERC: Ethics Review Committee
IMB: information-motivation-behavioral skills
KAP: knowledge, attitude, and practice
LMIC: low- and middle-income country
MI: motivational interviewing
MSM: men who have sex with men
STI: sexually transmitted infection
WHO: World Health Organization

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Protocol

Lumbar Intervertebral Motion in Healthy Male Participants: Protocol for a Motion Analysis During Flexion and Extension Cinematographic Recordings

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Abstract

Background: Physiological motion of the lumbar spine is a subject of interest for musculoskeletal health care professionals, as abnormal motion is believed to be related to lumbar conditions and complaints. Many researchers have described ranges of motion for the lumbar spine, but only a few have mentioned specific motion patterns of each individual segment during flexion and extension. These motion patterns mostly comprise the sequence of segmental initiation in sagittal rotation. However, an adequate definition of physiological motion of the lumbar spine is still lacking. The reason for this is the reporting of different ranges of motion and sequences of segmental initiation in previous studies. Furthermore, due to insufficient fields of view, none of these papers have reported on maximum flexion and extension motion patterns of L1 to S1. In the lower cervical spine, a consistent pattern of segmental contributions was recently described. In order to understand physiological motion of the lumbar spine, it is necessary to systematically study motion patterns, including the sequence of segmental contribution, of vertebrae L1 to S1 in healthy individuals during maximum flexion and extension.

Objective: This study aims to define the lumbar spines' physiological motion pattern of vertebrae L1, L2, L3, L4, L5, and S1 by determining the sequence of segmental contribution and the sequence of segmental initiation of motion in sagittal rotation of each vertebra during maximum flexion and extension. The secondary endpoint will be exploring the possibility of analyzing the intervertebral horizontal and vertical translation of each vertebra during maximum flexion and extension.

Methods: Cinematographic recordings will be performed on 11 healthy male participants, aged 18-25 years, without a history of spine problems. Cinematographic flexion and extension recordings will be made at two time points with a minimum 2-week interval in between.

Results: The study has been approved by the local institutional medical ethical committee (Medical Research Ethics Committee of Zuyderland and Zuyd University of Applied Sciences) on September 24, 2018. Inclusion of participants will be completed in 2020.

Conclusions: If successful, these physiological motion patterns can be compared with motion patterns of patients with lumbar conditions before or after surgery. Ultimately, researchers may be able to determine differences in biomechanics that can potentially be linked to physical complaints like low back pain.

Trial Registration: ClinicalTrials.gov NCT03737227; https://clinicaltrials.gov/ct2/show/NCT03737227

International Registered Report Identifier (IRRID): DERR1-10.2196/14741

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KEYWORDS

fundamental research; lumbar spine; cinematographic recordings; motion pattern; flexion; extension; rotation; translation

Introduction

Physiological motion of the lumbar spine is a subject of interest for musculoskeletal health care professionals. Although *physiological motion* is used in many instances, a proper definition is still lacking. More knowledge about physiological motion is essential to recognize abnormal motion caused by specific diseases, complaints, or medical interventions.

In 1929, Virchow et al [1] were the first to use sagittal radiographs to analyze normal range of flexion and extension of the cervical spine. In 1931, Dittmar et al [2] were the first to perform this type of research for the lumbar spine. Troke et al [3] developed a database of healthy individuals, aged 16-90 years, with ranges of motion from Th12 to S1. After these studies, more motion and range of motion research using radiographs followed, and later on, computed tomography– or magnetic resonance imaging–based 3D images were used[4-6]. However, ranges of motion have a high intra- and interindividual variability [3,7]. For this reason, recent studies have described the motion of individual segments and the sequence of segmental initiation of motion in flexion and extension of the lumbar spine. However, these studies still reported different motion sequences. This lack of a consistent sequence hampers the definition of *physiological motion* of the lumbar spine.

Boselie et al [8] have recently described a rather consistent sequence of segmental contribution in sagittal rotation during flexion and extension in the lower cervical spine. This research was used to create a definition of physiological motion. To our knowledge, research on the sequence of segmental contribution has not been carried out for the lumbar spine.

The aim of this study is to analyze the lumbar spine, regarding the sequence of segmental contribution and the sequence of segmental initiation of motion of L1 to S1 in sagittal rotation during flexion and extension in individual participants. Additionally, the researchers will explore the possibility of analyzing intervertebral horizontal and vertical translation to enable determination of the sequence of segmental contribution and the sequence of segmental initiation of motion of L1 to S1.

Sagittal cinematographic recordings will be conducted during lumbar flexion and extension in asymptomatic male participants to determine the sequences. If a consistent pattern of segmental contributions is found in asymptomatic participants, this pattern can be used to investigate potential abnormal motion in conditions in the future. Differences in biomechanics may result in physical complaints.

Methods

Participants, Recruitment, and Study Setting

Participants will be recruited at two hospitals and two universities of applied sciences by using information posters. Potential participants can send an email to author IC. IC will evaluate eligibility and inform participants about the study verbally and in writing. They will be contacted again at least 1 week later to inquire if they are willing to participate.

This study will include men aged 18-25 years with a Body-mass Index<25 kg/m^2, no medical history of spine problems and who are able to perform maximum lumbar flexion and extension without complaints. No medical history of spine problems is defined as no visits to a doctor for spine complaints, no former spine surgery, Oswestry Disability Index and Visual Analogue Scale scores of zero for back pain, and Kellgrens' classification of 0-1 in levels L4L5 and L5S1 on cinematographic recordings evaluated by two neurosurgeons or orthopedic surgeons (authors TB, HvS, WvH, or KR) [9-11]. Potential participants are excluded if x-rays were taken of the abdomen, pelvis, hip, lumbar, or sacral spine in the previous year or in cases of active spinal infection, immature bone, lumbar tumor, previous lumbar radiotherapy, congenital lumbar spine abnormality, or planned pregnancy of the participants' partner in the coming year. There are two reasons for these strict inclusion and exclusion criteria. First, only asymptomatic healthy participants are included, because they reflect normal motion. Second, the criteria minimize radiation exposure of participants during the study. Informed consent will be acquired from all participants.

Sample Size

Sample size calculation is based on previous studies that used the same method of cinematographic recordings to analyze spine motion. Boselie et al [12], Kanayama et al [13], and Harada et al [14] used 8-10 participants to perform adequate analysis and draw solid conclusions. To minimize radiation exposure in healthy participants, we will not include more participants than necessary for analysis. This results in a study population of 11 participants, assuming an expected maximum loss to follow-up of 10%. Flexion and extension cinematographic recordings are acquired twice for each participant with an interval of 2 weeks in order to determine reproducibility and consistency of sequence of motion between two time points (T1 and T2) [8,15].

Participants can cease study participation at any time for any reason without consequence. If participants leave the study before the second recording, only the first recording will be included and analyzed. Researchers can only withdraw participants that do not respond to calls before the first cinematographic recording or if abnormalities of the lumbar spine are observed during the first cinematographic recording.

Study Procedures

In order to acquire cinematographic recordings of flexion and extension of the lumbar spine, participants will be seated in a chair designed to set the pelvis in a fixed position. They will be instructed to perform maximum extension, followed by maximum flexion, and then return to maximum extension in 14 seconds using a metronome. Cinematographic recordings will be made from a lateral perspective to obtain sagittal images.

Participants perform these recordings twice with a 2-week interval.

Radiological Outcome Measures

The outcome of this study will define (1) the sequence of segmental contribution in rotation and, if possible, translation during flexion and extension and (2) the sequence of segmental initiation of motion in rotation and, if possible, translation during flexion and extension

Radiological Data, Radiological Acquisition, and Radiation Dose Calculation

Cinematographic recordings are made using the Philips Allura Xper FD20 x-ray system, capturing frames of 1024x1024 pixels at 7.5 frames per second. Radiation dose per cinematographic recording, determined by radiation experts, will be around 0.21 mSv. The settings used for calculation are an exposed tissue factor of 0.54 mSv/Gy (based on International Commission on Radiological Protection 103), tube voltage of 75-90 kV, record duration of 20 seconds, filter of 0.9 mm copper + 1 mm aluminum, 7.5 frames per second, focus-detector distance of 48 cm, and a field of view of 520 cm^2. Participants will perform cinematographic recordings twice, resulting in a total radiation dose of 0.42 mSv. This amount of radiation can be categorized in category IIa using the Neurocritical Care Society guidelines on risks of radiation dose (0.1-1.0 mSv) [16]. This category includes moderate risk that can be justified if there is a potential health benefit for future patients.

Radiological Data Processing

The researchers have developed custom software that uses image recognition algorithms to track vertebrae during flexion and extension throughout these series of frames [17]. The software follows bony structures within user-defined template areas throughout all frames using a best-fit principle to match normalized gradient field images. To define these template areas, the user draws polygons around all vertebrae on the median frame of the recording [17]. After the software has completed tracking these structures, they can be manually evaluated, and corrections can be made if necessary. The rotational data between frames for each bony structure enables the user to calculate segmental ranges of motion and sagittal rotations within a motion segment through time. The sequence of various segmental contributions to movement of the entire lumbar spine can therefore be established.

Radiological data will be stored on CDs coded with participant number and recording number (T1 or T2). The CDs will be locked up in a secured room in the hospital and kept for 15 years after end of the study. Handling of personal data will comply with the guidelines of the Dutch Personal Data Protection Act.

Interim Analysis

Interim analysis will be performed after cinematographic recordings of 2 participants, to determine if the images acquired with the Allura Xper are appropriate to perform computer software analysis. If segment L1 does not remain in the field of view, analyses will start downwards from segment L2.

Radiological and Statistical Analysis

Computer analysis will be performed by IC for all cinematographic recordings. Graphs will be made for flexion and extension. Segmental rotation (cumulative and between each pair of successive frames) of each individual segment L1 to S1 will be plotted against the cumulative rotation in segments L1 to S1 together, to describe the sequence of segmental contribution and sequence of segmental initiation of motion. These graphs will be made and analyzed for each individual participant to identify specific patterns in the sequence of segmental contributions. If possible, a sequence definition will be described for segmental contribution and initiation of motion in flexion and extension of the lumbar spine. Analysis will first be performed for T1 and then tested against T2 using the kappa coefficient to determine intraindividual variability.

Ten recordings will also be evaluated by second researcher TB to determine reproducibility when using two-way mixed intraclass correlation coefficient testing. If the intraclass correlation coefficient for intervertebral horizontal and vertical translation is higher than 0.60, the sequence of segmental contribution and sequence of segmental initiation of motion of intervertebral horizontal and vertical translation will be determined as well. If the intraclass correlation coefficient is less than 0.60, intervertebral horizontal and vertical translation will not be determined because reliability of results will be insufficient.

Data Monitoring, Safety Reporting, and Publication

Monitoring will be performed by independent, trained, and qualified monitors according to the good clinical practice guidelines. Monitoring will be performed three times: one site initiation visit, one interim monitoring visit, and one close out visit. Adverse events will be collected by questionnaires during T1 and T2. Adverse events will be followed until they have abated or until a stable situation has been reached. Serious adverse events will be reported through the Web portal ToetsingOnline to the accredited Medical Ethical Review Committee (METC) that approved the protocol. The researcher has a liability insurance that provides coverage for damage to research participants because of injury caused by the study.

Possible amendments of the study protocol have to be approved by the accredited METC.

Results of the study will preferably be published in open access, peer-reviewed journals. Data of participants will be anonymous and untraceable to any individual. Authors will not be able to veto whether to publish data.

Results

The study has been approved by the local institutional medical ethical committee (Medical Research Ethics Committee of Zuyderland and Zuyd University of Applied Sciences) on September 24, 2018. Furthermore, it was registered on ClinicalTrials.gov (NCT03737227) on November 9, 2018. Inclusion of participants will be completed in January 2020, followed by analysis of cinematographic recordings.

Discussion

The aim of this study is to describe the sequence of segmental contribution and the sequence of segmental initiation of motion in sagittal rotation and translation during maximum flexion and extension of the lumbar spine in asymptomatic male participants, with the intention of finding a consistent and reproducible motion pattern. In the future, the researchers will aim to use this physiological motion pattern to compare with potentially abnormal motion patterns in patients with lumbar spinal conditions or in patients after spine surgery to determine if differences in biomechanics are present, which may result in physical complaints.

Previous studies have used different imaging techniques to describe the range of motion and initiation of motion of individual segments during flexion and extension of the lumbar spine. Extension seems to correlate to a smaller translation and range of motion compared to flexion, where most studies describe L5S1 as least mobile. However, those studies reported different sequences and have not described motion patterns of maximum flexion and extension for L1 to S1 due to insufficient fields of view [8-13,18-26]. Furthermore, all studies described cumulative rotation of each individual segment at specific time points or at specific lumbar ranges of motion, which can result in missing drastic changes in intervertebral rotation between successive frames.

This study has several strengths. First, this study will use strict inclusion criteria to select only young adult male participants without low back complaints. Females are excluded to protect their ovaries from direct radiation exposure. However, Dvorak et al [19] and Wong et al [26] have shown that there is no statistically significant difference between sexes in motion of the lumbar spine. Comparable results were described by Boselie et al [8] for the cervical spine. Second, the researchers want to describe a more thorough motion pattern of the total lumbar spine, including information about all segments from L1 to S1 during maximum flexion and extension; sequences of segmental contribution (except the already described sequence of segmental initiation of motion); and information on rotation and, if possible, translation in the sagittal plane. This study will describe the definition of the physiological motion pattern based on information in only one plane. However, based on the study of Boselie et al [8], the researchers can conclude that the description of motion patterns in only one plane is a consistent parameter and can be used to differentiate between symptomatic and asymptomatic patients.

This study provides a clearer conclusion of physiological motion patterns of the lumbar spine. This will eventually be compared to motion patterns of patients with lumbar conditions or who have received lumbar surgery.

Conflicts of Interest

None declared.

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Abbreviations

METC: Medical Ethical Review Committee
T: time point

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Protocol

Impact of Removing Nonprescription Codeine in Australia: Protocol for a Prospective Cohort Study

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Abstract

Background: On February 1, 2018, Australia rescheduled codeine to a prescription-only medication. Many concerns were associated with this change, including increased financial costs, reduced service accessibility, the potential for poorer pain management, and a decline in physical and mental health if codeine could not be accessed. In the research literature, there is limited knowledge about the long-term consequences of rescheduling pharmaceutical opioids and, as Australia has followed many countries in implementing a restriction on codeine, further study of these consequences is critical.

Objective: The goal of this study was to examine the impact of rescheduling codeine from an over-the-counter (OTC) product to a prescription-only medicine on the primary measures of codeine use and dependence in a prospective cohort of people who are frequent consumers of OTC codeine. Secondary measures included pain and self-efficacy, health service use, and mental health.

Methods: The Codeine Cohort study aimed to recruit 300 participants in Australia who regularly (at least a few times per week for the past 6 months) used OTC codeine. Using an online survey, participants were followed up at three time points (February 2018, June 2018, and February 2019) after codeine was rescheduled.

Results: All four waves of data collection are complete, with the final round of data collection finalized in August 2019. Data analyses are yet to be completed. Information on demographics, codeine use and dependence, physical and mental health, medication use, and health service use will be analyzed using mixed models.

Conclusions: Results of this study will provide insight into the effectiveness of regulatory restriction in curtailing nonmedical use of and harms associated with codeine. Additionally, results will explore positive and negative outcomes of codeine rescheduling for individual patients, which informs health professionals who support patients who use codeine and further community education.

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KEYWORDS

codeine; opioids; dependence; rescheduling; drug policy

Introduction

Background

Codeine is the most commonly used opioid in the world [1]. Regulation of its availability varies among countries; in New Zealand, the United Kingdom, most of Canada, and Ireland, codeine is available as an over-the-counter (OTC) preparation and is often combined with paracetamol or a nonsteroidal anti-inflammatory drug (NSAID) such as ibuprofen [2]. Despite its wide use, there are a number of concerns about codeine as an analgesic, with risks of prolonged misuse of OTC codeine-ibuprofen products including life-threatening complications such as gastric bleeds, renal failure, hypokalemia, and opioid dependence [3,4].

