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Protocol for a Mixed Methods Feasibility Study for the Surviving Opioid Overdose with Naloxone Education and Resuscitation (SOONER) Randomized Control Trial

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Running Head: SOONER Feasibility Study Protocol

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Aaron Orkin: Evidence reviewer for ILCOR 2015, and writer for AHA/HSFC Guidelines on CPR and Resuscitation in 2015. Receives salary support from the Canadian Institutes of Health Research, the Schwartz/Reisman Emergency Medicine Institute, and the University of Toronto

Department of Family and Community Medicine. AMO is an evidence reviewer for the International Liaison Committee on Resuscitation and a co-author for the 2015 American Heart Association Guidelines for CPR and ECC concerning opioid overdose and 2019 American Heart Association Guidelines updates on First Aid.
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1 Abstract

Introduction:

The Surviving Opioid Overdose with Naloxone Education and Resuscitation (SOONER) Project combines co-design and trial methods to develop and evaluate a point-of-care overdose education and naloxone distribution (OEND) tool. We plan to conduct a randomized controlled trial to assess the effectiveness of our OEND tool in comparison to the standard of care by observing participants' performance in a simulated overdose. Recruiting and retaining people at risk of or likely to witness opioid overdose raises scientific, logistical, and bioethical challenges. A mixed methods feasibility study is needed to establish the effectiveness of recruitment and retention strategies and the acceptability of study procedures in local recruitment sites prior to launching a full trial.

Methods and Analysis:

Strategies to enhance recruitment include candidate-driven recruitment, verbal informed consent, and attractive, destigmatizing materials. Adults at risk of or likely to witness opioid overdose based on 2015 American Heart Association Guidelines will be recruited through an urban emergency department, inpatient and ambulatory addiction medicine service, and outpatient family practice. Participants randomized to the intervention arm will receive our OEND intervention, while those in the control arm will be referred to existing hospital or community OEND programs. Retention procedures include participant reminders, flexible scheduling, cash and comfort compensation, and continuity of relationship strategies. Within two weeks, participants will engage in a simulated overdose with a mannequin, and complete overdose knowledge and attitudes questionnaires. The primary outcome is recruitment and retention feasibility, defined as the recruitment of 28 participants within 4 weeks and less than 50% attrition at the overdose simulation. Staff and participant feedback will also be collected and considered.

Ethics & Dissemination

The study has been reviewed by ethics boards at St. Michael's Hospital, Toronto Public Health, and the University of Toronto. Results will be disseminated through peer-reviewed publication and presentations.

Trial registration: Pending

2 Article Summary

Strengths and limitations of this study

- This study tests the effectiveness of an integrated strategy to recruit and retain people who are at risk of or likely to witness opioid overdose.
- The strengths of the proposed recruitment and retention strategy are the involvement of community members in study design, cash and comfort compensation for participation, follow-up through multiple communications media, flexible scheduling for follow-up assessments, and attention destigmatizing language in research processes.
- If the study demonstrates feasibility, this recruitment and retention strategy will be ready for deployment in a full-scale randomized controlled trial.
- This strategy might be further enhanced through the involvement of peer workers and may require adaptation for use in other settings.

3 Background

Deaths from opioid overdose represent an important and expanding global epidemic [1]. Opioid Overdose Education and Naloxone Distribution programs (OEND) train and equip people who are likely to witness overdose to recognize these emergencies and administer essential first aid interventions including naloxone, a widely known and effective competitive opioid antagonist [2,3]. Policymakers and practitioners have called for expanded access to OEND programs in clinical settings or "point-of-care OEND". Point-of-care OEND would improve access to this potentially life-saving intervention, and may have a role in emergency departments, family practice, addiction medicine and other inpatient and ambulatory care settings. Although clinicians are willing to provide OEND in principle, the complexity, time requirements for training, and current design of naloxone kits remain a barrier to widespread implementation. Effective tools are a prerequisite for widespread OEND implementation in a variety of ambulatory and inpatient care settings [4,5,6,7].

We plan to conduct a randomized trial to assess the effectiveness of a point-of-care OEND intervention in comparison to the current standard of care in an emergency department, family medicine and addictions medicine settings, by observing participants' performance in a simulated overdose emergency.

Conducting trials among people who use drugs or who are likely to witness overdose involves scientific, logistical, socio-cultural, and bioethical challenges. These challenges contribute to the persistent under-evaluation of interventions to enhance the health of this population, and threats to study validity when retention rates are low [8]. There is also limited precedent for conducting resuscitation simulations for research participants who are patients or members of the lay public rather than health care trainees [9]. Most OEND research and program evaluations involve uncontrolled studies and convenience sampling without active follow-up, with elevated rates of attrition [10,11]. The only published simulation-based study of OEND education is an uncontrolled study among 103 people recently released from prison. The study achieved 82.5% retention (85 participants) at a 1-month follow-up simulation [12].

Before conducting a full-scale point-of-care OEND trial involving overdose simulations, a feasibility study is needed to establish the effectiveness of our planned recruitment and retention

strategies and the acceptability of study procedures in local recruitment sites. A feasibility study will permit the evaluation of basic randomization and data collection procedures, and create an opportunity to reconsider study design and analysis.

3.1 Study Objectives

The *primary objective* of this feasibility study is to identify if an integrated participant recruitment and retention strategy can recruit approximately 28 eligible participants within 4 weeks, and maintain less than 50% attrition at the study's primary 2-week outcome assessment. This is in the context of a randomized trial on point-of-care OEND and simulated overdose resuscitation performance in urban and inner-city academic family practice, emergency department, and addiction medicine setting.

The *secondary objectives* of this study are to:

1. assess the rate of participant recruitment in each of the family practice, emergency department, and addiction medicine sites at a single academic health care centre;
2. compare participant retention rates in the study intervention and control arms; and
3. to describe challenges and opportunities for improving study procedures for participants, study staff, and site staff with respect to all study processes including participant recruitment, randomization, implementation of the intervention and control, retention, follow-up, outcome assessment and data collection.

4 Methods

4.1 The SOONER Project

This feasibility study is part of the larger Surviving Opioid Overdose with Naloxone Education and Resuscitation (SOONER) Project, which combines co-design, clinical trial and community engagement methods. The goal of the SOONER Project is to develop and evaluate an effective point-of-care OEND tool, and to reduce opioid-related stigma and inequity. The SOONER Project consists of three phases: Phase I is a service design and participatory co-design initiative, where scientists, design researchers and community members co-created a point-of-care OEND toolkit [13,14] which will serve as the intervention for subsequent phases. Phase II is the feasibility study presented here, and Phase III is the subsequent randomized trial that will be developed based on the results of this feasibility study. Drawing on principles of community engagement and participatory research, community agencies and representatives with lived experience of opioid use and overdose are involved in all aspects of the project's development and implementation.[15,16]

4.2 Feasibility Trial Design

The proposed study is a mixed methods feasibility study to evaluate the recruitment and retention strategy and study logistics for a randomized trial.[17] The underlying randomized trial is a pragmatic, multi-site, 2-armed, parallel-group, best-available-care controlled, analyst- and outcome assessor-blinded, superiority trial of point-of care OEND training. The study protocol was developed as a feasibility study using the SPIRIT Statement and recommendations on

standard elements for protocols for interventional trials, adapted where necessary for a feasibility study.[18]

The study has completed review with the Research Ethics Board affiliated with St. Michael's Hospital, Toronto Public Health, and the Toronto Academic Health Sciences Network. The protocol is pending registration through ClinicalTrials.gov (protocol number:)

4.2.a Participants

Participants will be recruited through three study settings, all associated with St. Michael's Hospital: (1) Emergency Department, (2) inpatient and ambulatory Addiction Medicine Service, and (3) Family practice. Primary outcome assessment will occur through a follow-up visit at the St. Michael's Hospital Allan Waters Family Simulation Centre (SMH Simulation Centre). Although the three recruitment settings are all affiliated with the same hospital, the trial is termed "multi-site" because of the substantial difference between the clinical contexts in the three recruitment settings.

