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ED to EPI: Protocol for a Pragmatic Randomized Controlled Trial of an SMS (Text) Messaging Intervention to Improve the Transition from the Emergency Department to Early Psychosis Intervention for Young People with Psychosis

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Complete List of Authors:	<p>Polillo, Alexia; Centre for Addiction and Mental Health, Slaight Family Centre for Youth in Transition; University of Toronto, Psychiatry Foussias, George; Centre for Addiction and Mental Health, Slaight Family Centre for Youth in Transition; University of Toronto, Psychiatry Wong, Albert; Centre for Addiction and Mental Health, Campbell Family Mental Health Research Institute; University of Toronto, Psychiatry Ampofo, Augustina; Centre for Addiction and Mental Health Stergiopoulos, Vicky; Centre for Addiction and Mental Health; University of Toronto, Psychiatry Anderson, Kelly; Western University, Epidemiology & Biostatistics Bromley, Sarah; Centre for Addiction and Mental Health, Slaight Family Centre for Youth in Transition D'Arcey, Jessica; Centre for Addiction and Mental Health, Slaight Family Centre for Youth in Transition; University of Toronto, Institute of Medical Science de Oliveira, Claire; Centre for Addiction and Mental Health, Institute for Mental Health Policy Research; University of Toronto, Institute of Health Policy, Management and Evaluation Duda, Lillian; Centre for Addiction and Mental Health Henderson, Joanna; Centre for Addiction and Mental Health, Margaret and Wallace McCain Centre for Child, Youth and Family Mental Health; University of Toronto Faculty of Medicine, Psychiatry Kidd, Sean; Centre for Addiction and Mental Health; University of Toronto, Psychiatry Kurdyak, Paul; Centre for Addiction and Mental Health, Institute for Mental Health Policy Research; University of Toronto, Psychiatry Wang, Wei; Centre for Addiction and Mental Health; University of Toronto, Psychiatry Zaheer, Juveria; Centre for Addiction and Mental Health, Institute for Mental Health Policy Research; University of Toronto, Psychiatry Voineskos, Aristotle; Centre for Addiction and Mental Health, Slaight Family Centre for Youth in Transition; University of Toronto, Psychiatry Kozloff, Nicole; Centre for Addiction and Mental Health, Slaight Family Centre for Youth in Transition; University of Toronto, Psychiatry</p>
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Title

ED to EPI: Protocol for a Pragmatic Randomized Controlled Trial of an SMS (Text) Messaging Intervention to Improve the Transition from the Emergency Department to Early Psychosis Intervention for Young People with Psychosis

Authors

Alexia Polillo, PhD, Slaight Family Centre for Youth in Transition, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

George Foussias, MD, PhD, Slaight Family Centre for Youth in Transition, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

Albert H.C. Wong, MD, PhD, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

Augustina Ampofo, BA, Centre for Addiction and Mental Health, Toronto, Canada

Vicky Stergiopoulos, MD, MHSc, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

Kelly K. Anderson, PhD, Department of Epidemiology and Biostatistics, Western University, London, Canada

Sarah Bromley, OT, Slaight Family Centre for Youth in Transition, Centre for Addiction and Mental Health, Toronto, Canada

Jessica D'Arcey, MSc (candidate), Slaight Family Centre for Youth in Transition, Centre for Addiction and Mental Health and Institute of Medical Science, University of Toronto, Toronto, Canada

Claire de Oliveira, MA, PhD, Institute for Mental Health Policy Research, Centre for Addiction and Mental Health and Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada

Lillian Duda, MPA, Centre for Addiction and Mental Health, Toronto, Canada

Joanna Henderson, PhD, Margaret and Wallace McCain Centre for Child, Youth and Family Mental Health, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

Sean A. Kidd, PhD, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

Paul Kurdyak, MD, PhD, Institute for Mental Health Policy Research, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

Wei Wang, PhD, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

Juveria Zaheer, MD, MSc, Institute for Mental Health Policy Research, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

Aristotle N. Voineskos, MD, PhD, Slight Family Centre for Youth in Transition, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

Nicole Kozloff, MD, SM, Slight Family Centre for Youth in Transition, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

Corresponding author

Nicole Kozloff, Centre for Addiction and Mental Health
250 College Street, 7th floor
Toronto, ON M5T 1R8
n.kozloff@mail.utoronto.ca
416-535-8501

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ABSTRACT

Introduction

Psychosis is a disabling condition that typically has its onset in adolescence and early adulthood. Many young people with psychosis have difficulty navigating services or are reluctant to engage in treatment until their illness becomes an emergency. Consequently, nearly half of all new psychotic disorders are diagnosed in the emergency department (ED). Most young people who present to the ED with psychosis do not receive timely follow-up with a psychiatrist, and even fewer with early psychosis intervention (EPI) services. We aim to use short message service (SMS), a low-cost, low-complexity, youth-friendly approach, to improve transitions from the ED to EPI services.