In addition to risk of serious harm, there is limited evidence for the addition of low-dose codeine (16 to 25 mg of codeine per dose) to paracetamol or ibuprofen preparations for improved pain relief [5-9]. This, coupled with the known availability of effective nonopioid alternatives for pain relief [10-12], raises concerns about the place of low-dose codeine in ongoing pain management.

International awareness of the misuse of OTC pharmaceuticals containing codeine is growing [13-15], and government responses have predominantly focused on upscheduling (increasing prescribing restrictions), improving guidelines and procedures around the supply of low-dose codeine preparations. For instance, the United States, Japan, India, and most of Europe are moving toward making pharmaceuticals containing codeine prescription-only medications [16,17].

Although upscheduling is an important regulatory response, this is not reflected with many studies in the research literature. For example, when hydrocodone combination products became restricted in the United States in 2014 [18], few studies explored the impact of this change on individuals. One study was conducted through a pain association in the United States, following thousands of individuals seeking support [19]. An online survey was used to evaluate the short-term (100 days) impact following the rescheduling of hydrocodone. Participants reported being placed on less effective medications, increased costs, inconvenience, and negative shifts in their relationships with health professionals. As other countries consider making similar changes to codeine and other opioids, further research to review the longer term implications of rescheduling is needed. Unintended potential consequences of rescheduling and restricting supply include fewer pain relief options for consumers, movement toward stronger opioids, and an increased burden on health care systems [20,21].

Restriction of OTC codeine product availability in Australia began in May 2010 [22]. Codeine preparations were required to be stored behind the counter and pack sizes reduced to a maximum 5-day supply. Despite these restrictions, OTC codeine remained widely used. In 2013, more than 15 million packets of OTC codeine were sold in Australia [23], representing almost one pack per person aged over 15 years [24]. Furthermore, OTC codeine accounted for 37% of opioid sales in the general community [24]. Despite the initial upscheduling, concerns in Australia with the misuse of OTC codeine products increased [25], with reports of growing numbers of patients with codeine dependence presenting to emergency departments and drug treatment services [4,26,27].

In December 2016, the Therapeutic Goods Administration of Australia determined that the limited therapeutic gain offered was outweighed by the evidence of harm associated with OTC codeine use, and the products were moved to schedule 4 (prescription only), effective February 1, 2018 [28]. This decision was based on concerns regarding the harmful side effects of codeine use as well as the known availability of safer OTC products (eg, ibuprofen-paracetamol combinations) with comparable efficacy [28].

Prior to the upscheduling of codeine in Australia, regular consumers of OTC codeine and health professionals queried whether this decision would, in fact, reduce codeine-related harms [29]. Participants were concerned about other unintended consequences, including poorer pain management, limited physical health, and increased emotional distress. It is important to study the outcomes of rescheduling decisions to determine if health professional and consumer concerns are realized and also to understand the impact of rescheduling decisions more broadly, given that this is a common regulatory lever used by governments internationally. To address this need, this study sought to evaluate the impact of rescheduling codeine in a prospective cohort of regular codeine users who were assessed 3 months prior to and followed for 12 months after the February 2018 rescheduling.

Objectives

The goal of this study was to examine the impact of rescheduling codeine from an OTC product to a prescription-only medicine on the primary measures of codeine use and dependence in a prospective cohort of people who are frequent consumers of OTC codeine. Secondary measures included pain and pain self-efficacy, health service use, and mental health.

Methods

Study Design and Setting

The Codeine Cohort study was an online-based single-center prospective longitudinal study. Participants were recruited in November 2017, and those who were eligible were invited to complete the first online survey for November 2017 (baseline). Codeine was rescheduled to prescription-only on February 1, 2018, and follow-up surveys were completed 1 month (end of February 2018), 4 months (June 2018), and 12 months (February 2019) after this rescheduling. These time points were selected to allow sufficient evaluation of the immediate, short-term, and long-term effects of the rescheduling. To allow as many participants as possible to respond, data collection for the third time point (February 2019) was finalized by August 2019. Data analyses are yet to be completed.

Ethics Approval and Consent to Participate

This study was approved by the Human Research Ethics Committee of the University of Tasmania (HREC reference number: H0016685).

Participants

Participants were required to be at least aged 18 years and living in Australia. They were asked about the frequency of their codeine use at the screening stage and offered the following response options: every day, a few times a week, once a week, a few times a month, at least monthly, or less than monthly. Eligible participants were required to have used OTC codeine at least a few times per week or more for the previous 6 months. This threshold for frequency of use was based on results from a previous online study of codeine consumers where the top third of participants were using OTC codeine once a week or more [30]. A threshold of a few times per week or more was adopted to allow a sufficiently high baseline of codeine use from which any changes in this measure over time could be detected.

Participants who self-reported that they were in current treatment for codeine dependence were excluded from the study as changes in their codeine use as a result of treatment rather than policy change may confound the interpretability of the study results.

Study Measures

Measures used in this study covered a range of domains including demographic information, health service use, pain and coping, physical and mental health, and codeine use and codeine dependence. Areas evaluated in this study were based on key concerns raised by health professionals and consumers in a previous study evaluating attitudes about codeine rescheduling in Australia [29]. Measures used were based on recommendations made by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials [31] and previous studies exploring opiate use using online surveys [30,32]. Measures, domains, and time points at which data were collected are summarized in Table 1.

Table 1. Domains, measures, tools, and time points for data collection for the Codeine Cohort study.

Domain	Measure	Baseline	T1[a]	T2[b]	T3[c]
Demographics					
Age, sex, accommodation	—	x			
Education, employment	—		x		
Health service use					
Use of physician, pharmacist, and emergency department for codeine	—	x	x	x	x
Pain					
Pain and coping	PSEQ[d]	x	x	x	x
Physical functioning	PEG[e]	x	x	x	x
Mental health					
Depression	PHQ- 9[f]	x	x	x	x
Anxiety	GAD-7[g]	x	x	x	x
Codeine use and dependence	• AUDADIS-5 CIDI[h]: substance abuse module	x			x
	• SDS[i]	x	x	x	x
	• CDS[j]	x	x	x	x
Treatment					
Current medication	Self-complete 7-day medication diary	x	x	x	x
Nonmedication treatment options	—	x	x	x	x

[a]T1: 1 month after rescheduling.

[b]T2: 4 months after rescheduling.

[c]T3: 12 months after rescheduling.

[d]PSEQ: Pain Self-Efficacy Questionnaire.

[e]PEG: Pain Intensity, Enjoyment of Life and General Activity Assessment Tool.

[f]PHQ-9: Patient Health Questionnaire, 9-item.

[g]GAD-7: Generalized Anxiety Disorder 7-item Scale.

[h]AUDADIS-5 CIDI: Alcohol Use Disorder and Associated Disabilities Interview Schedule–5 Composite International Diagnostic Interview.

[i]SDS: Severity of Dependence Scale.

[j]CDS: Codeine Dependence Scale.

Measures

Primary Measures

Alcohol Use Disorder and Associated Disabilities Interview Schedule–5

Past year codeine use disorder symptoms were assessed using the Alcohol Use Disorder and Associated Disabilities Interview Schedule–5 (AUDADIS-5) [33]. The reliability and validity of the AUDADIS-5 in relation to substance abuse and dependence disorders for a range of drugs is well documented in several international studies [34,35]. To assess withdrawal symptoms, 12 symptoms were taken from the Composite International Diagnostic Interview (CIDI): substance abuse module. The CIDI is a standardized diagnostic interview designed for assessing mental disorders (including substance use disorders) according to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision,* and *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) [36]. Diagnosis of codeine withdrawal was operationalized consistently with DSM-5 opioid withdrawal criteria [37] (at least 3 opioid withdrawal symptoms present concurrently at a distressing level or withdrawal relief). As the AUDADIS-5 may only be administered every 12 months, this measure was used at baseline (November 2017) and the third time point (February 2019).

Medication Diary

A medication diary was used to assess all medication use retrospectively for the past 7 days. Included were questions about the medication name, strength (mg), dose, number of times taken per day, and how many days that dose was taken across the last week.

Secondary Measures

Severity of Dependence Scale

The Severity of Dependence Scale (SDS) was used as a brief screener for possible codeine dependence. This has been validated with a range of substances, including heroin, cocaine, amphetamines [38-40], benzodiazepines [41], cocaine [42], cannabis [43], and alcohol [44]. In addition to a range of substances, the SDS has also been validated with problematic analgesic use (including combination products containing codeine) [45] where a cutoff of 5 or more demonstrated reasonable sensitivity (72.3%) and specificity (78.6%) for identifying individuals who may be problematic users of analgesics [45,46].

Codeine Dependence Scale

The Codeine Dependence Scale (CDS) was used as an additional measure of possible codeine dependence [47]. The CDS has 4 questions and is statistically validated against the SDS (based on an SDS score of ≥5). It has a cutoff value of ≥2 and has high sensitivity (84%) and specificity (94%) for identifying likely cases of codeine dependence [47].

Pain Intensity, Enjoyment of Life, and General Activity Assessment Tool

The Pain Intensity, Enjoyment of Life, and General Activity Assessment Tool (PEG) is a brief measure of pain with 3 items evaluating pain intensity and the level of interference in general activity and enjoyment of life [48]. It is derived from the widely used Brief Pain Inventory. The PEG demonstrates excellent internal consistency and good construct validity, with a sensitivity to change (at 6 months postbaseline) consistent with the Brief Pain Inventory [48] and demonstrated responsiveness to clinical interventions [49].

Pain Self-Efficacy Questionnaire

The Pain Self-Efficacy Questionnaire (PSEQ) is a 10-item questionnaire that assesses the confidence people feel in completing a number of activities despite experiencing pain [50]. The PSEQ has demonstrated adequate reliability and validity [51] and has been used in a wide variety of clinical populations, countries, and languages [52-58].

Patient Health Questionnaire–9 Item

The Patient Health Questionnaire–9 item (PHQ-9) is a 9-item questionnaire that examines symptoms of depression as defined in the DSM-5 [59,60]. Scores indicate the severity of depressive symptoms, with a maximum score of 27. Scores of 5, 10, 15, and 20 represent mild, moderate, moderately severe, and severe depression, respectively [60]. The PHQ-9 has demonstrated validity [61,62] and has been used widely in research, clinical practice, and surveys of mental health [63-68].

Generalized Anxiety Disorder 7-Item Scale

The Generalized Anxiety Disorder 7-item Scale (GAD-7) is a 7-item questionnaire that evaluates symptoms of generalized anxiety disorder. Scores of 5, 10, and 15 indicated mild, moderate, and severe anxiety, respectively [69]. The GAD-7 has demonstrated satisfactory validity and strong clinical utility in primary care settings and in the broader population [69-71].

Health Service Use

The health service use questions included in this online survey assessed the number of visits with a physician, pharmacist, and emergency department in the past 3 months related to codeine use. These questions were adapted from the Pain and Opioids In Treatment cohort study [72].

Participant Recruitment and Procedure

Participants were recruited through professional and personal networks; posts on relevant internet health forums and organizations (eg, Pain Australia, Pharmacy Guild); and University of Tasmania, University of New South Wales, and National Drug and Alcohol Research Centre media releases and emails to research participants from a previous study who had consented to be contacted for future participation opportunities [29]. Social media, including Facebook advertisements and Twitter, was also used, as it has been demonstrated to enable recruitment of greater populations of participants with high levels of substance use and associated issues [73].

Potential participants were directed to an internet survey using Research Electronic Data Capture [74], where they were given detailed study information and asked to provide informed consent and answer a few brief screening questions to assess eligibility (including questions on age, living location, and frequency of codeine use). Eligible participants were invited to complete the first online survey (November 2017, baseline) by

email using a unique and secure link. The first survey took between 20 and 30 minutes to complete. Participants were placed in a prize draw to win one of twenty $100 gift vouchers at baseline (November 2017) and were reimbursed with a $20 gift voucher at each of the three follow-up time points (February 2018, June 2018, and February 2019). Data collection for the final time point was completed by August 2019. Contact details including an email address and phone number were collected at baseline to enable communication over the course of the study.

A number of cohort management strategies were employed based on a Cochrane review and meta-analysis of participant retention [75]. First, participants were reimbursed for their research contribution. Second, a number of methods were used to contact participants and encourage them to participate, including reminder emails when a follow-up stage of data collection had commenced. Additionally, text messages with their unique survey link and phone calls to participants were made, if email reminders were insufficient in encouraging participants to complete the survey at that time point.

Eligibility criteria were not disclosed so that participant responses could not be tailored to ensure study entry. Part of a participant's eligibility was determined from their answers to a screening question about the frequency of their codeine use in the last 6 months. Finally, at baseline (November 2017) participant reimbursement was a prize draw rather than a voucher to reduce the likelihood of those who would participate for monetary gain.

Data Analysis

Data analyses for the Codeine Cohort study are yet to be completed. Assuming statistical assumptions are met for the primary outcome of total daily codeine dose (mg; continuous variable), mixed-model analyses will be conducted. For the primary outcome of codeine dependence (categorical), generalized linear mixed models will be applied. In the case of missing data for both aims, sensitivity analyses will be conducted with a full information dataset (all data collected from each individual), a last observation carry-forward dataset, and a dataset derived from multivariate imputation of missing data. In the event of the number of usable observations not meeting requirements from power calculations, regression results from the dataset with multivariate imputation will be used (subject to sensitivity analyses).

Logical model-building processes (ie, stepwise regression) will be applied to the development of these models with covariates including demographics, physical and mental health, and pain. Secondary analyses will be conducted using similar analytic frameworks taking into account the nature of the outcome variable under study.

Sample Size and Power

Power analyses were conducted to estimate a sufficient sample size required to assess the potential effects of codeine restriction on two primary outcomes: continuous measures of codeine use per day and rates of dependence (categorical).

Average Total Codeine Use per Day (Averaged Dose in Milligrams Over the Preceding 7 Days)

Using a repeated measures analysis of variance framework with four assessment points and 200 participants, there is power of 0.8 or greater to detect an effect size as small as Cohen f=0.1 as statistically significant for the main effect of time where there are correlations among repeated measurements as low as r=.20 and even smaller magnitude effects (f=0.08) where correlations are the more likely r=.50. In a Web survey of codeine consumers by Nielsen et al [76], daily codeine use had a mean of 68 (SD 72) mg. These power calculations suggest that there would be sufficient power to identify a drop from 68 to 53 mg per day in the daily codeine dose variable as statistically significant, assuming this range of correlations and this standard deviation of scores. This is a little more than a single 12.8 mg nonprescription (OTC) codeine tablet, and therefore, is of an appropriate magnitude for this study.

Rates of Dependence

Detailed assessment of dependence was completed at baseline and T3 (only) using the AUDADIS-5 [33]. In order to compare rates of dependence at these two time points, a comparison of correlated proportions can be made with a McNemar test. A sample size of 249 pairs achieves 80% power to detect a difference between two paired proportions of 0.1 at an alpha level of .05, when the proportion at baseline is 0.2 and the proportion at T3 is 0.1. The proportion of discordant pairs is 0.3. Approximately 20% of regular OTC codeine users are dependent (46); therefore, it was assumed that 20% of the study cohort could be defined as dependent at baseline. Assuming a 20% dropout rate [77], a sample size of 300 was considered appropriate to meet both of these aims.

Results

All four rounds of data collection for the Codeine Cohort study are complete. Data analyses are underway currently and results from the study will be published in 2020.

Discussion

Preliminary Findings

Prior to the rescheduling of OTC codeine in Australia, individuals who regularly used codeine (consumers) indicated their concern whether rescheduling would minimize codeine-related harms (including dependence) and the impact the requirement of a prescription for codeine would have on their emotional and physical health, their pain management, and overall quality of life (29). Pharmacists shared consumer concerns and were focused on the burden regular doctor appointments would create in terms of finances for consumers.