The three recruitment settings provide routine clinical services to people at risk of opioid overdose and likely to witness overdose, but each with widely differing clinical interactions and follow-up procedures. These sites have been selected to strike a balance between study generalizability, pragmatism, and feasibility [19]. The chosen settings will permit recruitment of study participants representing a diverse urban population, with varied access to and use of emergency services, primary care and addiction treatment services.

4.2.b Eligibility

Participants will be adults ≥16 years of age who may benefit from OEND using criteria adapted from the 2015 American Heart Association Guidelines on Cardiopulmonary Resuscitation in Special Circumstances (see Table 1 for detailed inclusion and exclusion criteria).

Table 1: Study Inclusion and Exclusion Criteria

Inclusion Criteria: Participants are eligible by meeting any one or more of the following:	Exclusion Criteria: Participants are ineligible by meeting any one or more of the following:
1. Have a history of taking opioids at recognized 'high doses' (whether by prescription or otherwise, defined as >100mg morphine equivalent per day).	1. Have a community do not resuscitate order.
2. Live with or is in frequent contact with others who use opioids or heroin.	2. Have a terminal illness, end-of-life care, or illness likely to result in death within the study period.
3. Have required emergency care for opioid overdose previously.	3. Have no mode of contact or follow-up.
4. Are enrolled in opioid agonist treatment programs (or has been in the last 6 months), including methadone or buprenorphine maintenance programs, particularly at high risk periods such as induction or discharge.	4. Plan to move away from Toronto during the study period.
5. Are being released from prison, and have a history of non-medical opioid use.	5. Have insufficient English language skills to participate in the study.
6. Are receiving prescription opioid therapy with risk factors for adverse effects, including relevant comorbidities, co-prescriptions of benzodiazepines or other sedatives, concomitant ongoing alcohol use, or high dose prescription opioid therapy.	6. Are an active or previously practicing healthcare professional or professional first responder (e.g.: firefighter, police officer, lifeguard, industrial first responder).
7. Uses non-medical opioids, injects opioids, or acquires opioids from sources other than a pharmacy or healthcare setting.	

Sixteen was chosen as the minimum participant age to (a) recognize that opioid use is a growing concern among adolescents, (b) affirm the importance of including youth in low-risk research where this population stands to benefit, (c) recognize that other basic life support studies have been conducted in children, while (d) avoiding perceptions that the study extends to research with highly vulnerable populations if a lower minimum age were chosen. [20-,22]

Since the study concerns resuscitation and first aid training, people with a "Do Not Resuscitate" order or directive are excluded because such an order may reasonably alter a participant's interest in or desire to learn resuscitative skills. For candidates who decline to participate in the study, we will retain the data collected in the recruitment questionnaire and request consent to collect demographic data to compare the characteristics of study participants and non-participants.

4.2.c Sample Size

Approximately twenty-eight (28) participants will be recruited to the feasibility study, composed of between eight and twelve (8 and 12) participants from each of the St. Michael's

Family practice, Emergency Department, and Addiction Medicine Service (including hospital consult service and Rapid Access Clinic). We ran a sample size sensitivity analysis based on the computation of a confidence interval for the binomial distribution and selected 28 participants. With a sample size of 28 participants, we will be able to estimate a participation rate of 65% with a one-sided 95% confidence interval of 14.8%.

$$0.148 = 0.1645 \cdot \sqrt{0.65 \cdot (\frac{1 - 0.65}{28})}$$

Therefore, if at least 19 participants are retained we will be able to assert that any retention rate below 50% falls outside a 95% confidence interval for the retention rate point estimate. In a worst-case-yet-feasible scenario, the feasibility trial would require 4 weeks for recruitment and would observe a retention rate of 65%.

4.2.d Allocation

Participants will be assigned to either control or intervention group with 1:3 allocation by computerized randomisation schedule. Unbalanced allocation was selected for the feasibility study to gather additional information about study processes in the intervention arm, since the control arm incorporates existing processes of care.

In instances where eligible and consenting participants present as a part of a single clinical encounter (for example, a patient at risk of overdose presenting to the emergency department with his/her spouse), both participants will be randomized to the same study arm to avoid overt contamination between intervention and control arms. Randomisation will be stratified by site, using permuted blocks of random sizes. Block sizes will not be disclosed to ensure concealment.

4.2.e Interventions

Study participants randomized to the treatment arm of the study will receive brief overdose first aid training and a naloxone kit. The intervention will involve the following:

1. Abbreviated point-of-care OEND training according to the training program adapted from the Toronto Public Health Prevention Overdose in Toronto (POINT) Program [23,24]. The key aspects of this training are:
    a. Identify life threatening overdose.
    b. Activate 911 services.
    c. Prepare and administer intranasal naloxone.
    d. Perform chest compressions.
    e. Reassess and repeat naloxone administration.
    f. Continue chest compressions until paramedics arrive.
2. A naloxone kit containing 2 doses of Narcan© naloxone hydrochloride, each 4mg intranasal (Adapt Pharmaceuticals), and administration instructions.

Training will be provided at the three recruitment settings in the clinical environment in which the participant is receiving care (clinic room, emergency department room or hallway bed

etc.). A dedicated research staff person trained in basic cardiopulmonary resuscitation, first aid and overdose education, and anti-oppression techniques will provide training and naloxone kits to the participant. Clinicians will not provide training for the participant.

If the purpose-designed point-of-care OEND toolkit from Phase I of the SOONER Project is available before or during the feasibility study, participants randomized to the intervention arm will receive the custom-designed intervention instead. This will contain all of the elements of the intervention described above, but physically designed to facilitative brief training and distribution in clinical settings.

Study participants randomized to the control arm will receive the present best available standard of care. Control group instructions will recommend that clinicians proceed with care exactly as they would outside of the trial. Dedicated research staff will provide participants randomized to the control arm with a referral to the Toronto Public Health "The POINT" Program where intranasal naloxone and associated training is provided. If the Ontario Ministry of Health and Long-Term Care begins to supply intranasal naloxone at retail pharmacies before or during the study, participants will also be provided with a referral to local retail pharmacies that offer OEND with intranasal devices. If clinic or hospital-based naloxone distribution programs are in effect, control arm participants may also be referred or included in those programs.

4.2.f Study Procedures

Study procedures are shown in detail in Table 2. Study visits will involve (1) the initial enrolment session and training for participants randomized to the intervention arm, (2) a follow-up between 3 and 14 days post-enrolment to participate in the simulated overdose event and administer the knowledge and attitudes questionnaire, and (3) a follow-up at 3 months (+/- 14 days) to repeat knowledge and attitudes questionnaires by telephone or in-person. This latter 3-month follow-up is included to allow comparison of our results and study population with other studies using a 3-month follow-up with the same questionnaires. [25,26,27]

Participants who miss a scheduled visit may reschedule their visit at a mutually convenient time. Out-of-window visits will be permitted and noted in the final report. Study staff will also collect informal feedback from personnel at all study sites throughout recruitment to describe challenges, and opportunities for quality improvement of study processes.

Table 2: Study Procedures Timetable			
Assessment/Activity	Enrolment Visit	Outcome Simulation, Knowledge and Attitudes Questionnaires, Interview (3-14 days)	Knowledge and Attitudes Questionnaires (3 months)*
Eligibility Questionnaire	×		
Informed Consent	×		
Demographic Data Collection	×		
Tertiary Clinical Outcome Baseline Questionnaire	×		
Randomisation	×		
Intervention Training or Control Referral	×		
Outcome Simulation and Assessment		×	
Knowledge and Attitudes Questionnaire	×	×	×
Follow-Up Interview		×	
*3-month Knowledge and Attitudes Questionnaire completed only by participants who (a) inject drugs, or (b) are friends or family members of people who inject drugs (see Section 2.5.c: Tertiary Clinical Outcomes).			

4.3 Recruitment and Retention Strategies

We expect our underlying study could be affected by attrition, as many participants experience unstable housing or incarceration, overdose or other health problems, may be difficult to reach by phone, and may experience stigma associated with opioid use. The recruitment and retention strategies under investigation in this feasibility study build on existing research on incentivising and improving clinical trial participation among people who use opioids [42,43]. (See Figure 1: Study Schematic, Recruitment and Retention Strategies.)