Examination of administrative data such as sales, prescriptions, and emergency presentations provides some information as to the success of upscheduling at the population level. This study will contribute to an improved understanding of the outcomes, positive and negative, associated with codeine rescheduling for the individual patient, which informs where further community education and intervention are needed most. Also, by exploring

whether codeine rescheduling leads to reduced codeine use and levels of dependence, this study will provide insight into the overall effectiveness of regulatory restriction in curtailing misuse of pharmaceutical opioids.

Strengths and Limitations

In terms of strengths, this is a novel study; to the knowledge of the authors, a prospective online cohort investigating the longer term impacts (over 12 months) of codeine rescheduling on the individual patient has not been studied before. Additionally, a number of measures were used, including multiple measures of codeine dependence. In terms of limitations, the study has a modest sample size and the generalizability of findings to the general population might be limited, as the sample comprised self-selected participants in an online study.

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Authors' Contributions

The study was conceived by JM, RB, and SN. JM, RB, and SN provided input into the study design and research questions. RB and SN developed the statistical analysis plan. JM completed the first draft of the manuscript with input from RB and SN. JM, RB, and SN reviewed the manuscript and provided input into the final draft.

Conflicts of Interest

SN is an investigator on untied educational grants from Indivior that are unrelated to this work and has received honoraria for providing training on identification and treatment of codeine and other opioid dependence (Indivior). SN is an investigator on research grants from Seqirus to understand harms of ambulance and emergency department attendances from pharmaceutical opioids which is unrelated to this work. SN is the recipient of an National Health and Medical Research Council Research Fellowship (#1163961). RB was an investigator on an untied education grant from Mundipharma to conduct postmarketing surveillance on oxycodone and an untied educational grant from Reckitts Benkiser to develop a scale to identify extramedical use of pharmaceutical opioids.

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Abbreviations

AUDADIS-5: Alcohol Use Disorder and Associated Disabilities Interview Schedule–5
CIDI: Composite International Diagnostic Interview
CDS: Codeine Dependence Scale
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
GAD-7: Generalized Anxiety Disorder 7-item Scale
NSAID: nonsteroidal anti-inflammatory drug
OTC: over-the-counter
PEG: Pain Intensity, Enjoyment of Life, and General Activity Assessment Tool

PHQ-9: Patient Health Questionnaire–9
PSEQ: Pain Self-Efficacy Questionnaire
SDS: Severity of Dependence Scale

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Protocol

Automated Respiratory Rate Counter to Assess Children for Symptoms of Pneumonia: Protocol for Cross-Sectional Usability and Acceptability Studies in Ethiopia and Nepal

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Abstract

Background: Manually counting a child's respiratory rate (RR) for 60 seconds using an acute respiratory infection timer is the World Health Organization (WHO) recommended method for detecting fast breathing as a sign of pneumonia. However, counting the RR is challenging and misclassification of an observed rate is common, often leading to inappropriate treatment. To address this gap, the acute respiratory infection diagnostic aid (ARIDA) project was initiated in response to a call for better pneumonia diagnostic aids and aimed to identify and assess automated RR counters for classifying fast breathing pneumonia when used by front-line health workers in resource-limited community settings and health facilities. The Children's Automated Respiration Monitor (ChARM), an automated RR diagnostic aid using accelerometer technology developed by Koninklijke Philips NV, and the Rad-G, a multimodal RR diagnostic and pulse oximeter developed by Masimo, were the two devices tested in these studies conducted in the Southern Nations, Nationalities, and Peoples' Region in Ethiopia and in the Karnali region in Nepal.

Objective: In these studies, we aimed to understand the usability of two new automated RR diagnostic aids for community health workers (CHWs; health extension workers [Ethiopia] and female community health volunteers [Nepal]) and their acceptability to CHWs in Ethiopia and Nepal, first-level health facility workers (FLHFWs) in Ethiopia only, and caregivers in both Ethiopia and Nepal.

Methods: This was a prospective, cross-sectional study with a mixed methods design. CHWs and FLHFWs were trained to use both devices and provided with refresher training on all WHO requirements to assess fast breathing. Immediately after training, CHWs were observed using ARIDA on two children. Routine pneumonia case management consultations for children aged 5 years and younger and the device used for these consultations between the first and second consultations were recorded by CHWs in their patient log books. CHWs were observed a second time after 2 months. Semistructured interviews were also conducted with CHWs, FLHFWs, and caregivers. The proportion of consultations with children aged 5 years and younger where CHWs using an ARIDA and adhered to all WHO requirements to assess fast breathing and device manufacturer instructions for use after 2 months will be calculated. Qualitative data from semistructured interviews will be analyzed using a thematic framework approach.

Results: The ARIDA project was funded in November 2015, and data collection was conducted between April and December 2018. Data analysis is currently under way and the first results are expected to be submitted for publication in 2020.

Conclusions: This is the first time the usability and acceptability of automated RR counters in low-resource settings have been evaluated. Outcomes will be relevant for policy makers and are important for future research of this new class of diagnostic aids for the management of children with suspected pneumonia.

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KEYWORDS

community health worker; pneumonia; child; respiratory rate; Nepal; Ethiopia

Introduction

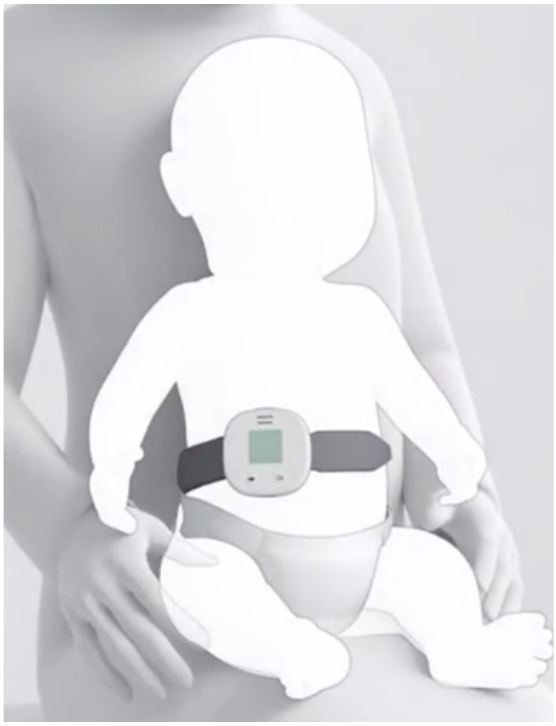
Acute respiratory infections (ARIs), primarily pneumonia, are the leading infectious causes of death among children aged 5 years and younger globally, accounting for an estimated 900,000 pneumonia-related deaths in 2015 [1]. Deaths from pneumonia in children result mostly from delayed presentation to appropriate health care providers and inappropriate treatment [2].

Classification of fast breathing by community health workers (CHWs) and first-level health facility workers (FLHFWs; collectively known as front-line health workers) is based on manually counting the number of breaths in 60 seconds in children aged 5 years and younger with cough and/or difficulty breathing to assess whether the respiratory rate (RR) is high enough for a particular age to prescribe antibiotics and treat suspected pneumonia, as defined by the World Health Organization (WHO) integrated management of childhood illness (IMCI) guidelines [3] for FLHFWs and their integrated community case management (iCCM) guidelines [4] for CHWs. IMCI was developed by WHO in 1995 and is an integrated approach to child health for FLHFWs that focuses on the well-being of the child aiming to reduce death, illness, and disability and promote improved growth and development among children aged 5 years and younger. iCCM is an approach recommended by WHO, United Nations Children's Fund (UNICEF), and partners where CHWs are trained to identify and treat symptoms of pneumonia, malaria, and diarrhea in children aged 5 years and younger, as well as to detect and refer malnutrition and severely ill children to the nearest health facility. In practice, front-line health workers admit that counting the RR can be difficult as children breath irregularly and faster than adults, the child may not be calm and still for a full minute, and it is difficult to define what is and is not a breath [5]. Misclassification of the observed rate remains high [6,7], often leading to inappropriate treatment [8].

UNICEF's acute respiratory infection diagnostic aid (ARIDA) project was initiated as a response to the call for better pneumonia diagnostic aids [9,10] and aims to identify and assess automated RR counting aids for classifying fast-breathing pneumonia for use by front-line health workers in resource-limited community settings and health facilities. The ARIDA project team conducted these field studies to test RR diagnostic aids that meet a target product profile developed by UNICEF and shared with industry, academia, and partners to encourage and guide development of new automated RR counting aids [11]. The ARIDA technical specification listed in UNICEF's request for proposals [12] outlines that any ARIDA device must automatically detect and display the RR to aid in the classification of fast breathing in children aged 5 years and younger and include a visual indicator for notification of above or below the age-specific fast-breathing thresholds as defined by the WHO IMCI/iCCM guidelines [3,4].

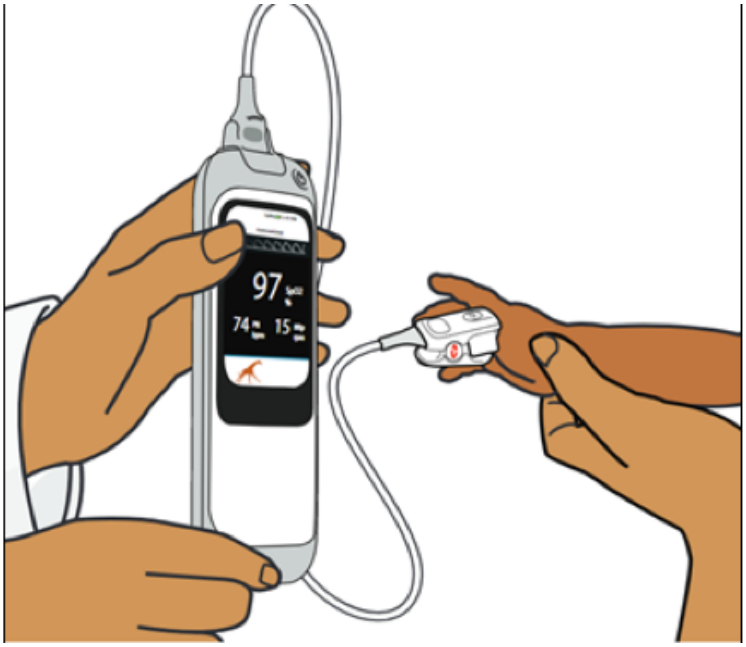
Two devices were newly developed that met the requirements of the UNICEF target product profile and were therefore selected for these studies. The Children's Automated Respiration Monitor (ChARM; Koninklijke Philips NV) uses an accelerometer-based system to measure the RR in children aged 0 to 59 months and automatically classifies the breathing rate according to the iCCM/IMCI guidelines [3,4]. The device is intended to be used by front-line health workers in low-resource settings. It is strapped around the belly of the child using an elastic belt (Figure 1) and costs approximately US $50.

Figure 1. Illustration of the Children's Automated Respiration Monitor (Koninklijke Philips NV) positioned on a child.



The Rad-G pulse oximeter (Masimo; Figure 2) uses differential light absorbance technology to measure oxygen saturation (SpO_2), respiration rate from plethysmograph, pulse rate, and perfusion index in children aged 0 to 59 months and classifies the breathing rate and oxygen saturation of the child according to IMCI/iCCM guidelines [3,4]. For this study, a revised iCCM algorithm to include oxygen saturation as well as RR measurements was used by the CHWs in the sick child consultations. The device has one universal probe or sensor suitable for all ages of children that is placed on the child's finger or toe (Figure 2) and costs approximately US $250. These studies were the first time these devices were field tested for usability and acceptability.

Figure 2. Illustration of the Rad-G pulse oximeter (Masimo) attached to a child.

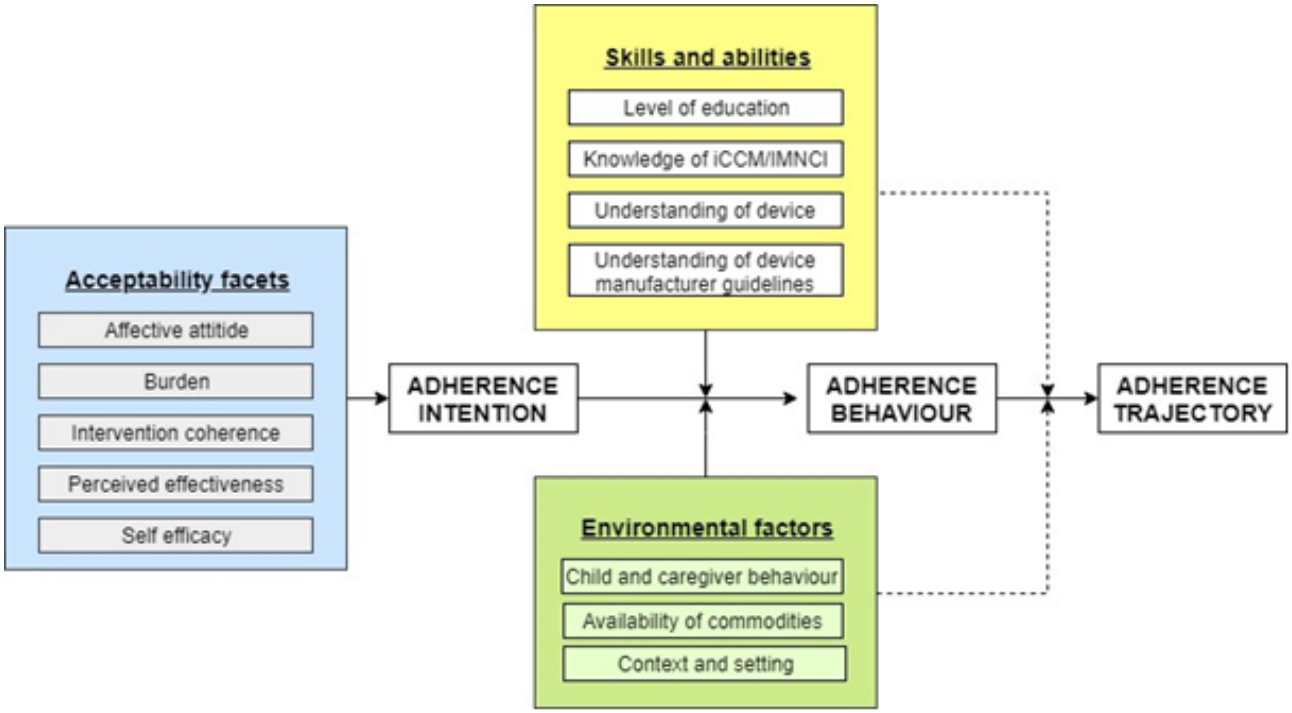


To gather evidence around the usability of ARIDA devices to CHWs, the ChARM and Rad-G devices were evaluated in the community in Ethiopia and Nepal. Acceptability of both devices to CHWs, FLHFWs (Ethiopia only), and caregivers was evaluated.

The framework in Figure 3 outlines the factors that might affect a front-line health workers' adherence to all WHO requirements to assess fast breathing and device manufacturer instructions for use, also known as implementation fidelity [13], when using ARIDA (current and future behavior), and how they are related. A front-line health workers' intention to adhere to guidelines

is affected by 5 facets of acceptability [14]: affective attitude, burden, intervention coherence, perceived effectiveness, and self-efficacy. These acceptability facets, combined with the health workers' skills and abilities (level of education, knowledge of relevant guidelines, understanding of how to use the device, and the device manufacturer guidelines) and other constraints (child behavior, caregiver behavior, context, and setting) will affect their adherence to guideline behavior and adherence trajectory over time.

Figure 3. Conceptual framework of front-line health workers' adherence to integrated community case management/integrated management of childhood illness/community-based integrated management of neonatal and childhood illness guidelines, adapted from Adams [15].



Conceptual framework of front-line health workers' adherence to integrated community case management/integrated management of childhood illness/community-based integrated management of neonatal and childhood illness guidelines, adapted from Adams [15].

The study aim was to understand the usability of two new automated RR diagnostic aids for CHWs and their acceptability to CHWs and caregivers in Ethiopia and Nepal (and FLHFWs in Ethiopia only) including facilitators and barriers to use.

The study objectives were as follows:

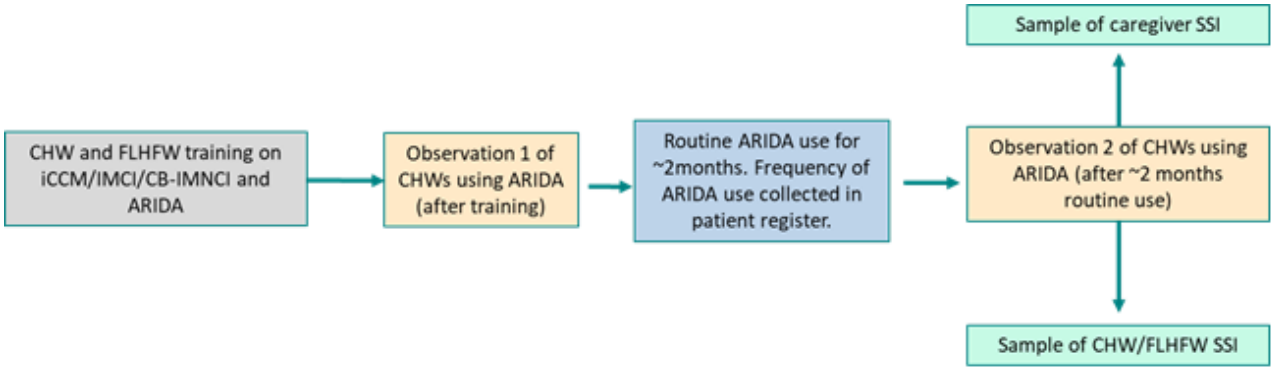
- Determine if CHWs in Ethiopia and Nepal adhere to all WHO requirements to assess fast breathing and device manufacturer instructions for use to assess and classify children aged 5 years and younger with cough and/or difficult breathing using an ARIDA
- Document the user experience of the ARIDA in a sick child consultation
- Explore the acceptability of the ARIDA to CHWs and caregivers of the sick children being assessed in Ethiopia and Nepal (and FLHFWs in Ethiopia only)

Methods

Study Design

The study was a prospective, cross-sectional study with a mixed methods design that included quantitative and qualitative data collected from study participants. Prior to starting the first quantitative data collection, a training of trainers and research teams and a cascade training for CHWs/FLHFWs were conducted (Figure 4).

Figure 4. Acute respiratory infection diagnostic aid acceptability study flow diagram.



Study Sites

The study was conducted in community settings and first-level health facilities in Shebedino, Dale, and Boricha districts in the Southern Nations, Nationalities, and Peoples' Region (SNNPR), Ethiopia, and around the town of Jumla, in the Karnali region, Nepal. These two settings were selected because of the high burden of childhood pneumonia, having a mixture of rural and periurban populations, sufficient numbers of CHWs and FLHFWs with experience and availability, political stability, and availability of oxygen at district hospitals in case the children needed to be referred (Table 1).

Table 1. Details of study sites selected from the acute respiratory infection diagnostic aid usability and acceptability studies.

Variable	Ethiopia	Nepal
Pneumonia deaths (percentage of total deaths in children aged 5 years and younger) [16]	18%	15%
Name for CHW[a]	HEW[b]	FCHV[c]
Length of initial CHW training program provided	1 year	18 days
Literacy level	High	Extremely low
Standard practice pneumonia diagnosis tool being used	Wristwatch/ARI[d] timer	ARI timer
WHO[e] case management algorithms used in country	HEW: iCCM[f]; FLHFW[g]: IMCI[h]	FCHV: CB-IMNCI[i]

[a]CHW: community health worker.

[b]HEW: health extension worker.

[c]FCHV: female community health volunteer.

[d]ARI: acute respiratory infection.

[e]WHO: World Health Organization.

[f]iCCM: integrated community case management.

[g]FLHFW: first-level health facility worker.

[h]IMCI: integrated management of childhood illness.

[i]CB-IMNCI: community-based integrated management of neonatal and childhood illness.

These districts also had logistical and operational feasibility for data collection and quality assurance (QA). In Ethiopia, Malaria Consortium (implementing partner) had a strong relationship with the SNNPR regional health bureau and public health officials in Shebedino, Dale, and Boricha districts because of previous pneumonia diagnostic research and a strong presence in the UNICEF field office. In Nepal, the Karnali region was a focus area for the UNICEF country office.

Study Populations

The studies, in Nepal and Ethiopia, included 528 children aged 5 years and younger with cough and/or difficult breathing presenting to CHWs for consultations. Also, 132 CHWs in Nepal and Ethiopia performing iCCM/community-based integrated management of neonatal and childhood illness (CB-IMNCI) at the community level participated in both the quantitative and qualitative elements of the study. In Ethiopia, the government has deployed more than 42,000 female CHWs, or health extension workers (HEWs), providing preventive, promotive, and curative health services to the community. There are typically two HEWs assigned to a health post in a subdistrict with a population of 3000 to 5000. The HEWs are supervised by health centers that oversee approximately 5 health posts each. In Nepal, CHWs are called female community health volunteers (FCHVs) [17].

The iCCM algorithm has been adapted for individual country settings, and in Nepal FCHVs are trained on a version called CB-IMNCI [18], while in Ethiopia HEWs are trained on iCCM [19]. In the CB-IMNCI in Nepal, the primary role of FCHVs is as health promoters/educators, and this includes dispensing essential commodities (eg, distribution of iron, zinc, oral rehydration solution, chlorhexidine). As per the WHO guideline, in the CB-IMNCI program in Nepal, amoxicillin is the first-line

drug of choice for the treatment of neonatal sepsis and pneumonia, but more recently a national policy change has meant that this is not provided by FCHVs, who instead refer the patient to the health center to receive the treatment there. In Ethiopia, HEWs are trained for 1 year on an extended iCCM algorithm and can provide treatment of amoxicillin as required [19].

Furthermore, the CB-IMNCI program has included various social and behavioral change community level activities including demand generation activities for newborn and child health services, primarily undertaken by FCHVs. In Ethiopia, 20 FLHFWs performing IMCI at the health center level were trained to use an ARIDA and participated in semistructured interviews but were not assessed for adherence to guidelines as it was felt adequate to test usability on the lowest level of health workers. For each study, 20 caregivers of children aged 5 years and younger were also recruited to participate in the qualitative semistructured interviews.

Sample Size

The study was powered for the primary outcome: the proportion of consultations of children aged 5 years and younger where CHWs using an ARIDA adhered to all WHO requirements to assess fast breathing and device manufacturer instructions for use after 2 months of routine use. The study used the sample size formula for a prevalence study with a specified level of confidence and precision: $n=Z^2*P(1–P)/e^2$, where Z=value from standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% confidence interval), P is the expected true proportion, and e is the desired precision, thereby allowing a device-specific sample size to be calculated.

Assuming that the proportion of RR assessments completed correctly with an ARIDA by a CHW is 75%, and of these 95% classify the child correctly, the estimated prevalence of the primary outcome is 71%. Based on a prevalence of 71%, a sample of n=141 sick child assessments was required to estimate the true value (primary outcome) with a precision of 7.5% and 95% confidence. Applying the design effect of 1.7 and a 10% increase in the sample to account for possible clustering due to the first and second observations (posttraining and postroutine practice) and loss to follow-up of CHWs between training, respectively, a sample size of n=264 child assessments per evaluation was required (141*1.7*1.1). Thus, 132 CHWs were observed completing 2 sick children consultations twice, one directly after being trained and one subsequently after having used the device for 2 months in routine practice. This totals 528 sick child consultations for the ChARM and Rad-G usability and acceptability studies in Nepal and Ethiopia.

Semistructured interviews were conducted with a subsample of HEWs immediately after their final observation. HEWs were purposefully selected with a range of years' experience; caregivers of children who were assessed by this subsample of HEWs were also interviewed. A convenience sample of FLHFWs available on the day we visited health facilities was used.

Selection Criteria

Inclusion criteria for the acceptability study were any child aged 0 to 59 months with parent or guardian consent. For those aged 2 to 59 months, the child also needed to have had cough and/or difficulty breathing. Exclusion criteria for children in all elements of the study were those with general danger signs of convulsions or no movement for children aged 0 to 59 months and lethargy or unconsciousness for children aged 2 to 59 months [3], those with a parent or guardian aged younger than 16 years, those not having parent or guardian consent, or those having any device manufacturer safety exclusion criteria. For ChARM, these were preterm babies (born before 37 weeks of gestation), children wearing a supportive device at area of chest/belly, or children whose skin was not intact on their chest/belly [20]; for Rad-G, these were children whose skin was not intact at the application site (finger or toe).

Outcomes

The primary outcome was the proportion of consultations on children aged 5 years and younger where CHWs using an ARIDA adhered to all WHO requirements to assess fast breathing and device manufacturer instructions for use after 2 months of routine use. Secondary outcomes included the difference in proportion of consultations on children aged 5 years and younger where CHWs using an ARIDA adhered to WHO requirements to assess fast breathing and device manufacturer instructions for use immediately after training and after 2 months of routine use; number of errors made during the consultation of the sick child (assessment, classification, treatment, referral) immediately after training and after 2 months of using an ARIDA routinely; mean time taken to complete the sick child consultation; number of unsuccessful attempts using an ARIDA; number of times no ARIDA reading could be obtained in up to 3 attempts; number of children assessed for respiratory signs and symptoms by CHWs with an ARIDA during routine practice; and for Rad-G, number of children assessed for respiratory signs and symptoms by CHWs with standard practice in the same period of the previous year. Qualitative outcomes focused on acceptability were derived from the 7 facets of acceptability as presented in the work by Sekhon et al [21].

Training

A 2-day joint training was held for the country-level research teams of project manager, data manager, and 7 teams each consisting of 2 research assistants and the trainers of CHWs/FLHFWs. This training was led by the Malaria Consortium capacity building specialist and supported by the relevant Ministry of Health regional health authorities, UNICEF country office, and the global ARIDA project team. The 2 days focused on introducing the team to the ARIDA study, required WHO case management and manufacturer RR instructions for use, and how to use the ARIDA devices. The research teams and trainers then separately attended a third day of training which was more specific to their role in the study. The 7 research teams focused on the study procedures including the informed consent process, how to use the CommCare data collection application (version 2.38.1, Dimagi Inc), data collection and management procedures, and QA procedures. Before the second

observation, there was a 1-day training on conducting the qualitative semistructured exit interviews with caregivers, HEWs, and FLHFWs for all research teams led by the Malaria Consortium project team. In their training-of-trainers session, the 7 trainers focused on developing the modules for the CHW/FLHFW training and adult learning techniques. The 132 CHWs in each study were trained in 6 cohorts of approximately 22 CHWs each. In Ethiopia, a seventh FLHFW training for 20 FLHFWs was also done. Each cohort was trained over 2 days by one trainer supported by a member of the Malaria Consortium project team, implementing partner project team, and local research teams, as required. The training consisted of the following modules: introduction to training, ARIDA study overview, assessment of fast breathing with an ARIDA, field evaluation data forms, case management of pneumonia, and ethical considerations and subject safety. CHWs/FLHFWs were guided through the information giving and consent process. For each study, a comprehensive job aid was developed and provided to each health worker. The job aid contained all the information to conduct the required WHO case management and device manufacturer instructions for use, along with further information on pneumonia prevention (Multimedia Appendix 1). The training included a half-day practice session that allowed each health worker to practice using the device on a range of different aged children. All CHWs had to pass a competency-based assessment at the end of the training in order to be included in the study. This involved a 12-question assessment including a practical exam on device use, with a pass mark of 75%. One research team and trainer participated in a 5-day master pretest of all procedural activities that followed the exact procedures of the study to ensure all members of the research team and trainers were conversant with the study procedures and data collection materials. The pretest piloted the training of CHWs/FLHFWs, subject screening, subject consent, quantitative evaluation, data collection with the draft data collection tools, data entry into the CommCare data collection application, and the log-book review. The research team visited up to 3 research sites with a trainer and conducted the quantitative assessment. There was a 5-day debrief, revision, and finalization of all quantitative study data collection materials after the pretest, plus translation of relevant study materials. There was a second 1-day pretest for all 7 quantitative research assistants to practice using the finalized data collection tools. Within each research team, one research assistant participated in a 1-day pretest of qualitative data collection tools before the second quantitative evaluation during the 2 months of routine data collection. Each research assistant conducted a semistructured interview with 2 CHWs/caregivers. There was a 1-day debrief, revision, and finalization of the qualitative data collection materials after the pretest, plus translation of relevant study materials.

Study Procedures

The ChARM assessments took place between May and July 2018 in Ethiopia and between September and December 2018 in Nepal. The Rad-G assessments took place between September and December 2018 in Ethiopia. Patients were screened by the CHWs using the ARIDA job aid, children were enrolled prospectively based on eligibility, and the research assistants obtained the parent or guardian's consent.

For each consultation, 2 research assistants independently observed the CHW conduct the sick child consultation and silently recorded their actions on tablet-based observation checklists. In some instances, the research assistants needed to capture source documentation in the form of photographs of the age group selected and the ARIDA RR reading. The research assistants also took photographs of the patient registers for later review. Once the evaluation was completed, the research assistants gave feedback to the CHWs if they had observed any incorrect actions. The CHWs' actions for the 8 steps involved in using ChARM were recorded (Table 2).

There were also 8 steps that were observed when the Rad-G was used (Table 3).

Table 2. Steps of the child consultation that community health workers using the Children's Automated Respiration Monitor were observed completing.

Consultation step	Definition	Category
Correct child position	Back fully supported, either in the arms of the caregiver (younger child), sitting on caregiver's lap with their back against the caregiver's front (older child), or lying on their back on a flat surface (older child)	Device manufacturer instructions for use
Correct device position	Device on the belly line in line with the nipple	Device manufacturer instructions for use
Correct belt attachment	ChARM[a] touching skin/clothing and belt not tangled	Device manufacturer instructions for use
Correct age group	Age group selected by HEW[b] on ChARM matches screening checklist	WHO[c] requirements to assess fast breathing
Correct child behavior immediately before ChARM attempt	Calm: not actively crying or moving	WHO requirements to assess fast breathing
Correct child eating/breastfeeding status during successful ChARM attempt	No eating/breastfeeding	WHO requirements to assess fast breathing
Correct child behavior during successful ChARM attempt	Calm: not actively crying or moving	WHO requirements to assess fast breathing
Correct classification	According to CB-IMNCI[d] guidelines, based on screening age group and breathing status of the child	WHO requirements to assess fast breathing

[a]ChARM: Children's Automated Respiration Monitor.

[b]HEW: health extension worker.

[c]WHO: World Health Organization.

[d]CB-IMNCI: community-based integrated management of neonatal and childhood illness.

Table 3. Steps of the child consultation that community health workers using Rad-G were observed completing.

Consultation step	Definition	Source of step
Child calm before assessment	Calm: not actively crying or moving	WHO[a] requirements to assess fast breathing
Correct mode selected	Screening mode	Device manufacturer instructions for use
Correct age group	Age group recorded by HEW[b] on Rad-G device matches screening checklist	WHO requirements to assess fast breathing
Correct probe position	Fully inserted	Device manufacturer instructions for use
Correct probe direction	Picture on top of finger or toe	Device manufacturer instructions for use
Child not eating/feeding during assessment	No eating/breastfeeding	WHO requirements to assess fast breathing
Child calm during assessment	Calm: not actively crying or moving	WHO requirements to assess fast breathing
Correct classification	According to iCCM[c] guidelines, based on screening age group and breathing status of the child	WHO requirements to assess fast breathing

[a]WHO: World Health Organization.