Figure 1.

4.3.a Recruitment

Candidate-driven recruitment: Candidates will be identified and recruited to the study according to a uniform general procedure, with site-specific modifications according to the practice patterns and operational needs of the 3 different clinical settings. All patients will be given an ultra-brief information card asking (a) if they take opioids or have a friend or family member who uses opioids, and (b) if they would be interested in participating in a study concerning OEND training. The card will indicate that patients should notify any of the clinical staff if they answer "yes" to both of these questions. The clinician or administrative staff will then notify study personnel, who will approach the candidate to determine eligibility, obtain informed consent, randomize the participant and implement the intervention.

This "candidate-driven" recruitment procedure was designed to reduce recruitment biases and the stigma of study recruitment by informing all patients of the study and allowing people in clinical settings to self-identify as interested and potentially eligible for study enrolment. By distributing the informational card to all patients, this recruitment method reduces the effect of

clinician biases and prejudices regarding which patients are at risk of opioid overdose because all patients are alerted to the study. Candidates may self-identify their potential eligibility in circumstances where clinicians are unaware of their eligibility. By using an informational card rather than the more conventional practice of recruitment posters, patients and study candidates can be alerted to the study and discuss their interest in participating with staff discreetly, without having to point at or read a poster placed in a public area. This serves to protect confidentiality, normalize the information given to all patients, and positions patients as the initiators of the recruitment process.

Improved informed consent: Lengthy written consent forms may deter study candidates from participating in research, without improving the quality of informed consent or the knowledge of participants.[28] Written signed consent may be perceived as an attempt to legalize the consent process and may itself deter participants in this study. We therefore favour oral or verbal consent for this trial.[29] A systematic review on strategies to improve informed consent processes in trials found that having a study team member spend more time talking one-on-one with trial candidates was the most effective available way of improving research participants' understanding.[30] Informed consent will be obtained through a verbal process, assisted with a visual map of study procedures and a brief 2-page script, with ample time for participants to ask questions and discuss each phase of the study.

Attractive, destigmatizing trial materials: Study informational materials, consent forms, and consent processes have also been designed to reduce barriers to trial recruitment. Developed through the SOONER Project's collaboration with design researchers and drawing on participatory co-design methods, study handouts have been written in plain, destigmatizing and inviting language, and graphically designed to avoid stigmatizing imagery associated with opioid use and overdose.

4.3.b Retention

Gathering contact information: At enrolment, participants will know that they will be followed over time, and we will specify the timetable and methods that will be used to contact them. We will collect multiple points of contact based on participant preferences, including phone numbers (for phoning and text messages), email addresses, and mailing addresses. As an alternate means of contact, we will ask to collect the names of two friends, relatives, case managers, clinics, community centres, or shelters with whom participants have regular contact. Participants will be provided with multiple methods to contact study personnel, including dropping in at recruitment sites, phoning, emailing, or speaking to any of the staff associated with the study.

Flexible scheduling: Outcome Assessment Simulations will be scheduled flexibly and outside business hours if required. We will offer to meet participants at their recruitment location and walk with them to the simulation centre if needed. The short (maximum 2-week) interval for

the primary outcome evaluation will reduce attrition for our primary outcome. Research staff will schedule participants' follow-up simulation for between 4 days and 1 week after randomization. This leaves at least 1 week for rescheduling before the 2-week maximum follow-up time. Participants will be able to select a time for the simulation outcome assessment that meets their scheduling needs. Participants will also receive a study card with the simulation time and location as well as contact information of the research coordinator.

Reminders and follow-up: Based on advice from community representatives on the study steering committee, we developed a communication and reminder strategy to suit the participants' diverse needs and contexts. Many members of the target population face tenuous housing and limited financial resources, but many do have cellular phones. For many, communication by letter mail will be untimely and ineffective. Limited financial resources mean that many participants may not have daytime telephone "minutes" and do not take incoming calls, preferring instead to communicate by text message. We emphasize the use of text message reminders, drawing on research demonstrating the feasibility and effectiveness of text messaging for participant retention in randomized trials.[31]

Participants will be asked to choose their preferred and secondary method of contact from phone call, text message or email. Participants will be contacted by their preferred and secondary method 5, 3 and 1 day(s) before their scheduled simulation and on the morning of their simulation to confirm attendance or reschedule, with up to 3 attempts on each of the days of contact. In addition, consenting participants will receive a letter prior to the outcome assessment. Participants will be contacted one week before the 3-month assessment via their preferred method of contact. Communication scripts will be used when contacting participants and messages will not refer to details of the study or to opioid use.

Continuity of relationships: We will strive for consistency in research staff-participant pairing to enhance rapport and build trust, which has been shown to improve patient recruitment and retention.[32] All staff have received anti-oppression training. Wherever possible, the same SOONER staff person who conducts informed consent and recruits a study participant will serve as the point of contact for a given study participant. Study staff will welcome participants at the research institute lobby for outcome visits and accompany them to the assessment centre.

Cash and other compensation: Participants will receive cash per study visit: (1) $15 after consenting to trial activities, (2) $40 upon arrival for the simulation, and (3) $20 upon completion of a follow up interview. Participants will be offered public transit tokens for travel to and from each study visit, snacks, and light refreshments at each study visit. The amount of remuneration proposed in our study for the time required from our participants is consistent with amounts provided in other studies with this population, and payments like those proposed here are effective to improve retention without demonstrating a coercive effect on participants nor precipitating drug use behaviours.[33,34]

4.4 Feasibility Outcomes

4.4.a Primary Outcome

The primary outcome is the feasibility of recruitment and retention. The recruitment and retention strategy will be deemed "feasible" if approximately 28 eligible participants are recruited within 4 weeks and if attrition is less than 50% for the underlying study's primary outcome assessment (overdose simulation) at 3-14 days (see Table 2). We will optimize our recruitment strategy at each site before setting "time zero" for 4 weeks of recruitment. These outcomes will be recorded using data from the recruitment and retention log. We will compute the attrition at the Outcome Simulation and 95% binomial proportion confidence interval.

4.4.b Secondary Outcomes:

The secondary outcomes will be:

(1) Proportion of eligible participants (people who meet enrolment criteria) who do not consent to the study, as reported in the study log.

(2) Proportion of participants who drop out at the outcome assessment simulation. Dropout at the outcome assessment will be defined as people who attend the outcome simulation but do not complete the simulation or withdraw from the study, as reported in the study log.

4.4.c Tertiary Outcomes

The perspectives of participants will be gathered through a 15-minutes individual semi-structured interview conducted at the outcome simulation visit. The interviews will be audio recorded and transcribed and the acceptability of study processes and opportunities for quality improvement will be analyzed thematically and reported by theme, and with representative quotes. The tertiary outcomes will be acceptability of recruitment, retention and outcome assessment procedures for study participants, and for staff at recruitment sites and the Simulation Centre.

The recruitment and retention strategy will undergo basic quality improvement throughout the study based on the observations of research personnel and their interactions with recruitment site staff. Research personnel will gather informal feedback from recruitment site staff and simulation centre staff regarding quality improvement of the study procedures, and difficulties encountered with respect to recruitment and retention of study participants. The insights gained will be used to make minor changes to improve the quality of study processes. Study staff will keep a quality improvement log to record the feedback received from site staff and discuss feedback at weekly team meetings.

4.5 Clinical Outcomes

Clinical outcomes will be gathered but will not be analyzed or reported within the feasibility study.

4.5.a Primary Clinical Outcome:

The primary outcome will be the proportion of resuscitation failures in a standardized high-fidelity overdose simulation conducted at the Simulation Centre. Simulations will be conducted with individual participants privately, and not in a group or with other participants observing.