[b]HEW: health extension worker.

[c]iCCM: integrated community case management.

The total time taken to get a successful ARIDA reading was recorded using a stopwatch. Once the assessment was completed, the CHW recorded the result of the RR and informed the research assistants of the classification and treatment. If an RR count could not be obtained on the first attempt, the attempt was recorded as unsuccessful and repeated up to two more times before the CHW moved to current practice (ARI timer, phone, watch).

On completion of the assessment, the CHW explained the classification to the caregiver and gave them treatment, referral, or home care advice as appropriate. CHWs were asked to use ARIDA during the 2 months of routine use but could revert to standard practice if they needed to and were instructed to record which device they used in their patient register using colored stickers (one patient register per health post).

Data Collection

Quantitative data was collected using an electronic data collection platform (CommCare) installed onto password-protected 7C Pro (Tecno Mobile) tablets and backed up to a protected cloud server. Unique identification codes were used to anonymize patient data and CHW data. All RR evaluation data were independently entered by each research

assistant. The data manager downloaded data daily and entered it into a data checker with in-built validation checks. Trial conduct was audited internally and externally. In Ethiopia, Malaria Consortium (United Kingdom and Ethiopia) and UNICEF (Supply Division and Ethiopia Country Office) conducted weekly QA visits to the research site during data collection. In Nepal, Malaria Consortium (UK), UNICEF Country Office, and HERD International (Nepal implementing partner) also conducted QA visits to the research site during data collection. Malaria Consortium created a QA form template (Multimedia Appendix 2) which was completed by team members when shadowing the research teams. All data collected by research assistants from the CHW assessments was checked and verified by the Malaria Consortium research team daily. A 1-day refresher training was provided to the quantitative research team before the start of the second data collection. Qualitative data was audiorecorded for each semistructured interview, and all audio recordings were translated into English and transcribed by the research assistants.

The project had an 11-person advisory committee of global experts to facilitate dissemination and uptake of any findings within participating countries as well as with key partners in the global childhood pneumonia community.

Data Analysis

Descriptive information about the CHWs will be presented including CHW participation (number trained and number completing first and second observation), sex, district, number of years qualified as a CHW, CHW education level, last integrated refresher training and last supervision (Ethiopia only), and literacy level (Nepal only). Descriptive information about the number of children enrolled, number of evaluations started, number of evaluations completed by ARIDA and standard practice, and child age and sex will also be presented.

The primary outcome will be calculated as the proportion of consultations with children aged 5 years and younger where CHWs using an ARIDA adhered to all WHO requirements to assess fast breathing and device manufacturer instructions for use after 2 months of routine use. This analysis will be disaggregated by age group, breath rate, and SpO_2 classification (Rad-G only). Secondary outcomes including the proportion of CHWs correctly performing steps reflecting the device manufacturer instructions for use and steps that reflect all WHO requirements to assess fast breathing will also presented, as will the difference in the proportion of consultations that were completed correctly between observation 1 and observation 2. For the main outcomes, the most conservative estimates will be used (ie, if the two research assistants disagreed on how the CHW performed a step in the assessment, the one that recorded an inconsistency/error for that step was used over the one who recorded that the step was performed correctly). A sensitivity analysis using less conservative observations will also be presented. The mean time taken to complete the full assessment will be calculated for ChARM as from the time the CHW straps on the device to when the device displays an RR reading. For Rad-G, it will be from the time when the CHW turns on the Rad-G (prior to probe placement) to when the Rad-G displays an SpO_2 and RR reading. The number of children who were assessed for signs of respiratory illness by CHWs with ARIDA or standard practice during routine care will also be presented. For the qualitative analysis, semistructured interview data will be summarized and presented for caregivers and front-line health workers separately. All qualitative data will be analyzed using MAXQDA (VERBI GmbH). Transcripts will be loaded into the software and a coding frame for the CHW/FLHFW interviews and caregiver interviews developed. Underlying themes should emerge iteratively. Each theme will be critically analyzed by the research team until the final themes are agreed upon.

Ethical Approval and Consent to Participate

The study was approved by ethical review boards in each study country at national or regional level: in Ethiopia, from the SNNPR Health Bureau Health Research Review Committee (ref -241/20852) on May 4, 2018; in Nepal, from the Nepal Heath Research Council (Ref 2334); and in the United Kingdom, from the Liverpool School of Tropical Medicine (Ref 18-026) on July 10, 2018. Participants and health workers were recruited into the study only after written informed consent.

Results

The ARIDA project was funded in November 2015, and data collection was conducted between April and December 2018. Data analysis is currently under way, and the first results are expected to be submitted for publication in 2020.

Discussion

Summary

The aim of this study is to understand usability (Can CHWs in Ethiopia and Nepal adhere to all WHO requirements to assess fast breathing and device manufacturer instructions for use to assess and classify children aged younger than 5 years with cough and/or difficult breathing using ARIDA after 2 months of routine use?) and acceptability (ie, front-line health worker and caregiver perceptions on benefits and barriers to ARIDA use). This is the first study that has been done to build the evidence base around the usability and acceptability of new automated RR diagnostic aids in low-resource settings.

Strengths and Limitations

A potential strength of the study is that we used two research assistants to observe the CHWs' consultations and can perform a sensitivity analysis to understand how disagreement between research assistants could affect adherence rate for different assessment stages. Another strength is that we measured adherence to the algorithm after 2 months without any refresher training, which should provide evidence on how adherence could change between training and second evaluation with no additional support.

A study limitation could be the Hawthorne effect [22] where the CHWs could change their behavior because the research assistants are observing the consultation. In the study procedure, the research team took steps to minimize this by silently observing child consultations and not interfering with the consultations. There was also the potential for response bias

from the self-reported routine data collected through the patient register from the CHWs who may have had a tendency to inflate their reporting of the number of times they used the ARIDA.

Conclusion

We hope that the results of this study will add to the evidence base for automated RR counters and support decision making around their adoption and increased use in these settings and among these types of health workers. The findings can also be used to help device manufacturers in the development and refinement of such technologies for use in low-resource settings.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Rad-G job aid, Ethiopia.
[PDF File (Adobe PDF File), 2020 KB - resprot_v9i3e14405_app1.pdf]

Multimedia Appendix 2
Quality assurance assessment form.
[DOCX File , 16 KB - resprot_v9i3e14405_app2.docx]

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Abbreviations

ARI: acute respiratory infection
ARIDA: acute respiratory infection diagnostic aid
CB-IMNCI: community-based integrated management of neonatal and childhood illness
ChARM: Children's Automated Respiration Monitor
CHW: community health worker
FCHV: female community health volunteer
FLHFW: first-level health facility worker
HEW: health extension worker
iCCM: integrated community case management
IMCI: integrated management of childhood illness
QA: quality assurance
RR: respiratory rate
SNNPR: Southern Nations, Nationalities, and Peoples' Region
SpO_2: oxygen saturation
UNICEF: United Nations Children's Fund
WHO: World Health Organization

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Protocol

Regenerative Therapy for Liver Cirrhosis Based on Intrahepatic Arterial Infusion of Autologous Subcutaneous Adipose Tissue-Derived Regenerative (Stem) Cells: Protocol for a Confirmatory Multicenter Uncontrolled Clinical Trial

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Abstract

Background: Liver cirrhosis results from chronic hepatitis, and is characterized by advanced fibrosis due to long-term hepatic inflammation. Cirrhosis ultimately leads to manifestations of jaundice, ascites, and encephalopathy, and increases the risk of hepatocellular carcinoma. Once cirrhosis is established, resulting in hepatic failure, no effective treatment is available. Therefore, novel therapies to inhibit disease progression of cirrhosis are needed.

Objective: The objective of this investigator-initiated clinical trial is to assess the safety and efficacy of autologous adipose tissue-derived regenerative (stem) cell therapy delivered to the liver via the hepatic artery in patients with liver cirrhosis.

Methods: Through consultation with the Japan Pharmaceuticals and Medical Devices Agency, we designed a clinical trial to assess a therapy for liver cirrhosis based on autologous adipose tissue-derived regenerative (stem) cells, which are extracted using an adipose tissue dissociation device. The primary endpoints of the trial are the serum albumin concentration, prothrombin activity, harmful events, and device malfunction.

Results: Enrollment and registration were initiated in November 2017, and the follow-up period ended in November 2019. Data analysis and the clinical study report will be completed by the end of March 2020.

Conclusions: Completion of this clinical trial, including data analysis, will provide data on the safety and efficacy of this novel liver repair therapy based on autologous adipose tissue-derived regenerative (stem) cells using an adipose tissue dissociation device.

Trial Registration: UMIN Clinical Trials Registry UMIN000022601; https://tinyurl.com/w9uqw3q
International Registered Report Identifier (IRRID): DERR1-10.2196/17904

(JMIR Res Protoc 2020;9(3):e17904) doi:10.2196/17904

KEYWORDS

adipose tissue-derived regenerative (stem) cells; stromal cells; stem cells; liver cirrhosis; investigator-initiated clinical trial protocol; adipose tissue dissociation device; protocol; stem cell therapy; liver

Introduction

Background

Liver cirrhosis is the eventual outcome of chronic liver diseases, including chronic hepatitis, autoimmune hepatitis, primary biliary cholangitis, alcoholic hepatitis, and nonalcoholic steatohepatitis (NASH), which is currently increasing in prevalence relative to other liver conditions and is associated with metabolic disease [1,2]. Liver cirrhosis leads to various complications, including esophageal varix, hepatic encephalopathy, ascites, jaundice, and hepatocellular carcinoma, which result in a worse prognosis for patients with cirrhosis [3]. The end stage of cirrhosis is hepatic failure, for which liver transplantation is the only treatment as an extremely invasive procedure that requires continuous immunosuppressive therapy for the remainder of the patient's life. Moreover, there are very few cadaveric donors in Japan, with only 69 cadaveric donors (and 347 living donors) for liver transplantation available in 2017 [4]. Therefore, novel treatments for cirrhosis should be explored.

Fatty liver disease and NASH are emerging chronic liver diseases. Although steatohepatitis is strongly correlated with metabolic syndrome, it is not clear why steatosis of the liver causes chronic inflammation and ultimately leads to cirrhosis [5].

Objectives

Mesenchymal stem cells are somatic pluripotent stem cells that can differentiate into various cell types [6,7] and have immunomodulatory capabilities [8]. Freshly isolated adipose tissue is a rich source of mesenchymal stem cells [9]. Similar to bone marrow cells, autologous mesenchymal cells can be used therapeutically. Therefore, freshly isolated autologous adipose tissue-derived stromal cells have attracted substantial attention for potential therapeutic use in various organs [10]. We previously conducted a clinical study to confirm the safety of a liver cirrhosis therapy based on adipose tissue-derived stromal cells [11]. To determine the practicality of this treatment strategy, we designed an open-label, uncontrolled multi-institutional clinical trial for a regenerative therapy for liver cirrhosis based on adipose tissue-derived regenerative (stem) cells (ADRCs). This trial was designed to assess the safety and efficacy of the treatment in consultation with the Japan Pharmaceuticals and Medical Devices Agency (PMDA). Herein, we describe the detailed protocol for the trial.

Methods

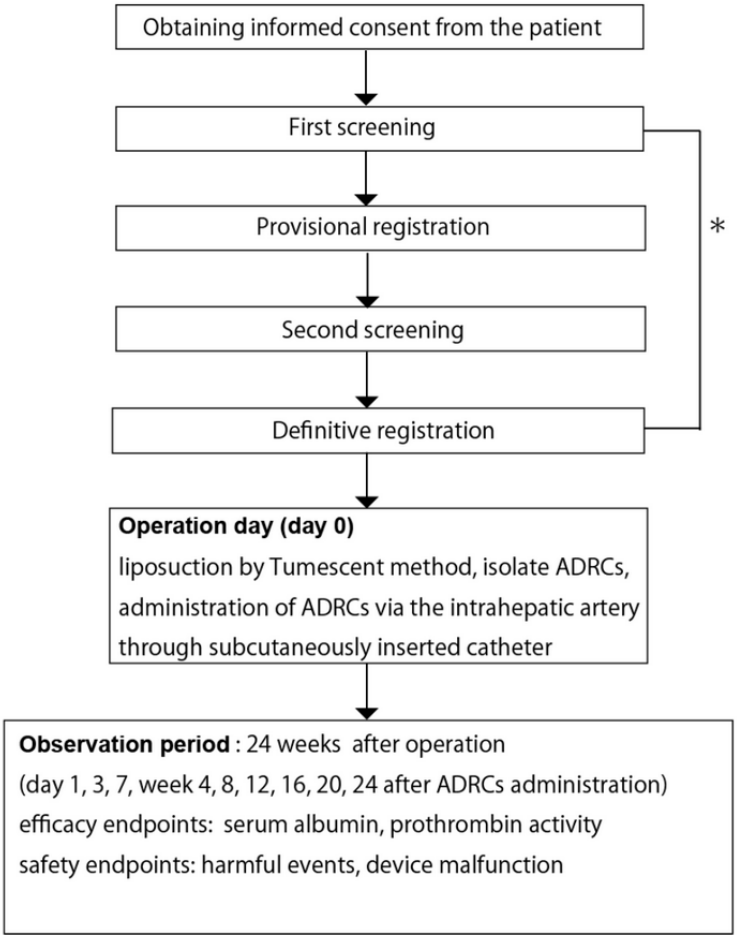
Study Objectives

The objective of the study is to assess the efficacy and safety of an autologous ADRC therapy delivered to the liver via the hepatic artery.

Study Design and Enrollment

This is a multicenter, collaborative, nonblinded, uncontrolled clinical trial carried out in Japan (Kanazawa University Hospital, Osaka Medical College Hospital). The adipose tissue dissociation device used to isolate ADRCs is the investigational trial device. All patients who meet the eligibility criteria and provide informed consent will be enrolled (Figure 1). Multimedia Appendix 1 shows the detailed schedule of the clinical study.

Figure 1. Case enrollment procedure. This trial will enroll patients with nonalcoholic steatohepatitis or fatty liver disease who provided written informed consent. Regarding the steps indicated by the asterisk, screening and registration involve the following: nonalcoholic steatohepatitis patients who drink ≤20 g alcohol per day will simultaneously undergo the first and second screening stages, as well as provisional and definitive registration. Patients who drink >20 g but ≤70 g alcohol will undergo the initial screening and be provisionally registered. These patients are expected to restrict their alcohol consumption to ≤20 g per day for 8 weeks and then undergo the second screening stage. Patients meeting the enrollment criteria at this stage will be definitively registered to undergo the treatment described in this protocol followed by observation for 24 weeks after treatment. ADRCs: adipose tissue-derived regenerative (stem) cells.



Eligibility Criteria

Inclusion Criteria

Patients who meet all of the following criteria are eligible for the study. A diagnosis of liver cirrhosis is obtained based on imaging or histological examination due to two types of etiology: NASH or fatty liver. NASH is determined according to the following criteria: alcohol intake ≤20 g/day, no other obvious liver injury etiologies, and association with complications such as obesity (especially visceral fat), metabolic syndrome, and diabetes mellitus. Fatty liver disease is determined according to the following criteria [12,13]: alcohol intake >20 g/day but ≤70 g/day (note that the criterion for the amount of alcohol consumed is the same for men and women in accordance with previous publications [12,13]; although the duration of alcohol drinking is not specified, most hepatologists assume that the patient has consumed the defined amount of alcohol for more than 5 years); no other obvious liver injury etiologies or association of complications such as obesity (especially visceral fat), metabolic syndrome, and diabetes mellitus; and ability to maintain alcohol intake at ≤20 g/day from the provisional registration until the second screening (≥8 weeks). Other eligibility criteria include age at the time of providing consent ≥20 years or older but <80 years, total bilirubin concentration ≤3.0 mg/dL at screening, platelet count ≥5.0×10^4/μL at screening, prothrombin activity ≥70% at screening, serum creatinine level ≤1.5 mg/dL at screening, serum albumin ≤4.0 g/dL at screening, and patients able to provide written informed consent themselves.

Exclusion Criteria

Patients are excluded if they meet any of the following conditions: presence of severe pulmonary hypertension such as esophageal gastric varix, which poses a risk of rupture; presence of severe heart diseases, renal diseases, respiratory diseases, blood diseases, blood coagulation disorders, or other serious complications; presence or presumed presence of severe infectious diseases requiring intravenous treatment with antibiotics, antimycotics, or antiviral agents; presence of concurrent malignancy or history of malignancy within the past 5 years not deemed to be fully cured; history of cerebrovascular disease (eg, cerebral infarction, cerebral hemorrhage); known or suspected pregnancy; active treatment with adrenal corticosteroids; inability to maintain alcohol intake at <20 g/day after providing informed consent and for 24 weeks after

treatment or discontinuation; treatment with other cell therapies within 6 months before providing informed consent; enrollment in other clinical trials; presumed life expectancy <1 year at the time of providing informed consent; allergy to drugs (eg, anesthetics) used in the trial; history of taking prohibited concomitant medications (antiplatelet drugs, anticoagulant drugs) within 7 days before providing informed consent; and judged to be inappropriate for enrollment by the principal investigator or subinvestigator.

Treatment

Subcutaneous adipose tissue from the abdomen or buttock of the patient will be obtained by Tumescent liposuction, a standard cosmetic surgery method, under general anesthesia or local/lumbar spine local anesthesia. Regenerative (stem) cells will be isolated using the adipose tissue dissociation system Celution 800/IV (Cytori Therapeutics, San Diego, CA, USA), followed by measurements of cell number and viability in a collected cell aliquot using a nucleocounter (ChemoMetec, Gydevang, Denmark). Cell viability should be at least 70%. Cell aliquots will be prepared at a density of 1×10^6/mL in Ringer's lactate. ADRCs, at a density of 3.3×10^5 cells/kg, will be administered through the common hepatic artery via the tip of microcatheter IV (Asahi Intec Co Ltd, Seto, Aichi, Japan), inserted subcutaneously into a femoral or upper arm artery. For 24 weeks after providing informed consent, albumin products, antiplatelets, and anticoagulants will be prohibited. The following drugs can be continued only when administered after informed consent has been provided: branched-chain amino acids, vitamin E, other nutritional therapies, hepatic protection drugs, and antihyperlipidemia drugs.

Image Analysis of Chronic Liver Disease and Liver Biopsy

Abdominal computed tomography or magnetic resonance images of the liver will be obtained using a contrast reagent before registration and 24 weeks after treatment. These images will be analyzed by a radiologist and hepatologist who will assess the morphological changes in the liver, spleen, and vasculature due to chronic liver disease. The pathology will be assessed using the nonalcoholic fatty liver disease activity score, which covers steatosis, lobular inflammation, hepatocellular ballooning, and fibrosis [14], in addition to the Matteoni classification [15].

Follow up

The observation period after treatment will be 24 months during which examinations will be performed at various time points (Multimedia Appendix 1).

Endpoints

Efficacy endpoints are the serum albumin level and prothrombin activity. The safety endpoints are adverse reactions and device malfunction.

Sample Size

The serum albumin level is considered a key efficacy endpoint with respect to the proof of concept and mode of action of this treatment. In an earlier clinical study, we observed that 3 of 4 cirrhotic patients who underwent the same treatment as applied in this clinical trial had improved serum albumin levels after 3-6 months [11]. A sample size of 7 patients provided a power of over 85% with a one-sided significance level of .05 to reject the null rate of 3% under the expectation of 40%. This clinical trial was designed to explore safety and efficacy, and therefore a total of 8 patients was considered to be sufficient for this purpose.

Statistical Analysis

A detailed statistical analysis of efficacy will be performed, and a per-protocol analysis will also be conducted secondarily. Subjects who underwent treatment will be used for the safety analysis. The statistical analysis protocol will be designed before data confirmation and fixation.

Regulatory Compliance

Approval of this clinical trial was obtained from the institutional review boards of Kanazawa University Hospital and Osaka Medical College Hospital. The study has been registered in the Japanese UMIN Clinical Trials Registry (UMIN000022601). This investigator-initiated clinical trial design was discussed with, and submitted to, the Japan PMDA before enrollment commenced. All treatment procedures in this trial will be carried out in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines [16]. Written informed consent will be obtained from the patients before the first and second screenings as well as at registration.

Results

The study is supported by the Japan Agency of Medical Research and Development. The required number of patients has been registered. The data analysis and study report will be completed in March 2020.

Discussion

Liver cirrhosis is a serious condition that results from chronic liver diseases [1]. Unless the cause of chronic liver disease can be addressed, liver cirrhosis typically worsens, leading to complications such as esophageal varix, ascites, jaundice, and hepatic encephalopathy. Thus, preventing the progression of liver cirrhosis is extremely important for maintaining quality of life and improving the prognosis of patients with cirrhosis.

Mesenchymal stem cells are somatic stromal stem cells that can differentiate into mesodermal lineage cells, adipocytes, osteocytes, and chondrocytes, as well as hepatocytes of the endodermal lineage. In addition, mesenchymal stem cells have immunomodulatory characteristics [8,17], which makes them a promising cell source for treating organ injury associated with inflammation. In this context, many nonclinical and clinical studies have investigated the application of mesenchymal stem cells in regenerative therapy for diseases of various organs [18]. We previously reported the use of murine adipose tissue-derived mesenchymal stem cells to repair murine liver cirrhosis caused by NASH, demonstrating enhancement of albumin production in hepatic parenchymal cells as well as suppression of hepatic inflammation [7]. In addition, we found that freshly isolated

stromal vascular cells of the adipose tissue contained a fraction that was immunosuppressive to hepatitis of mice [10]. Thus, ADRCs are considered to be potentially useful for treatment of cirrhosis, contributing to repairing/regenerating the damaged liver.

Treatment procedures involve aspiration of the patient's own subcutaneous adipose tissue [19,20], isolation of stromal cells from the obtained adipose tissue, and administration of the stromal cells into the cirrhotic liver via the hepatic artery using a catheter. As per our PMDA consultation, this clinical trial of cirrhosis will employ an adipose tissue dissociation system that automatically isolates ADRCs. The benefit of this approach is that it does not involve a complex cell manufacturing process requiring good manufacturing and clinical practice. In addition, the therapy is autologous, which may help avoid unexpected harmful intense immune responses such as allergies.

Chronic liver diseases have various antecedents [21]. Most chronic liver diseases are associated with hepatitis B or C virus infection. Recently, direct-acting antivirals have been developed to treat hepatitis C virus infection and nucleotide analogues are available for the treatment of hepatitis B virus infection. With the former treatment, almost all patients achieve complete elimination of hepatitis C virus [22]. Although fibrosis is not always ameliorated and recovery of the impaired hepatic reserve is gradual [23], the population of hepatitis C virus-infected patients is decreasing rapidly [24]. Nucleotide analogues for hepatitis B are extremely effective at inhibiting virus replication, thus attenuating chronic hepatitis activity. Although the pathogenic mechanisms underlying autoimmune hepatitis and primary biliary cholangitis are not fully understood, they are believed to be related to immune disorders; autoimmune hepatitis responds to steroids and immunosuppressants [25] and primary biliary cholangitis responds to ursodeoxycholic acid [26]. By contrast, there is no established treatment for steatohepatitis.

If the results of this clinical trial are satisfactory and lead to approval of this novel regenerative therapy, a practical treatment will be available for liver cirrhosis that is especially beneficial for patients with steatohepatitis, for which there is currently no effective treatment.

Acknowledgments

We thank Dr Tadami Fujwara and Dr Masaaki Mizuno for general advice regarding this clinical trial. This trial is supported by the Research Project for Practical Applications of Regenerative Medicine of the Japan Agency of Medical Research and Development (grant number: 19bk0104072h0003) and the Kanazawa University Hospital subsidy.

Authors' Contributions

YS was intensively involved in overall preparation of this clinical trial, including the design and initiation processes. SF, YT, AA, and KH extensively contributed to initiating and conducting this clinical trial at Osaka Medical College. YS, MT, OI, ST, SU, AS, KK, TY, TY, EM, and MH are involved in this clinical trial as subinvestigators at Kanazawa University Hospital. SF, YT, and AA are involved as subinvestigators at Osaka Medical College. AN and TH contribute to this clinical trial as technical assistants. TW contributed to manuscript preparation and review. KH helped with the pathological assessment. KH and SK are the principal investigators of this trial. SK is a coordinating investigator.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Trial design overview.
[XLSX File (Microsoft Excel File), 15 KB - resprot_v9i3e17904_app1.xlsx]

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Abbreviations

ADRCs: adipose tissue-derived regenerative (stem) cells
NASH: non-alcoholic steatohepatitis
PMDA: Japan Pharmaceuticals and Medical Devices Agency

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Corrigenda and Addenda

Correction: A Patient-Centered PaTH to Address Diabetes: Protocol for a Study on the Impact of Obesity Counseling

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Related Article:

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In the article “A Patient-Centered PaTH to Address Diabetes: Protocol for a Study on the Impact of Obesity Counseling” (JMIR Res Protoc 2019;8(4):e12054), there were three instances of incorrectly written code. The following corrections have been made:

In the Introduction section, under the subheading “Objectives”, under the bullet point of “Aim 1”, the code has been changed from “G0477” to “G0447”. The text was revised from:

> *We will determine how the annual probability of receiving obesity counseling (as defined by Common Procedural Treatment [CPT] codes G0477, G0473, S9470, and/or S9449)*

to:

> *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)*

In the Methods section, under the subheading “PaTH Patients With Diabetes and At Increased Risk for Diabetes”, the code has been changed from “G0477” to “G0447”. The text was revised from:

> *For this study, receipt of IBT will include the presence of the G0477, G0473, S9470, and/or S9449 CPT codes*

to:

> *For this study, receipt of IBT will include the presence of the G0447, G0473, S9470, and/or S9449 CPT codes*

In the Methods section, under the subheading “Definition and Measurement of Key Diabetes Outcomes and Covariates”, the code has been changed from “G0477” to “G0447”. The text was revised from:

> *Receipt of counseling for obesity will be assessed through PaTH EHRs and supplemented by claims data when available, utilizing G0477, G0473, S9470, and/or S9449 CPT codes*

to:

> *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*

These corrections do not impact the results or findings of the paper.

These corrections will appear in the online version of the paper on the JMIR Research Protocols website on March 4, 2020, 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 has also been resubmitted to those repositories.

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Corrigenda and Addenda

Sub-study Correction: Use of Human-Centered Design to Improve Implementation of Evidence-Based Psychotherapies in Low-Resource Communities: Protocol for Studies Applying a Framework to Assess Usability

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Related Article:

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The authors of “Use of Human-Centered Design to Improve Implementation of Evidence-Based Psychotherapies in Low-Resource Communities: Protocol for Studies Applying a Framework to Assess Usability” (JMIR Res Protoc 2019;8(10):e14990) have identified several errors in reporting some details of one of the UW ALACRITY Center’s sub-studies.

Specifically, in the Methods section under the "Project Descriptions of the University of Washington’s Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults With Mental Illness Center Research" subsection, Study 1 (the learnability study) was reported as being delivered:

> *by bachelor degree–level social work students who manage health care for migrant farm workers in Eastern Washington State.*

This has been amended to:

> *by bachelor degree–level social work students who manage health care for migrant farm workers in central Washington State.*

In the Methods section, under the "Identification of Stakeholders" subsection, another error was identified. The sentence formerly stating:

> *the pool of stakeholder participants will include 15 bachelor’s degree–level social workers*

Has been changed to:

> *the pool of stakeholder participants will include 15 bachelor degree-level social work students*

Finally, in the Methods section under the "Test Phase" subsection, the manuscript stated that the intelligent tutoring system (ITS):

> *was selected for Study 1 because it can be scaled for broad use and reflects a standardized method that can help mitigate trainer drift.*

This has been revised to indicate that the ITS:

> *reflects a standardized method that can help mitigate trainee drift.*

The authors apologize for these oversights.

The correction will appear in the online version of the paper on the JMIR website on March 4, 2020, 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 has also been resubmitted to those repositories.

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Protocol

Innovative Approaches to Obtain Minors' Consent for Biomedical HIV Prevention Trials: Multi-Site Quasi-Experimental Study of Adolescent and Parent Perspectives

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Abstract

Background: Despite the high burden of new HIV infections in minor adolescents, they are often excluded from biomedical HIV prevention trials, largely owing to the ethical complexities of obtaining consent for enrollment. Researchers and ethics regulators have a duty to protect adolescents—as a special category of human subjects, they must have protection that extends beyond those afforded to all human subjects. Typically, additional protection includes parental consent for enrollment. However, parental consent can present a risk of harm for minor adolescents. Research involving minor adolescents indicate that they are unwilling to join biomedical trials for stigmatized health problems, such as HIV, when parental consent is required. This presents a significant barrier to progress in adolescent HIV prevention by creating delays in research and the translation of new scientific evidence generated in biomedical trials in adult populations.

Objective: This protocol aims to examine how parental involvement in the consent process affects the acceptability of hypothetical participation in biomedical HIV prevention trials from the perspectives of minor adolescents and parents of minor adolescents.

Methods: In this protocol, we use a quasi-experimental design that involves a simulated consent process for 2 different HIV prevention trials. The first trial is modeled after an open-label study of the use of tenofovir disoproxil fumarate and emtricitabine as preexposure prophylaxis for HIV. The second trial is modeled after a phase IIa trial of an injectable HIV integrase inhibitor. There are 2 groups in the study—minor adolescents aged 14 to 17 years, inclusive, and parents of minor adolescents in the same age range. The adolescent participants are randomized to 1 of 3 consent conditions with varying degrees of parental involvement. After undergoing a simulated consent process, they rate their willingness to participate (WTP) in each of the 2 trials if offered the opportunity. The primary outcome is WTP, given the consent condition. Parents undergo a similar process but are asked to rate the acceptability of each of the 3 consent conditions. The primary outcome is acceptability of the consent method for enrollment. The secondary outcomes include the following: capacity to consent among both participant groups, the prevalence

of medical mistrust, and the effects of the study phase (eg, phase IIa vs the open-label study) and drug administration route (eg, oral vs injection) on WTP (adolescents) and acceptability (parents) of the consent method.

Results: Enrollment began in April 2018 and ended mid-September 2019. Data are being analyzed and dissemination is expected in April 2020.

Conclusions: The study will provide the needed empirical data about minor adolescents' and parents' perspectives on consent methods for minors. The evidence generated can be used to guide investigators and ethics regulators in the design of consent processes for biomedical HIV prevention trials.

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KEYWORDS

HIV; biomedical ethics; adolescence; parental consent

Introduction

Background

Minor adolescents (those aged younger than 18 years) and young adults (aged 18-24 years) account for more than 1 in 5 new HIV infections in the United States. Sexual and gender minorities make up 80% of incident infections in adolescents and young adults, and African American men and transgender women account for 80% of infections among the sexual and gender minority youth [1]. Across age groups, minor adolescents are the least likely to know they have HIV, be connected to HIV care, and be virally suppressed [1]. Other at-risk populations have experienced significant declines in HIV rates with access to biomedical prevention interventions such as preexposure prophylaxis (PrEP), but similar declines have not been observed in minor adolescents [2]. PrEP, which involves taking antiretroviral medication, is up to 95% effective in preventing HIV acquisition. The first PrEP regimen, once daily oral tenofovir disoproxil fumarate and emtricitabine (TDF-FTC), was approved for use in adults at risk of HIV in 2012. Labeling for use with at-risk minor adolescents (those aged younger than 18 years) was delayed by 6 years owing to scarce data on the safety and tolerability of TDF-FTC as PrEP for minors [3].