The simulation itself is adapted from analogous studies and, refined to mimic a realistic overdose situation [12,35,36,37]. The resuscitation sequence checklist is based on the 2015 American Heart Association bystander resuscitation recommendations. [38] The scenario is intended to simulate a critically life-threatening opioid overdose, where the victim will be found with no signs of life and deteriorate rapidly to opioid-related cardiac arrest. A telephone in the simulation room will be available to simulate a phone call to 911 dispatch. Study participants will be briefed and oriented to the room using a standardized script and instructed to perform as if the simulation were real. The simulation will end with the announcement of paramedics' arrival, after approximately 10 minutes. Dedicated staff will provide a standardized semi-structured debrief for participants using a standardized framework [39]. This debrief can include direct feedback and opportunities to correct techniques, affirm positive behaviours, as well as set the stage for reflection [39,40].

Simulations will be video recorded, and performance assessments will be conducted based on the video recordings. Data collection will occur using a combination of a simple checklist and resuscitation simulator manikin, arranged to create a high-fidelity simulated overdose situation similar to the simulation described by Kobayashi et al [12]. Assignment of the global assessment score will be based on a consensus of two assessors. Any discrepancy in the assessments of the simulation evaluators will be adjudicated by a lead investigator.

4.5.b Secondary Clinical Outcome

The secondary clinical outcome will be performance on eight skills: (1) Recognize the emergency, (2) Position the victim, (3) Activate emergency medical services, (4) Administer naloxone (prepare device, administer correctly), (5) Hand placement, (6) Chest compressions (rate and depth), (7) Continue compressions until end of simulation, and (8) Order of operations and organization.

These eight indicators were adapted from previous CPR and first response training intervention studies, and include both objective measures recorded by the resuscitation manikin and subjective measures assessed by the simulation assessor.[35,36,37] Assessors will rate each skill as satisfactory or unsatisfactory. Data collection will occur using a validated basic life support checklist and resuscitation manikin data, modified for OEND.[41] Non-indicated resuscitative actions will also be documented. These include rescue breathing, incorrect naloxone administration, or any other medication administration. For rescue breathing, we will collect the ventilation data automatically recorded by the resuscitation manikin.

4.5.c Tertiary Clinical Outcomes:

An interviewer-administered questionnaire will be used at enrolment, at the simulation and at 3 months to measure tertiary clinical outcomes related to participants' knowledge about overdose, confidence and willingness to intervene in overdose, reported responses to witnessing overdose events, self-assessed barriers to responding to an overdose, and self-reported drug overdose risk behaviours. The questionnaire will be scripted to reduce variability between interviewers.

The questionnaires contain both close-ended questions and open-ended questions, developed for the Toronto Public Health OEND program evaluation [23]. Questionnaire items were developed using data points from other OEND programs and from the validated Opioid Overdose Knowledge and Attitudes Scales (OOKS and OOAS) [25]. Although the OOKS and OOAS are validated tools, they have been validated only among people who inject drugs and the family members of people who inject drugs, especially heroin [26,27]. These studies have assessed the effectiveness of OEND programs using comparisons of OOKS and OOAS scores before and 3 months after training. Therefore, to permit comparison with these studies, participants who inject drugs or who are friends or family members of people who inject drugs will be asked to return to complete the OOKS and OOAS at 3 months after enrolment.

5 Discussion

The proposed study will test study procedures and the feasibility of an integrated recruitment and retention strategy for people likely to witness opioid overdose in the context of an OEND trial using a simulated opioid overdose event for outcome assessment.

Published strategies to improve participant retention include the involvement of community members in study design and implementation, cash and comfort compensation for study participation, regular follow-up through multiple communications media, building trust and improving communication around trial methods, and flexible hours and scheduling for follow-up assessments [32,42,43,44]. Attention to patient-centered, destigmatizing and participatory language in research processes may also enhance participant recruitment and retention [45]. The integration of these elements is the primary strength of our proposed recruitment and retention strategy. Additional strengths include our use of participatory co-design methods for the development of study interventions and materials, and ongoing engagement with people with lived experience of opioid use for study implementation. Recruitment and retention for this study might be further strengthened by engaging peer workers directly in participant recruitment and retention. Although this approach has been successful in other studies with similar populations, in the context of a study designed to test the effectiveness of OEND in a broad variety of clinical settings, we felt that the introduction of peer workers would act as a cointervention and reduce the scalability of the intervention.[19,46,47,48]. Since the study is occurring in an urban population and a randomized trial, our results may not be generalizable to other settings, clinical contexts or study designs. However, if the study demonstrates feasibility, this recruitment and retention strategy will be ready for deployment in a full-scale trial, and potentially for adaptation to other settings.

6 Ethics and Dissemination

The study has been reviewed by ethics boards at St. Michael's Hospital, Toronto Public Health, and the University of Toronto. Results will be disseminated through peer-reviewed publication and scholarly presentations, and through the SOONER Project's network of community agencies and people with lived experience of opioid use and overdose.

7 Author Statement

All authors conceptualized the study and acquired funding. RS, MC and AO undertook project administration, and LM and CS supervised the project. All authors contributed to the design and methodology of the study. AO prepared the first drafted the manuscript. All authors contributed to revising and approving the final manuscript.

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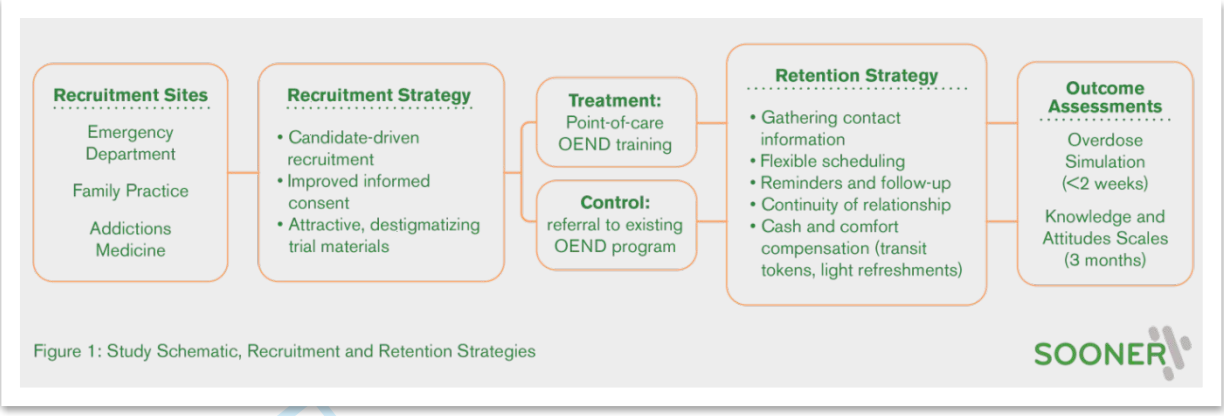

Figure 1: Study Schematic, Recruitment and Retention Strategies

BMJ Open

Protocol for a Mixed Methods Feasibility Study for the Surviving Opioid Overdose with Naloxone Education and Resuscitation (SOONER) Randomized Control Trial

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Title: Protocol for a Mixed Methods Feasibility Study for the Surviving Opioid Overdose with Naloxone Education and Resuscitation (SOONER) Randomized Control Trial

Running Head: SOONER Feasibility Study Protocol

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Conflict of Interest Statement:

AO: Evidence reviewer for ILCOR 2015, and writer for AHA/HSFC Guidelines on CPR and Resuscitation in 2015. Receives salary support from the Canadian Institutes of Health Research, the Schwartz/Reisman Emergency Medicine Institute, and the University of Toronto Department of Family and Community Medicine. AO is an evidence reviewer for the International Liaison Committee on Resuscitation and a co-author for the 2015 American Heart Association Guidelines for CPR and ECC concerning opioid overdose and 2019 American Heart Association Guidelines updates on First Aid.

CH: Contract with Toronto Central Local Health Integration Network as primary care clinical lead for the mid-east Toronto sub-region.

SH: No conflicts of interest declared

MK: Speaker honoraria from the Ontario Pharmacists Association continuing education programs on the topic of opioid use disorder. I do not address take home naloxone beyond mentioning that the program exists (Major >$5,000). Advisory Committee Member, Health Quality Ontario, Quality Standard on Opioid Use Disorder, but recused from voting on standards that involved take-home naloxone.