Minor adolescents are often excluded from biomedical research. A recent analysis of 388 phase III and phase IV National Institutes of Health (NIH)–funded trials indicated minor adolescents and children were excluded from 75% of the studies [4]. In biomedical HIV prevention, less than 1% of clinical trials included minor adolescents [5,6]. The exclusion of minors and other vulnerable populations from clinical trials impedes the translation of science to public health practice, as is evident in the 6-year lag between the approval of TDF-FTC as PrEP for adults and the labeling indication for use with minors.

Investigators are often reluctant to engage minor adolescents in biomedical research on stigmatized conditions owing to the ethical complexities involved [5-7]. Minors are considered a vulnerable research population, and there are additional regulatory requirements for research with minors that extend beyond those afforded to all research participants [8-10]. The cornerstone of these additional protections for minors has been parental involvement in the consent process [8]. In this assent/permission model, a minor must assent to participation in the study, and their parent or guardian must provide permission for the minor to enroll.

Researchers have examined the negotiation of minor assent and parental permission within the context of therapeutic trials for chronic illnesses such as asthma and cancer. In this context, roughly 60% to 70% of adolescent-parent dyads agree on the enrollment decision [11,12]. Recent research suggests a similar concordance (56%) among adolescent-parent dyads who were asked to consider a hypothetical scenario in which the minor adolescent would enroll in a biomedical HIV prevention study [13,14]. The same research team found that 73% of discordant dyads were able to resolve their discordance through communication about their perspectives, often in a short time (median 2.5 min) [14].

Although the assent/permission model works reasonably well for enrolling minors in nonstigmatized research, it fails for research that poses greater than minimal risk of harm and addresses a stigmatized health condition or targets a socially marginalized population [15-18]. Parental engagement in the consent process introduces the risk of social harm, as research participation may result in the disclosure of sexual behaviors, sexual orientation, or gender identity. This type of disclosure, particularly for sexual and gender minority adolescents, can result in physically or psychologically abusive responses from parents or the minor being kicked out of their home. Exploratory work with minor adolescents whose sexual behaviors or demographic characteristics are indicative of a risk of HIV acquisition indicates that they are unwilling to risk social harm to enroll in biomedical research [19,20].

Research on decision making and cognition indicates that minor adolescents are reliably capable of understanding research concepts and providing informed consent [21,22]. These works argue for the consideration of the ways in which adolescents are vulnerable, rather than using age alone as a proxy for vulnerability [21,22]. Minors' capacity to consent is recognized in the willingness of institutional review boards (IRBs) to waive parental permission and allow adolescent self-consent for behavioral studies. For biomedical HIV prevention, regulatory concerns have been specifically addressed by the Food and Drug Administration, which states that minor self-consent for biomedical HIV prevention research is permissible under federal regulations [9,23]. However, our own work demonstrates that researchers and IRB members are concerned about minor

self-consent, and many see parental permission as a way to protect minors, support parent rights, and decrease liability for institutions [24,25].

Missing in the discussion are data from the youth and parents on acceptability and preferences around consent to biomedical HIV prevention trials. It is especially critical to understand the role of participants' racial and ethnic identity, their sexual orientation and disclosure to parents, and features of the biomedical HIV prevention drug or device as well as its stage of development. Black Americans experience structural and individual barriers to accessing health care [26], and their history of unequal treatment in both clinical care and research settings has resulted in the mistrust of health care providers and researchers. This mistrust is evident in research with young black sexual and gender minorities, who describe not only a general mistrust of research and pharmaceutical companies but also a specific concern that HIV prevention interventions could be designed to infect them with HIV rather than prevent infection [27,28]. Black parents who participated in a study of parental perspectives on minor participation in biomedical HIV prevention research also mentioned that the historic mistreatment of black research participants may affect black parents' willingness to allow their minors to enroll in research [29].

Recent research has indicated *outness* (the degree to which a sexual minority adolescent has disclosed their sexual orientation to parents, family members, and friends) has a significant association with willingness to participate (WTP) in HIV research. For example, Nelson et al [30] report that minors who were not out to guardians had 5 times greater odds of saying they would not participate in a future HIV study than those who were out to guardians. Mustanski et al [31] report similar associations between outness and WTP in HIV prevention trials.

Recently, 2 biomedical HIV prevention studies have included minor adolescents. The first, Adolescent Medicine Trials Network for HIV/AIDS Interventions protocol 113 (ATN 113), enrolled minor adolescents aged 15 to 17 years in an open-label study of the safety of and adherence to TDF-FTC as HIV PrEP. The second, Microbicide Trials Network (MTN) 023, enrolled adolescents aged 15 to 17 years in a phase IIa trial of the safety of and adherence to a dapivirine (25 mg) vaginal ring. These two trials differed in several important ways. First, the approaches to consent were different—participants in ATN 113 were permitted to self-consent, whereas MTN 023 required participants to have parental consent. Second, the drug delivery mechanisms were different—a tablet taken by mouth (TDF-FTC, ATN 113) vs a vaginal ring delivery system (dapivirine 25 mg, MTN 023). Finally, the stages of drug development and testing were different—the ATN 113 study was an open-label study of a drug with a well-known safety and tolerability profile owing to its long history of use in HIV treatment. Conversely, the MTN 023 study was a phase IIa study of an investigational new drug. Although the approaches to minor consent were different, to the best of our knowledge, there are no published studies that explore the effects of the drug delivery mechanism and the stage of drug development on (1) minors' WTP in biomedical HIV prevention trials or (2) parents' perspectives on the acceptability of minor consent. We add to the body of work on minor consent to participation in biomedical HIV prevention trials by examining the relationship between participant characteristics and features of the HIV prevention intervention as well as its stage of development.

Objective

Here, we describe the protocol for our ongoing study researching consent for minors. The project is titled *Consent 2.0* and is supported by the NIH-funded Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN). *Consent 2.0* examines the issue of minor consent to enrollment in biomedical HIV prevention trials from the perspective of the youth and parents. The study will expand the body of empirical evidence available to guide regulators, IRB members, researchers, and policy makers as they consider approaches to the ethical engagement of minor adolescents in biomedical research on stigmatized topics or with highly vulnerable populations. The purpose of the study is to examine how parental involvement in the consent process affects the acceptability of hypothetical participation in biomedical HIV prevention trials, from the perspective of minor adolescents and parents of minor adolescents. We use a simulated consent process, which emulates real consent processes for 2 different types of biomedical HIV prevention trials that have included minor adolescents.

With both adolescent and parent participants, we examine the effects of 3 possible consent processes: condition 1: minor self-consent; condition 2: adult permission required, with an option to select either a parent/guardian or a study-appointed ombudsperson; and condition 3: parental permission required. Under condition 1, the minor adolescent can consent to enrollment without seeking parental permission. Under condition 2, the minor adolescent is required to obtain permission to enroll from an adult and may choose between a parent/guardian or an ombudsperson. The ombudsperson is an adult who is familiar with the study and its risks and benefits and helps the adolescent arrive at the best decision for themselves. Under condition 3, the minor is required to have parental permission to enroll and assent to enrollment.

The study has 3 aims. First, we aim to describe how consent conditions influence minor adolescents' WTP in biomedical HIV prevention trials. In particular, we will evaluate if WTP in biomedical trials is affected by adolescents' concern about HIV, demographic characteristics (eg, race, ethnicity, and sexual and gender identity), family context, and medical mistrust. The second aim is to describe parents' attitudes toward the various consent models, their opinions of the risks and benefits of each model, and their conceptualization of a shared decision-making process for consent. Finally, the third aim is to describe the effects of the study agent's stage of development (eg, a drug with a well-established safety profile vs a new drug with an unknown safety profile) and the mechanism of delivery (eg, oral vs injection or intravaginal delivery) on minors' WTP and parents' perspectives on the acceptability of the different consent conditions.

Methods

Study Design Overview

We are using a quasi-experimental design to explore how the informed consent process affects the acceptability of biomedical HIV prevention trials from the perspective of sexually active minor adolescents and the parents of minor adolescents. All study participants complete a computer-assisted self-interview (CASI) that collects demographic, social, behavioral, and attitudinal measures. Then, participants undergo a simulated consent process for 2 different studies. The first study is modeled after the ATN 113, an open-label study of oral TDF-FTC as PrEP. The second study is modeled after the HIV Prevention Trials Network protocol 077 (HPTN 077), a phase IIa trial of an injectable HIV integrase inhibitor that is preceded by an oral lead-in of the same drug. Participants answer questions about the 2 studies.

Study Setting

We are recruiting participants from 4 partnering research sites in the following US cities: Baltimore, Maryland (partnering organization: Johns Hopkins University), Chicago, Illinois, (partnering organization: the University of Chicago), Aurora, Colorado (partnering organization: the University of Colorado School of Medicine), and Tampa, Florida (partnering organization: the University of South Florida). These cities have diverse populations, high rates of incident HIV infection among adolescents and young adults, and demonstrated success in recruiting minor adolescents for biomedical HIV research. Our partnering organizations have a history of recruiting sexual and gender minority adolescents of color for HIV research, which is also a strength of our selected sites.

Study Population

We are recruiting adolescents between the ages of 14 and 17 years, inclusive, who are able to read and speak English, are either HIV negative or uncertain of their HIV status, and have engaged in at least one sexual behavior associated with an increased risk of HIV (see Textboxes 1 and 2) in the last 12 months. The study is also recruiting adults who are able to read and speak English and are currently parenting an adolescent between the ages of 14 and 17 years, inclusive, whose HIV status is either negative or unknown. Adult participants are not parents or guardians of youth participants. All potentially eligible participants are asked to provide partial addresses that are assessed for matched pairs; any participant whose partial address matches that of a previously enrolled participant is rendered ineligible to participate in the study. Recruitment efforts begin with on-site outreach within the adolescent medicine clinics affiliated with our research sites. Our research sites were chosen for their diverse patient populations, their location in urban areas with ongoing HIV clinical trials, and their history of service to sexual and gender minority youth. Site-based recruitment efforts are supplemented by further recruitment via social media advertising, printed fliers, and word of mouth. Social media advertisements are designed with support from a racially and ethnically diverse group of adolescents and young adults from 2 of our partnering research sites.

Textbox 1. Sexual behavior inclusion criteria, by the sex assigned at birth—male. The adolescent must indicate engagement in at least one of the following behaviors to be considered eligible.

During the last 12 months, which of the following is true for you? (check all that apply):

- I had unprotected anal sex with a male
- I had protected anal sex with 3 or more males
- I had sex with a male for money, gifts, shelter, or drugs
- I had sex with a male, and I have had a sexually transmitted infection (gonorrhea, chlamydia, syphilis, herpes)
- I had sex with someone who is HIV+
- I had anal sex with a male and the condom slipped off or broke

Textbox 2. Sexual behavior inclusion criteria, by the sex assigned at birth—female. The adolescent must indicate engagement in at least one of the following behaviors to be considered eligible.

During the last 12 months, which of the following is true for you? (check all that apply):

- I had unprotected anal or vaginal sex with a male
- I had sex with someone who is HIV+
- I had protected vaginal or anal sex with 3 or more males
- I had sex with a male for money, gifts, shelter, or drugs
- I have had sex with one or more males, and I have had a sexually transmitted infection (gonorrhea, chlamydia, syphilis, herpes)
- I had vaginal or anal sex with a male and the condom slipped off or broke

Randomization

Adolescents are being randomized in a 1:1:1 ratio into 1 of 3 consent conditions (see the Study Visit section) using block randomization with a block size of k=3 (in every 3 subjects, exactly 1 is allocated to each condition). The randomization is stratified by study site and sex assigned at birth. Within the study site, the sex assigned at birth, and consent condition, the order in which the hypothetical trials are presented to adolescents is block randomized with a block size of k=2.

Parents indicate the acceptability of each of the 3 consent conditions for each of the 2 hypothetical trials. Independent of the sex strata, the order of hypothetical trial presentation is block randomized with a block size of k=2. Separately for each hypothetical trial, the order of evaluation for the 3 consent conditions is randomized so that each ordering is equally likely.

Compensation

All participants receive US $50, in cash or gift cards, to compensate for their time. An additional US $25 is provided to participants who complete the debriefing interview. Each site determines the most appropriate form of compensation. In addition, sites offer reimbursement for transportation. Each site determines the most appropriate form of transportation reimbursement (eg, bus fare, subway tokens, taxi vouchers, or cash). Participants who make a separate or unnecessary trip to the study site for screening but are deemed ineligible for any reason—including the lack of interest—receive US $10 (cash or gift cards) as well as US $5 transportation reimbursement (eg, bus pass).

Study Visit

All participants will be asked to complete the interview until we meet our aim of 48-64 interviews—6-8 adolescents and 6-8 parents from each of the 4 study sites At the initiation of the visit, participants review the Consent 2.0 study information sheet with a research assistant and verbally consent to proceed with the study. The study visit has 2 key elements—simulated consent procedures for the 2 clinical trials and a CASI. As previously mentioned, a subset of participants complete a debriefing interview.

Simulated Consent Procedures

We adapted the consent forms from 2 existing biomedical HIV prevention trials. These 2 trials differed by route of administration, phase of the trial, and if the study drug was already approved as PrEP for adults. The first was an open-label study of the safety of and tolerability to oral TDF-FTC as PrEP for minors (ATN 113), and the second was a phase IIa randomized controlled trial of cabotegravir as PrEP, delivered via an oral lead-in followed by a long-acting injection (HPTN 077). All participants undergo simulated consent procedures for both trials. As noted above, to prevent ordering effects on the outcomes of interest, half of our participants begin with the ATN 113 consent, and the other half begin with the HPTN 077 consent. For each, participants read study summaries on their own and then have a consent conversation with a research assistant who talks to the participant as though they are actually preparing to enroll in the trial.

Adolescents

At enrollment in our study, adolescents are randomized to 1 of the 3 consent conditions (minor self-consent, adult permission required with the option to select either a parent/guardian or a study-appointed ombudsperson, and parental permission required). Their consent condition is emphasized at the end of the simulated consent procedure. For example, if assigned to condition 3 (parental permission required), the research assistant will conclude the consent conversation saying, “Now we’ve come to the point at which you would decide if you want to join this study. If you did want to join the study, you would need to ask your parent or guardian to give your permission to join.” Next, the adolescent answers a series of questions via a CASI, including the primary outcome question, *If offered the chance, how likely would you be to participate in the study you just heard about?* which is a Likert-type question with a range of 1 to 5, where 1 is *definitely would not participate*, and 5 is *definitely would participate*. After the participant answers the CASI questions, the research assistant asks a series of questions focused on the understanding of the study, adapted from the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC) [32]. The process is then repeated for the second trial.

Parents

Parents undergo the simulated consent procedures as described above. However, they are not randomized to a consent condition. Instead, they answer a Likert-type question about the acceptability of each consent condition, which is described in a brief vignette. For example, the vignette for consent condition 2, adult permission required, is as follows:

> *Imagine your teen wants to join the study we just described. Your teen comes to the research clinic on their own. They read the consent form and have an opportunity to ask questions. Your teen is required to have an adult’s permission to sign up for the study. They can choose to ask either you or a neutral adult, called an “ombudsman.” The ombudsman is not in charge of the study; the ombudsman’s job is to ensure your teen understands the research study and to help your teen think about the risks and benefits of joining the study. Your teen would need either your permission OR the ombudsman’s permission to join the study.*
>
> *In this approach to consent, your teen must have an adult’s permission to join the study; your teen would be able to choose whether to seek permission from you or the ombudsman.*

After reading the scenario, the parent rates the acceptability of this approach to research consent on a scale of 1 to 5, with 1 being *completely unacceptable* and 5 being *completely acceptable*. These vignettes are presented in a random order to prevent ordering effects. The research assistant asks the series of questions focused on the understanding of the study, and then the entire process is repeated for the second trial.

Computer-Assisted Self-Interview Questions

All participants answer demographic, behavioral, and attitudinal questions via a CASI. A brief description of measures can be found in the following section.

Debriefing Interviews

At the end of the study visit, participants are asked if they would like to stay for a debriefing interview to further explain their perspectives on consent and HIV prevention trials. All participants will be asked to complete the interview until we have at least eight adolescent and eight parent participants from each site. If we find a substantive variation in the interviews, we will continue interviewing participants. For adolescents, the questions include: *Tell me about your parents*, *What is your relationship like with them?* and *What are your thoughts on medical research?* For parents, questions focus on the teen (eg, *Have you talked to your teen about their sexual orientation?Tell me about that conversation*, and *Is it ever okay for teens to self-consent?*

Sample Size and Power Calculation

This study will enroll approximately 144 (36 per study site) minor adolescents and 120 (30 per study site) parents. On the basis of a linear regression model with consent condition as the independent categorical variable, we calculated that we will need 120 participants (40 per consent condition) to achieve an 80% power for detecting an effect size (f^2) of 0.084, which is between a small (f^2=0.02) and a medium (f^2=0.15) effect size for consent conditions, under alpha=.05. This power calculation, which assumed a single observation per participant, is conservative as the actual study will have 2 observations per participant (1 for each simulated consent process). Therefore, the actual study will have a larger statistical power to detect an effect size of 0.084 for the consent condition. As the test of consent condition effect sizes based on the parental WTP scores is a within-participant comparison rather than an across-participant comparison, a test of the parental consent condition effect size will have at least 80% power to detect an even smaller effect size compared with tests for consent condition effect sizes using the adolescent WTP scores. We project the total enrollment of 264 participants; however, as this is a multi-site project with simultaneous recruitment of a hard-to-reach population, we may schedule and enroll more subjects than anticipated.

Measures

Quantitative Measures

In addition to the primary outcomes, the CASI includes questions that measure covariates of interest, including socioeconomic status, gender identity and sexual orientation, degree of parental monitoring, extent of worry about HIV infection, and medical mistrust. The measures are summarized in Table 1.

Table 1. Consent 2.0 quantitative measures.

Content	Scale (administered to adolescents, parents, or both)	Description of items included
Demographics	ATN[a] data harmonization guidelines [33]	• Age, race or ethnicity, sexual orientation, gender identity, education, employment, health insurance status, city, living situation
Socioeconomic status	FAS-III[b] (adolescents) [34,35]	• Seven questions adapted from the FAS-III, measuring a family's financial status based off of the number of vehicles, computers, bathrooms; adolescents having their own bedroom; if the family has a dishwasher; the number of times the family traveled outside the United States; and overall perception of the family's financial status
Social support	MSPSS[c]—modified (adolescents) [36]	• Four Likert questions on a 7-point scale ranging from very strongly disagree to very strongly agree, measuring parental support and relationships with adolescents
Parental monitoring	Parental monitoring scale—modified (adolescents and parents) [37]	• Twenty-five statements on a 5-point scale ranging from strongly disagree to strongly agree, measuring parental knowledge, disclosure, solicitation, and control. • Adolescent statements such as "My parent(s) know what I do during my free time." • Parent statements such as "I know what my teen does during their free time."
Medical mistrust	The group-based medical mistrust scale—modified (adolescents and parents) [38]	• Six 5-point Likert items that measure the degree to which the participant trusts medical researchers
Communication	Communication with parents (adolescents and parents) [39]	• Five questions asking the number of times parents and adolescents have communicated about relationships, sex, sexually transmitted infections (HPV[d] and HIV), same-sex relationships, and using a condom. Answers range from Never, Once/twice, Many times, and Don't know
Concern about HIV	HIV risk perception (adolescents and parents) [40]	• Two 5-point Likert questions about adolescent worry of being infected with HIV/AIDS and parent worry of their adolescent being infected with HIV/AIDS
Sexual behavior	Sexual behavior (adolescents) [41]	• Five questions for adolescents regarding sexual intercourse partners

[a]ATN: Adolescent Medicine Trials Network for HIV/AIDS Interventions.

[b]FAS-III: family affluence scale-III.

[c]MSPSS: multidimensional scale of perceived social support.

[d]HPV: human papillomavirus.

Qualitative Measures

The debriefing interview is designed to explore adolescent and parent perspectives on the various consent conditions in greater depth and to better understand the role of study features, family, and adolescent characteristics in WTP or support the hypothetical research studies. At the start of the interview, the participants are informed that the interview will be recorded and transcribed and are asked to select a pseudonym for the researchers to use. The adolescent debriefing interview consists of 5 sections: (1) general opinions about participating in HIV prevention studies, (2) opinions on the 2 specific studies, (3) relationship with parents, (4) opinions about parental involvement in the consent process, and (5) options and opinions for consenting to future studies. The parent debriefing interview consists of 4 sections: (1) general opinions about HIV prevention studies, (2) relationship with their teenager, (3) opinions about parental involvement in the consent process, and (4) options and opinions for consenting in future studies.

Data Collection Methods

Screening

Adolescents and parents of adolescents are screened either online or in-person using CASIs developed in Qualtrics. Qualtrics is a Web-based system appropriate for use with sensitive data, including those data protected by the Health Insurance Portability and Accountability Act of 1996. Data are stored on secure servers and protected by firewalls. Information regarding their eligibility for the study will be collected, along with the first 5 digits of their street address and first 4 characters of their apartment or unit, where applicable, which together create a 9-digit household ID code. At the time of enrollment, an eligible participant's household ID code is checked for matches to previously enrolled participants to ensure an independent sample.

Study Visit

Participants complete the CASI within the Qualtrics system, using iPad tablets (Apple Inc) provided by the study. No data are stored on the iPad tablet's hard drive. The entire study visit, including UBACCs and debriefing interviews, is digitally audio-recorded with participant consent. Immediately upon completion, the digital audio files are uploaded to a secure server

in Indiana University (IU). The audio recordings are transcribed verbatim. Transcripts are checked against audio recordings for accuracy.

Data regarding study completion or early termination and protocol deviations are collected using case report forms developed within Qualtrics. These reports remain confidential; no personal identifying information is collected.

Analysis Plan

Quantitative Analysis

All analyses will be performed separately for adolescents and parents. Analysis plans for each set of participants are described in the following sections.

Analysis of Primary Adolescent Outcomes

Total WTP (sum of scores for both ATN 113 and HPTN 077) will be assessed by a linear model with the categorical consent condition acting as an independent term. Cohen effect size will be calculated from the model's R^2 as $R^2/(1-R^2)$. To obtain 95% CIs**,** 2000 bootstrap samples will be generated by resampling the data with a replacement, fitting the model, and obtaining the R^2 for each sample. We will then calculate the aforementioned Cohen effect size for each bootstrap sample and select the 2.5th and 97.5th percentiles of the bootstrap distribution to calculate the corresponding 95% CIs.

Adolescents' scores of WTP for each study will be modeled by a repeated measures model with independent variables of (1) the consent condition and (2) the study and an exchangeable covariance structure. The covariance structure incorporates into the model the potential correlation of observations from the same subject. The model will be fit using generalized estimating equation methodology. R^2_{marg} and Cohen effect size will be calculated [42]. A bootstrap algorithm similar to the aforementioned description will be used to obtain the 95% CIs of the effect size.

Analysis of Primary Parent Outcomes

Parent acceptability scores for each of the vignettes and studies will be assessed by a linear model with an independent term of consent condition, similar to the analysis of the adolescent outcomes. Cohen effect size will be calculated from the model's R^2 as $R^2/(1-R^2)$. To obtain 95% CIs**,** 2000 bootstrap samples will be generated by resampling the data with a replacement, fitting the model, and obtaining the R^2 for each sample. We will calculate the aforementioned Cohen effect size for each bootstrap sample and select the 2.5th and 97.5th percentiles of the bootstrap distribution to calculate the corresponding 95% CIs.

Model for Primary Outcomes

Adolescents' scores of WTP for each study will be modeled by a repeated measures model with independent variables of (1) the consent condition and (2) the study and an exchangeable covariance structure. The covariance structure incorporates into the model the potential correlation of observations from the same subject. The model will be fit using generalized estimating equation methodology; R^2_{marg} and Cohen effect size will be calculated [42]. A bootstrap algorithm similar to the aforementioned description will be used to obtain the 95% CIs of the effect size. For both adolescents and parent outcomes, aside from the consent condition and trial type, the models will also account for the 2 stratification variables: adolescent's sex assigned at birth and the study site.

Heterogeneity of consent condition and trial type effects across study sites will be evaluated under the closed testing procedure paradigm [43,44]. First, we will conduct a single overall hypothesis test at the level alpha=.05 for testing the null hypothesis that there is no interaction between consent condition and trial type effects by study site. If this test is statistically significant, we will consider separate interaction tests for the consent condition and trial type. If any of these tests are statistically significant, site-specific estimates of the corresponding effects will be presented to supplement the preplanned analyses.

We will also evaluate if race, ethnicity, outness, concern about HIV, family context (frequency of communication and parental monitoring), medical mistrust, and other demographic and socioeconomic factors affect the primary outcomes (adolescents' hypothetical WTP and parents' perceptions of acceptability of consent methods). We will examine these effects by adding variables into the models to determine if they moderate the relationship between the consent condition and WTP (adolescents) and acceptability (parents) scores.

The primary outcome analyses will be based on the observed data. Type B multiple imputation [45] will be used to address the missing data instead of the traditional Rubin type A multiple imputation. This is because the latter method, unlike type B multiple imputation, produces biased standard error estimates and *P* values if there are auxiliary variables in the imputation models owing to model uncongeniality [46,47]. The use of auxiliary variables can make the missing at random assumption more plausible in practice [48,49].

Qualitative Analysis

Our analytic approach to the qualitative data collected during debriefing interviews is a qualitative description, as described by Sandelowski [50]. Qualitative descriptive methods provide an in-depth description of experiences shared by a group facing a common challenge and are particularly useful for generating summaries of information to guide future interventions. The qualitative analysis team will analyze the transcripts using conventional content analysis techniques as described by Hsieh and Shannon [51]. Using QSR International's NVivo version 12 textual analysis software, each text unit (eg, meaningful phrase, sentence, or story relevant to the study aims) will be coded with a short phrase that reflects its essence. A case-ordered meta-matrix [52] will be constructed, with each row representing an individual case and each column representing selected variables drawn from quantitative measures (eg, sexual orientation and gender identity) or salient constructs derived from the interviews (eg, relationship with parent/teen). For ease of comparison, separate matrices will be made for adolescents and parents. The research team will categorize all the codes in each column and provide a description of each category to describe the variable fully from the parents'

and adolescents' perspectives. For example, all the codes under barriers to parental involvement will be categorized to provide a list of barriers, and the barriers identified by each group will be compared with considerable differences in the 2 groups' perspectives. An example data matrix is shown in Figure 1.

Figure 1. A sample qualitative data analysis matrix for adolescent participants. UBACC: University of California, San Diego Brief Assessment of Capacity to Consent.

Participant ID	Demographic Data				UBACC	Qualitative Interview Constructs					
	Age	Gender Identity	Education	Living Situation	Willingness to participate	Relationship to parent	Relationship to parent	Willingness to involve a parent	Barriers to parent involvement	Facilitators of parent involvement	Concerns about protocol
NNNNNN											
NNNNNN											
NNNNNN											

Human Subjects

This protocol was reviewed and approved by the IRB at IU, which served as the single IRB by a reliance agreement between it and the IRBs affiliated with our research sites. After a screened participant is determined to be eligible, she or he receives a study information sheet. The study purpose and procedures are discussed, and all questions are answered during the informed consent process. Verbal informed consent is obtained before any study-related procedures are performed. Minors do not require parental consent to participate. Enrollment occurs after participant consent is obtained.

Monitoring

Study Monitoring

Implementation of the study is monitored by the study team review committee (STRC), which includes the protocol chair, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) health science administrator, 1 coinvestigator, the Consent 2.0 program manager, and the IU data manager. The STRC meets at least monthly. During these meetings, the STRC reviews enrollment reports, reports on early discontinuation of the 1-day study visit, and reports on adverse events (AEs) that have occurred since the last STRC meeting or previously reported AEs for which new information is available. All AEs are reviewed within one week of occurrence; if the next scheduled STRC meeting is more than 7 days after an AE occurred, the team will convene a special meeting to address it.

Data Monitoring

Data monitoring is conducted on a weekly basis by the IU data manager to detect any issues that require reporting or correction. If any data corrections are necessary, the data manager will contact the PI to discuss and review any necessary corrections. A query notifications system is used to track any protocol deviations or problems that arise during study visits. Preliminary analyses will be conducted to detect potential errors in the data collection process and to assess the adequacy of planned enrollment.

Results

Funding for this study began in late 2016. Initial IRB approval was secured in July of 2017. All recruitment, enrollment, and data collection occurred between April 2018 and September 2019. The study enrolled 131 adolescents and 125 parents. As of January 2020, analysis is underway with a primary results manuscript anticipated to be published by mid-2020.

Discussion

Strengths and Limitations

Adolescents—especially adolescents of color—are disproportionately affected by HIV but underrepresented in biomedical HIV prevention trials that may benefit them as individuals and as a collective. The low engagement of adolescents in biomedical research creates delays in their access to new prevention tools and subsequently contributes to HIV disparities in this age group. Researchers and policy makers have called for the inclusion of adolescents in biomedical research as a matter of justice [4,6,7,53,54]. However, there are

limited empirical data regarding the consent-related needs and preferences of minor adolescents at a high risk of HIV acquisition and limited data about parents' perspectives on the issue. This project responds to both the identified disparities in minors' access to clinical trials and the limited empirical data available for creating resolutions to the problem that are acceptable for both adolescents and parents. Furthermore, the project specifically explores the intersection of race, ethnicity, sexual orientation, gender identity, and medical mistrust as they relate to ethical concerns about engaging minors in biomedical HIV prevention research studies.

There are several anticipated limitations of this study. First, we are enrolling a relatively small sample size of approximately 144 adolescents and 120 parents. The sample comes from 4 geographic regions in the United States and is recruited through a variety of methods to ensure socioeconomic, racial, ethnic, and sexual diversity, but it cannot be considered representative of all relevant stakeholders. A second limitation is the hypothetical nature of the study. We made every effort to simulate a real clinical trial—we are using risk criteria from real trials, we are recruiting from sites that participate in trials similar to those that we selected for the study, and we are simulating the consent process by acting just as though the participant is actually enrolling in the trial. Nevertheless, a participant's hypothetical choice may be different from the choice they make in reality. A third limitation is the possibility of sampling bias. Participants in this study are volunteers, many of whom self-refer to the study. Thus, they may be more likely to participate in medical research or more open to the idea, generally. A random community sample may produce different results than this volunteer sample. Finally, our sample size calculation has not accounted for the possibility of unbalanced covariates owing to chance. If we need to adjust the model to account for unbalanced covariates, this will result in a reduction in the effect size detectable with 80% power.

Conclusions

We anticipate the results of this project will be useful to research networks, principal investigators, policy makers, and regulatory bodies who must make decisions about inclusion and exclusion criteria and consent requirements for research participants.

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Conflicts of Interest

None declared.

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Abbreviations

AE: adverse event
ATN: Adolescent Medicine Trials Network for HIV/AIDS Interventions
ATN 113: Adolescent Medicine Trials Network for HIV/AIDS Interventions protocol 113
CASI: computer-assisted self-interview
HPTN 077: HIV Prevention Trials Network protocol 077
IRB: institutional review board
IU: Indiana University
MTN: Microbicide Trials Network
NICHD: Eunice Kennedy Shriver National Institute of Child Health & Human Development
NIH: National Institutes of Health
PrEP: preexposure prophylaxis
STRC: study team review committee
TDF-FTC: tenofovir disoproxil fumarate and emtricitabine
UBACC: University of California, San Diego Brief Assessment of Capacity to Consent
WTP: willingness to participate

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