PL: Advisory Committee Member, Health Quality Ontario, Quality Standard: Opioid Use Disorder; Quality Statement 6 pertains to access to naloxone and overdose education.

LM: contributor to the 2015 guidelines and ILCOR consensus on science where opioid management was reviewed and updated.

DC, JP, RSh, CS, KT, KS, GM, AW, MC, RSn: No conflicts of interest declared

Abstract

Introduction:

The Surviving Opioid Overdose with Naloxone Education and Resuscitation (SOONER) Project uses co-design and trial methods to develop and evaluate a point-of-care overdose education and naloxone distribution (OEND) tool. We plan to conduct a randomized controlled trial to assess the effectiveness of our OEND tool in comparison with existing standard of care by observing participants' performance as a responder to a simulated overdose. Recruiting and retaining people at risk of or likely to witness opioid overdose raises scientific, logistical, and bioethical challenges. A feasibility study is needed to establish the effectiveness of recruitment and retention strategies and acceptability of study procedures prior to launching the full trial.

Methods and Analysis:

Strategies to enhance recruitment include candidate-driven recruitment, verbal informed consent, and attractive, destigmatizing materials. Adults at risk of or likely to witness opioid overdose will be recruited through an urban emergency department, inpatient and ambulatory addiction medicine service, and outpatient family practice settings. Participants randomized to the intervention arm will receive our OEND intervention; those in the control arm will be referred to existing OEND programs. Retention procedures include participant reminders, flexible scheduling, cash and comfort compensation, and strategies to maintain a consistent relationship between individual study staff and participants. Within two weeks following recruitment, participants will engage as a responder to a mannequin-simulated overdose, and complete overdose knowledge and attitudes questionnaires. The primary outcome is recruitment and retention feasibility, defined as the recruitment of 28 participants within 28 days of recruitment and less than 50% attrition at the overdose simulation. Staff and participant feedback will also be collected and considered.

Ethics & Dissemination

The study has been reviewed by ethics boards at St. Michael's Hospital, Toronto Public Health, and the University of Toronto. Dissemination will occur through peer-reviewed publication and presentations.

Trial registration:

ClinicalTrials.gov NCT03821649

1 Article Summary

Strengths and limitations of this study

- This project's main strength is the use of a feasibility study to assess and refine a recruitment and retention strategy among people who are at risk of or likely to witness opioid overdose prior to initiating a randomized controlled trial.
- The strengths of the proposed recruitment and retentions strategy include cash and comfort compensation for participation, follow-up through multiple communications media, flexible scheduling for follow-up assessments, verbal consent processes, and attention to destigmatizing language in research processes.
- The study's central limitation is that the proposed recruitment and retention strategy may require adaptation for use in other settings.

2 Background

Deaths from opioid overdose represent an important and expanding global epidemic [1]. Opioid Overdose Education and Naloxone Distribution programs (OEND) train and equip people who are likely to witness overdose to recognize these emergencies and administer essential first aid interventions including naloxone, a widely known and effective competitive opioid antagonist [2,3,4]. Policymakers and practitioners have called for expanded access to OEND programs in clinical settings or "point-of-care OEND". Point-of-care OEND would improve access to this potentially life-saving intervention, and may have a role in emergency departments, family practice, addiction medicine and other inpatient and ambulatory care settings. Although clinicians are willing to provide OEND in principle, the complexity, time requirements for training, and current design of naloxone kits remain a barrier to widespread implementation. Effective tools are a prerequisite for widespread OEND implementation in a variety of ambulatory and inpatient care settings [5,6,7,8].

We plan to conduct a randomized trial to assess the effectiveness of a point-of-care OEND intervention in comparison to the current standard of care in an emergency department, family medicine and addictions medicine settings, by observing participants' performance in a simulated overdose emergency.

Conducting trials among people who use drugs or who are likely to witness overdose involves scientific, logistical, socio-cultural, and bioethical challenges. These challenges contribute to the persistent under-evaluation of interventions to enhance the health of this population, and threats to study validity when retention rates are low [9]. There is also limited precedent for conducting resuscitation simulations for research participants who are patients or members of the lay public rather than health care trainees [10]. Most OEND research and program evaluations involve uncontrolled studies and convenience sampling without active follow-up, with elevated rates of attrition [11,12]. The only published simulation-based study of OEND education is an uncontrolled study among 103 people recently released from prison. The study achieved 82.5% retention (85 participants) at a 1-month follow-up simulation [10]. Before conducting a full-scale point-of-care OEND trial involving overdose simulations, a feasibility study is needed to establish the effectiveness of our planned recruitment and retention strategies and the acceptability of study procedures in local recruitment sites. A feasibility study will permit the evaluation of basic randomization and data collection procedures, and create an opportunity to reconsider study design and analysis.

2.1 Study Objectives

The *primary objective* of this feasibility study is to identify if an integrated participant recruitment and retention strategy can recruit approximately 28 eligible participants within 28 days of recruitment, and maintain less than 50% attrition at the study's primary 2-week outcome assessment. This is in the context of a randomized trial on point-of-care OEND and simulated overdose resuscitation performance in urban and inner-city academic family practice, emergency department, and addiction medicine settings.

The *secondary objectives* of this study are to:

1. assess the rate of participant recruitment in each of the family practice, emergency department, and addiction medicine sites at a single academic health care centre;
2. compare participant retention rates in the study intervention and control arms; and
3. to describe challenges and opportunities for improving study procedures for participants, study staff, and site staff with respect to all study processes including participant recruitment, randomization, implementation of the intervention and control, retention, follow-up, outcome assessment and data collection.

3 Methods

3.1 The SOONER Project

This feasibility study is part of the larger Surviving Opioid Overdose with Naloxone Education and Resuscitation (SOONER) Project, which combines co-design, clinical trial and community engagement methods (www.soonerproject.ca). The goal of the SOONER Project is to develop and evaluate an effective point-of-care OEND tool, and to reduce opioid-related stigma and inequity. The SOONER Project consists of three phases: Phase I is a service design and participatory co-design initiative, where scientists, design researchers and community members co-created a point-of-care OEND toolkit [13,14] which will be evaluated in subsequent phases. Phase II is the feasibility study presented in this protocol, and Phase III is the subsequent randomized trial that will be developed based on the results of this feasibility study.

3.2 Patient and Public Involvement

Drawing on principles of community engagement and participatory research, community agencies and representatives with lived experience of opioid use and overdose are involved in all aspects of the SOONER Project's development and implementation.[15,16] A group of community representatives are also engaged as *ad hoc* members of the study's Steering Committee, to refine the study research questions and measures and assess the appropriateness of study procedures and interventions. A summary of study results will be disseminated to participants, community agencies and representatives and made available through open access publication.

3.3 Feasibility Trial Design

The proposed study is a mixed methods feasibility study to evaluate the recruitment and retention strategy and study logistics for a randomized trial.[17] The underlying randomized trial is a pragmatic, multi-site, 2-armed, parallel-group, best-available-care controlled, analyst- and outcome assessor-blinded, superiority trial of point-of care OEND training. The study protocol was developed as a feasibility study using the SPIRIT Statement and recommendations on standard elements for protocols for interventional trials, adapted where necessary for a feasibility

study.[18] The protocol is registered prospectively through ClinicalTrials.gov (NCT03821649). Recruitment is anticipated to launch in January 2019.

3.3.a Participants

Participants will be recruited through three study settings:

(1) Emergency Department: the St. Michael's Hospital Emergency Department,

(2) Family Practice: both the St. Michael's Academic Family Health Team and St. Michael's-affiliated Inner City Family Health Team, and

(3) Addiction Medicine: the St. Michael's Hospital Addiction Medicine Service, including both inpatient and ambulatory services.

Primary outcome assessment will occur through a follow-up visit at the St. Michael's Hospital Allan Waters Family Simulation Centre (SMH Simulation Centre). Although the three recruitment settings are all affiliated with the same hospital, the trial is termed "multi-site" because of the substantial difference between the clinical contexts in the three recruitment settings.

The three recruitment settings provide routine clinical services to people at risk of opioid overdose and likely to witness overdose, but each with widely differing clinical interactions and follow-up procedures. These sites have been selected to strike a balance between study generalizability, pragmatism, and feasibility [19]. The chosen settings will permit recruitment of study participants representing a diverse urban population, with varied access to and use of emergency services, primary care and addiction treatment services.

3.3.b Eligibility

Participants will be adults ≥16 years of age who may benefit from OEND using criteria adapted from the 2015 American Heart Association Guidelines on Cardiopulmonary Resuscitation in Special Circumstances and World Health Organization Guidelines [20,21]. See Table 1 for detailed inclusion and exclusion criteria).

Table 1: Study Inclusion and Exclusion Criteria

Inclusion Criteria: Participants are eligible by meeting any one or more of the following:	Exclusion Criteria: Participants are ineligible by meeting any one or more of the following:
1. Have a history of taking opioids at recognized 'high doses' (whether by prescription or otherwise, defined as >100mg morphine equivalent per day). 2. Live with or is in frequent contact with others who use opioids or heroin. 3. Have required emergency care for opioid overdose previously. 4. Are enrolled in opioid agonist treatment programs (or has been in the last 6 months), including methadone or buprenorphine maintenance programs, particularly at high risk periods such as induction or discharge. 5. Are being released from prison, and have a history of non-medical opioid use. 6. Are receiving prescription opioid therapy with risk factors for adverse effects, including relevant comorbidities, co-prescriptions of benzodiazepines or other sedatives, concomitant ongoing alcohol use, or high dose prescription opioid therapy. 7. Uses non-medical opioids, injects opioids, or acquires opioids from sources other than a pharmacy or healthcare setting.	1. Have a community do not resuscitate order. 2. Have a terminal illness, end-of-life care, or illness likely to result in death within the study period. 3. Have no mode of contact or follow-up. 4. Plan to move away from Toronto during the study period. 5. Have insufficient English language skills to participate in the study. 6. Are an active or previously practicing healthcare professional or professional first responder (e.g.: firefighter, police officer, lifeguard, industrial first responder).

Sixteen was chosen as the minimum participant age to (a) recognize that opioid use is a growing concern among adolescents, (b) affirm the importance of including youth in low-risk research where this population stands to benefit, (c) recognize that other basic life support studies have been conducted in children, while (d) avoiding perceptions that the study extends to research with highly vulnerable populations if a lower minimum age were chosen. [22-,24] Since the study concerns resuscitation and first aid training, people with a "Do Not Resuscitate" order or directive are excluded because such an order may reasonably alter a participant's interest in or desire to learn resuscitative skills. For candidates who decline to participate in the study, we will retain the data collected in the recruitment questionnaire and request consent to collect demographic data to compare the characteristics of study participants and non-participants.

3.3.c Sample Size

Based on our budget and timelines for the proposed RCT, we determined that a minimum recruitment rate of 1 participant per day of active recruitment and a minimum retention rate of 50% are required for the underlying RCT to be logistically feasible and scientifically acceptable. For logistical and budgetary reasons, we prepared to operate 28 days of participant recruitment. Therefore, we plan to recruit approximately twenty-eight (28) participants to the feasibility study, composed of between eight and twelve (8 and 12) participants from each of emergency department, family medicine, and addictions medicine sites. Study investigators working at each of the study sites confirmed that many more than 1 eligible patient candidate present to each of the recruitment sites per day. Given that both patients and visitors to the study sites are eligible

for recruitment, we therefore conclude that a recruitment rate of 1 participant per day is a viable target.

To exclude retention rates below 50%, we computed a confidence interval for the binomial distribution based on 28 participants. With a sample of 28 enrolled participants, we will be able to estimate a retention rate of 65% with a one-sided 95% confidence interval of 14.8%.

$$0.148 = 0.1645 \cdot \sqrt{0.65 \cdot (\frac{1 - 0.65}{28})}$$

Therefore, if at least 19 participants are retained we will be able to assert that any retention rate below 50% falls outside a 95% confidence interval for the retention rate point estimate. In a worst-case-yet-feasible scenario, the feasibility trial would therefore require 28 days of recruitment and would observe a retention rate of 65%.

3.3.d Allocation

Participants will be assigned to either control or intervention group with 1:2 allocation by computerized randomisation schedule. Unbalanced allocation was selected for the feasibility study to gather additional information about study processes in the intervention arm, since the control arm incorporates existing processes of care.

In instances where eligible and consenting participants present as a part of a single clinical encounter (for example, a patient at risk of overdose presenting to the emergency department with his/her spouse), both participants will be randomized to the same study arm to avoid overt contamination between intervention and control arms. Randomisation will be stratified by site, using permuted blocks of random sizes. Block sizes will not be disclosed to ensure concealment.

3.3.e Interventions

Study participants randomized to the treatment arm of the study will receive brief overdose first aid training and a naloxone kit. The intervention will involve the following:

1. Abbreviated point-of-care OEND training according to the training program adapted from the Toronto Public Health Prevention Overdose in Toronto (POINT) Program [25,26]. The key aspects of this training are:
    a. Identify life threatening overdose.
    b. Activate 911 services.

c. Prepare and administer intranasal naloxone.
d. Perform chest compressions.
e. Reassess and repeat naloxone administration.
f. Continue chest compressions until paramedics arrive.

2. A naloxone kit containing 2 doses of Narcan© naloxone hydrochloride, each 4mg intranasal (Adapt Pharmaceuticals), and administration instructions.

Training will be provided at the three recruitment settings in the clinical environment in which the participant is receiving care (clinic room, emergency department room or hallway bed etc.). A dedicated research staff person trained in basic cardiopulmonary resuscitation, first aid and overdose education, and anti-oppression techniques will provide training and naloxone kits to the participant. Clinicians will not provide training for the participant.

If the purpose-designed point-of-care OEND toolkit from Phase I of the SOONER Project is available before or during the feasibility study, participants randomized to the intervention arm will receive the custom-designed intervention instead. This will contain all of the elements of the intervention described above, but physically designed to facilitative brief training and distribution in clinical settings.

Study participants randomized to the control arm will receive the present best available standard of care. Control group instructions will recommend that clinicians proceed with care exactly as they would outside of the trial. Dedicated research staff will provide participants randomized to the control arm with a referral to (1) the Toronto Public Health "The POINT" Program, where intranasal naloxone and associated training is provided and (2) retail pharmacies where the Ontario Ministry of Health and Long-Term Care provides OEND with intranasal devices. Both of these OEND programs are available to the general public free of charge. If clinic or hospital-based naloxone distribution programs are in effect, control arm participants may also be referred or included in those programs at the attending clinician's discretion.

3.3.f Study Procedures

Study procedures are shown in detail in Table 2. Study visits will involve (1) the initial enrolment session and training for participants randomized to the intervention arm, (2) a follow-up between 3 and 14 days post-enrolment to participate in the simulated overdose event and administer the knowledge and attitudes questionnaire, and (3) a follow-up at 3 months (+/- 14

days) to repeat knowledge and attitudes questionnaires by telephone or in-person. This latter 3-month follow-up is included to allow comparison of our results and study population with other studies using a 3-month follow-up with the same questionnaires. [27,28,29]

Participants who miss a scheduled visit may reschedule their visit at a mutually convenient time. Out-of-window visits will be permitted and noted in the final report. Study staff will also collect informal feedback from personnel at all study sites throughout recruitment to describe challenges, and opportunities for quality improvement of study processes.

Table 2: Study Procedures Timetable			
Assessment/Activity	Enrolment Visit	Outcome Simulation, Knowledge and Attitudes Questionnaire, Interview (3-14 days)	Knowledge and Attitudes Questionnaires (3 months)*
Eligibility Questionnaire	×		
Informed Consent	×		
Demographic Data Collection	×		
Tertiary Clinical Outcome Baseline Questionnaire	×		
Randomisation	×		
Intervention Training or Control Referral	×		
Outcome Simulation and Assessment		×	
Knowledge and Attitudes Questionnaire	×	×	×
Follow-Up Interview		×	
*3-month Knowledge and Attitudes Questionnaire completed only by participants who (a) inject drugs, or (b) are friends or family members of people who inject drugs (see Section 3.6.c: Tertiary Clinical Outcomes).			

3.4 Recruitment and Retention Strategies

We expect our underlying study could be affected by attrition, as many participants experience unstable housing or incarceration, overdose or other health problems, may be difficult to reach by phone, and may experience stigma associated with opioid use. The recruitment and retention strategies under investigation in this feasibility study build on existing research on incentivising and improving clinical trial participation among people who use opioids [30,31]. (See Figure 1: Study Schematic, Recruitment and Retention Strategies.)

[Figure 1 inserted approximately here]

3.4.a Recruitment

Candidate-driven recruitment: Candidates will be identified and recruited to the study according to a uniform general procedure, with site-specific modifications according to the practice patterns and operational needs of the 3 different clinical settings. All patients will be given an ultra-brief information card asking (a) if they take opioids or have a friend or family member who uses opioids, and (b) if they would be interested in participating in a study concerning OEND training. The card will indicate that patients should notify any of the clinical staff if they answer "yes" to both of these questions. The clinician or administrative staff will then notify study personnel, who will approach the candidate to determine eligibility, obtain informed consent, randomize the participant and implement the intervention.

This "candidate-driven" recruitment procedure was designed to reduce recruitment biases and the stigma of study recruitment by informing all patients of the study and allowing people in clinical settings to self-identify as interested and potentially eligible for study enrolment. By distributing the informational card to all patients, this recruitment method reduces the effect of clinician biases and prejudices regarding which patients are at risk of opioid overdose because all patients are alerted to the study. Candidates may self-identify their potential eligibility in

circumstances where clinicians are unaware of their eligibility. By using an informational card rather than the more conventional practice of recruitment posters, patients and study candidates can be alerted to the study and discuss their interest in participating with staff discreetly, without having to point at or read a poster placed in a public area. This serves to protect confidentiality, normalize the information given to all patients, and positions patients as the initiators of the recruitment process. The candidate-driven approach is further enhanced by encouraging clinicians to discuss the study with potentially eligible patients or visitors directly.

Improved informed consent: Lengthy written consent forms may deter study candidates from participating in research, without improving the quality of informed consent or the knowledge of participants.[32] Written signed consent may be perceived as an attempt to legalize the consent process and may itself deter participants in this study. We therefore favour oral or verbal consent for this trial.[33] A systematic review on strategies to improve informed consent processes in trials found that having a study team member spend more time talking one-on-one with trial candidates was the most effective available way of improving research participants' understanding.[34] Informed consent will be obtained through a verbal process, assisted with a visual map of study procedures and a brief script, with ample time for participants to ask questions and discuss each phase of the study.

Attractive, destigmatizing trial materials: Study informational materials, consent forms, and consent processes have also been designed to reduce barriers to trial recruitment. Developed through the SOONER Project's collaboration with design researchers and drawing on participatory co-design methods, study handouts have been written in plain, destigmatizing and inviting language, and graphically designed to avoid stigmatizing imagery associated with opioid use and overdose.

3.4.b Retention

Gathering contact information: At enrolment, participants will know that they will be followed over time, and we will specify the timetable and methods that will be used to contact them. We will collect multiple points of contact based on participant preferences, including phone numbers (for phoning and text messages), email addresses, and mailing addresses. As an alternate means of contact, we will ask to collect the names of two friends, relatives, case managers, clinics, community centres, or shelters with whom participants have regular contact. Participants will be provided with multiple methods to contact study personnel, including dropping in at recruitment sites, phoning, emailing, or speaking to any of the staff associated with the study.

Flexible scheduling: Outcome Assessment Simulations will be scheduled flexibly and outside business hours if required. We will offer to meet participants at their recruitment location and walk with them to the simulation centre if needed. The short (maximum 2-week) interval for the primary outcome evaluation will reduce attrition for our primary outcome. Research staff will schedule participants' follow-up simulation for between 4 days and 1 week after randomization. This leaves at least 1 week for rescheduling before the 2-week maximum follow-up time. Participants will be able to select a time for the simulation outcome assessment that meets their scheduling needs. Participants will also receive a study card with the simulation time and location as well as contact information of the research coordinator.

Reminders and follow-up: Based on advice from community representatives on the study steering committee, we developed a communication and reminder strategy to suit the participants' diverse needs and contexts. Many members of the target population face tenuous housing and limited financial resources, but many do have cellular phones. For many, communication by letter mail will be untimely and ineffective. Limited financial resources mean that many participants may not have daytime telephone "minutes" and do not take incoming calls, preferring instead to communicate by text message. We emphasize the use of text message reminders, drawing on research demonstrating the feasibility and effectiveness of text messaging for participant retention in randomized trials.[35]

Participants will be asked to choose their preferred and secondary method of contact from phone call, text message or email. Participants will be contacted by their preferred and secondary method 5, 3 and 1 day(s) before their scheduled simulation and on the morning of their simulation to confirm attendance or reschedule, with up to 3 attempts on each of the days of contact. In addition, consenting participants will receive a letter prior to the outcome assessment. Participants will be contacted one week before the 3-month assessment via their preferred method of contact. Communication scripts will be used when contacting participants and messages will not refer to details of the study or to opioid use.

Continuity of relationships: We will strive for consistency in research staff-participant pairing to enhance rapport and build trust, which has been shown to improve patient recruitment and retention.[30] All staff have received anti-oppression training. Wherever possible, the same SOONER staff person who conducts informed consent and recruits a study participant will serve as the point of contact for a given study participant. Study staff will welcome participants at the research institute lobby for outcome visits and accompany them to the assessment centre.

Cash and other compensation: Participants will receive cash per study visit: (1) $15 after consenting to trial activities, (2) $40 upon arrival for the simulation, and (3) $20 upon completion of a follow up interview. Participants will be offered public transit tokens for travel to and from each study visit, snacks, and light refreshments at each study visit. The amount of remuneration proposed in our study for the time required from our participants is consistent with amounts provided in other studies with this population, and payments like those proposed here are effective to improve retention without demonstrating a coercive effect on participants nor precipitating drug use behaviours.[36,37]

3.5 Feasibility Outcomes

3.5.a Primary Feasibility Outcome

The primary outcome is the feasibility of recruitment and retention. The recruitment and retention strategy will be deemed "feasible" if approximately 28 eligible participants are recruited in 28 days of recruitment and if attrition is less than 50% for the underlying study's primary outcome assessment (overdose simulation) at 3-14 days (see Table 2). We will optimize our recruitment strategy at each site before setting "time zero" for recruitment days at each site. These outcomes will be recorded using data from the recruitment and retention log. We will compute the attrition at the Outcome Simulation and 95% binomial proportion confidence interval.

3.5.b Secondary Feasibility Outcomes:

The secondary outcomes will be:

(1) Proportion of eligible participants (people who meet enrolment criteria) who do not consent to the study, as reported in the study log.

(2) Proportion of participants who drop out at the outcome assessment simulation. Dropout at the outcome assessment will be defined as people who attend the outcome simulation but do not complete the simulation or withdraw from the study, as reported in the study log.

3.5.c Tertiary Feasibility Outcomes:

The perspectives of participants will be gathered through a 15-minutes individual semi-structured interview conducted at the outcome simulation visit. The interviews will be audio recorded and transcribed and the acceptability of study processes and opportunities for quality improvement will be analyzed thematically and reported by theme, and with representative quotes. The tertiary outcomes will be acceptability of recruitment, retention and outcome assessment procedures for study participants, and for staff at recruitment sites and the Simulation Centre.

The recruitment and retention strategy will undergo basic quality improvement throughout the study based on the observations of research personnel and their interactions with recruitment site staff. Research personnel will gather informal feedback from recruitment site staff and simulation centre staff regarding quality improvement of the study procedures, and difficulties encountered with respect to recruitment and retention of study participants. The insights gained will be used to make minor changes to improve the quality of study processes. Study staff will keep a quality improvement log to record the feedback received from site staff and discuss feedback at weekly team meetings.

3.6 Outcomes of the Underlying RCT

Outcome measures of the underlying RCT will be gathered but will not be analyzed or reported within the feasibility study.

3.6.a Primary Outcome of the Underlying RCT:

The primary outcome will be the proportion of resuscitation failures in a standardized high-fidelity overdose simulation conducted at the Simulation Centre. Simulations will be conducted with individual participants privately, and not in a group or with other participants observing.

The simulation itself is adapted from analogous studies and, refined to mimic a realistic and imminently fatal overdose situation [10,38,39]. The resuscitation sequence checklist is based on the 2015 American Heart Association bystander resuscitation recommendations. [20] The scenario is intended to simulate a critically life-threatening opioid overdose, where the victim will be found with no signs of life and deteriorate rapidly to opioid-related cardiac arrest. A telephone in the simulation room will be available to simulate a phone call to 911 dispatch.

Study participants will be briefed and oriented to the room using a standardized script and instructed to perform as if the simulation were real. The simulation will end with the announcement of paramedics' arrival, after approximately 10 minutes. Dedicated staff will provide a standardized semi-structured debrief for participants using a standardized framework [40]. This debrief can include direct feedback and opportunities to correct techniques, affirm positive behaviours, as well as set the stage for reflection [40,41].

Simulations will be video recorded, and performance assessments will be conducted based on the video recordings. Data collection will occur using a combination of a simple checklist and resuscitation simulator manikin, arranged to create a high-fidelity simulated overdose situation similar to the simulation described by Kobayashi et al [10]. Assignment of the global assessment score will be based on a consensus of two assessors. Any discrepancy in the assessments of the simulation evaluators will be adjudicated by a lead investigator.

3.6.b Secondary Outcome of the Underlying RCT

The secondary clinical outcome will be performance on eight skills: (1) Recognize the emergency, (2) Position the victim, (3) Activate emergency medical services, (4) Administer naloxone (prepare device, administer correctly), (5) Hand placement, (6) Chest compressions (rate and depth), (7) Continue compressions until end of simulation, and (8) Order of operations and organization.

These eight indicators were adapted from previous CPR and first response training intervention studies, and include both objective measures recorded by the resuscitation manikin and subjective measures assessed by the simulation assessor.[38,39] Assessors will rate each skill as satisfactory or unsatisfactory. Data collection will occur using a validated basic life support checklist and resuscitation manikin data, modified for OEND.[42] Non-indicated resuscitative actions will also be documented. These include rescue breathing, incorrect naloxone administration, or any other medication administration. For rescue breathing, we will collect the ventilation data automatically recorded by the resuscitation manikin.

3.6.c Tertiary Outcome of the Underlying RCT:

An interviewer-administered questionnaire will be used at enrolment, at the simulation and at 3 months to measure tertiary clinical outcomes related to participants' knowledge about overdose, confidence and willingness to intervene in overdose, reported responses to witnessing overdose events, self-assessed barriers to responding to an overdose, and self-reported drug overdose risk behaviours. The questionnaire will be scripted to reduce variability between interviewers.

The questionnaires contain both close-ended questions and open-ended questions, developed for the Toronto Public Health OEND program evaluation [25]. Questionnaire items were developed using data points from other OEND programs and from the validated Opioid

Overdose Knowledge and Attitudes Scales (OOKS and OOAS) [27]. Although the OOKS and OOAS are validated tools, they have been validated only among people who inject drugs and the family members of people who inject drugs, especially heroin [28,29]. These studies have assessed the effectiveness of OEND programs using comparisons of OOKS and OOAS scores before and 3 months after training. Therefore, to permit comparison with these studies, participants who inject drugs or who are friends or family members of people who inject drugs will be asked to return to complete the OOKS and OOAS at 3 months after enrolment.

3.7 Data Sharing

As stipulated in the study informed consent documents, data will not be shared directly with researchers outside the study investigator group. Investigators wishing to undertake further analyses of quantitative study data should contact the corresponding author.

4 Discussion

The proposed study will test study procedures and the feasibility of an integrated recruitment and retention strategy for people likely to witness opioid overdose in the context of an OEND trial using a simulated opioid overdose event for outcome assessment.

Published strategies to improve participant retention include the involvement of community members in study design and implementation, cash and comfort compensation for study participation, regular follow-up through multiple communications media, building trust and improving communication around trial methods, and flexible hours and scheduling for follow-up assessments [31,35,30,37]. Attention to patient-centered, destigmatizing and participatory language in research processes may also enhance participant recruitment and retention [43]. The integration of these elements is the primary strength of our proposed recruitment and retention strategy. Additional strengths include our use of participatory co-design methods for the development of study interventions and materials, and ongoing engagement with people with lived experience of opioid use for study implementation. Recruitment and retention for this study might be further strengthened by engaging peer workers directly in participant recruitment and retention. Although this approach has been successful in other studies with similar populations, in the context of a study designed to test the effectiveness of OEND in a broad variety of clinical settings, we felt that the introduction of peer workers would act as a cointervention and reduce the scalability of the intervention.[19,44,45,46].

Since the study is occurring in an urban population and a randomized trial, our results may not be generalizable to other settings, clinical contexts or study designs. However, if the study demonstrates feasibility, this recruitment and retention strategy will be ready for deployment in a full-scale trial, and potentially for adaptation to other settings.

5 Ethics and Dissemination

The study has been reviewed by ethics boards at St. Michael's Hospital and the Toronto Academic Health Sciences Network, Toronto Public Health, and the University of Toronto. Protocol amendments will also be managed through these research ethics boards. Results will be disseminated through peer-reviewed publication and scholarly presentations, and through the

SOONER Project's network of community agencies and people with lived experience of opioid use and overdose. Participants and study recruitment sites will be sent a lay summary of study results.

6 Author Statement

In addition to the authors named, the SOONER Investigators also includes contributors Leigh Chapman, Nick Goso, Richard Hunt, Peter Jüni. Vicky Stergiopoulos, Suzanne Turner, and Daniel Werb. All authors and contributors conceptualized the study and acquired funding (AO DC, CH, SH, MK, PL, JP, RSh, CS, KT, KS, GM, AW, MC, RSn, LM, LC, NG, RH, PJ, VS, ST and DW). RS, MC and AO undertook project administration, and LM and CS supervised the project. All authors contributed to the design and methodology of the study. AO prepared the first drafted the manuscript. All authors contributed to revising and approving the final manuscript.

7 Acknowledgements

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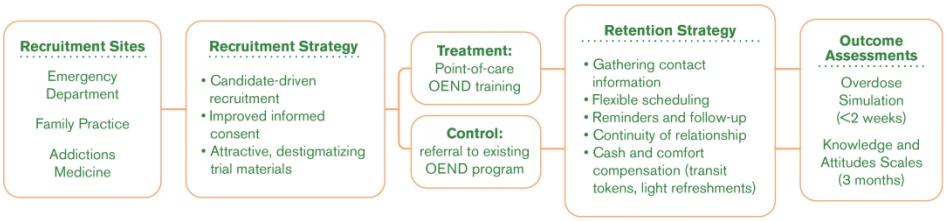

Figure 1: Study Schematic, Recruitment and Retention Strategies

SOONER

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
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	3,6
	2b	All items from the World Health Organization Trial Registration Data Set	N/A to manuscript
Protocol version	3	Date and version identifier	N/A to manuscript
Funding	4	Sources and types of financial, material, and other support	1, 17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 16-17
	5b	Name and contact information for the trial sponsor	1
	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	1, 16-17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A to manuscript
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	5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5-6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9,11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9, 11-13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-15

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9,10
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	7-8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10-12
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 enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9, 11, (some aspects N/A)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6 (some aspects N/A to feasibility study)
	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, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13-15 (some aspects N/A to feasibility study)
	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	12-13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	N/A to manuscript
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A to feasibility study)
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); 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 DMC is not needed	N/A to feasibility study
	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	N/A to feasibility study

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	N/A to manuscript
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A to feasibility study
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
	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	16 (some aspects N/A to feasibility study)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	1-2
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	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial 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, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	6,16

	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	16
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A for feasibility study protocol
Biological specimens	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	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.