Methods and analysis

This is a protocol for a pragmatic randomized, single blind, controlled trial with accompanying economic and qualitative evaluations conducted at the Centre for Addiction and Mental Health (CAMH) in Toronto, Canada. A consecutive series of 186 participants aged 16 to 29 referred by the CAMH ED to CAMH's EPI program will be recruited for a trial of a 2-way SMS intervention involving reminders, psychoeducation, and check-ins. The primary outcome will be attendance at the first consultation appointment assessed through chart reviews. Secondary outcomes will include indicators of longer-term service engagement as well as symptoms and functioning 6 months following study enrollment, and health service utilization for up to 2 years using administrative data. A cost-effectiveness analysis and qualitative analysis exploring user perspectives of the intervention will also be performed. Patients and families with lived experience will be engaged in all aspects of the project.

Ethics and dissemination

Research ethics board approval has been obtained from CAMH. Findings will be reported in scientific journal articles and shared with key stakeholders including youth, family members, knowledge users, and decision makers.

Trial registration number [clinicaltrials.gov #NCT04298450](https://clinicaltrials.gov/ct2/show/study/NCT04298450)

ARTICLE SUMMARY

Strengths and limitations of this study

- Pragmatic randomized controlled trial leveraging mobile health technology, chart reviews, routinely collected administrative data, and economic and qualitative evaluations.
- Intervention well-positioned for local adoption as well as scale and spread to other EPI programs and youth mental health services more broadly.
- Collaboration with health system decision-makers, knowledge users, team members with clinical and research expertise, people with lived experience of psychosis, and key relationships with organizations well-positioned to support widespread implementation.
- Conducting the trial at a single site will support streamlined recruitment but may limit generalizability of our findings.

INTRODUCTION

Psychosis, characterized by delusions and/or hallucinations, typically manifests during adolescence or early adulthood. It is the characteristic presentation of schizophrenia and schizoaffective disorder, and often occurs in bipolar disorder.¹ These disorders can cause significant dysfunction: in disability weighting surveys used to establish global disease burden, participants rated schizophrenia as the disorder most disabling for individuals.² Young people experience greater mortality by up to 24-fold in the year following a first psychotic disorder diagnosis compared to peers in the general population.³ In the long term, psychotic disorders are associated with ongoing increased mortality particularly by suicide,⁴ substance use disorders, homelessness, victimization, acts of violence,⁵ and high economic costs due to healthcare use as well as lost productivity.^{6,7} Early psychosis intervention (EPI) is a model developed to provide treatment early in the course of illness to improve patients' long-term trajectories and reduce the burden on individuals and their families. The rationale for EPI has been strengthened by consistent findings that long duration of untreated psychosis is associated with greater symptom burden, lower likelihood of remission and poor social functioning and global outcomes.⁸ Members of our team have shown that EPI service use is associated with a four-fold reduction in all-cause mortality for young people with psychosis compared to those who do not access EPI services.⁹ EPI services have also been associated with improved access to psychiatric care, reduced risk of relapse, fewer hospital readmissions, and increased employment rates.⁹⁻¹³ EPI can be a lifechanging and lifesaving intervention for young people with psychosis.

EPI programs are well-established in Ontario and provide services to young people with early psychosis across the province.¹⁴ Despite this, and the clear mandate for EPI programs to promote their services and minimize barriers to care, many youth with psychosis in Ontario either never access these services, or enter them far later than indicated.¹⁵ In Canada, nearly half of all new psychotic disorders are diagnosed in the ED.¹⁶ We recently found that among young people across Ontario presenting with psychotic disorders to the ED for the first time, 40% received no outpatient mental health follow-up within 30 days and only 45% saw a psychiatrist.¹⁷ The reasons young people with psychosis discharged from the ED did not receive follow-up were unclear in this study: both issues of access (availability and awareness of services) and engagement (youth following through on referrals) are potential explanations. Our experience at the Centre for Addiction and Mental Health (CAMH) in Toronto, where our EPI program sees referred patients for consultation within 2 weeks on average, suggests a problem of engagement: according to clinic data, 50% of the youth referred from the ED do not attend their first EPI consultation appointment (compared with approximately 30% from all other referral sources). It is clear that new approaches are required to engage this population in accessing evidence-based care that is life-saving and improves illness outcomes. In surveys of patients and families in EPI services, appointment reminders are cited as a top factor that would improve service engagement, with a preference for email and text communication.¹⁸⁻²⁰

Mobile health technologies are increasingly being tested to improve outcomes among young people with mental illness. Short message service (SMS) or text message is a commonly used mode of communication by adolescents and young adults: in a survey of users of community mental health services, access to mobile phones approached 100%.²¹ SMS is associated with low user and financial burden. SMS does not require people to own a smartphone, have data plans, or have access to wireless internet. In a study of people with psychosis, participants were found to be highly engaged with an SMS intervention.²² SMS reminders have been associated with improved service engagement in psychosis across studies,²³ including twice the attendance rates for initial appointments in an EPI program.²⁴ An ongoing pilot study at CAMH investigating the effect of a weekly 2-way SMS intervention on

service engagement during the first year of EPI treatment found this approach to be feasible and valued by participants.²⁵ We are unaware of any studies examining interventions specifically to improve the transition in care from the ED to EPI for young people with psychosis, using mobile health technologies or otherwise.

Objectives

“ED to EPI,” a pragmatic randomized, single blind, controlled trial²⁶ with accompanying economic and qualitative evaluations, aims to improve the transition from the ED to EPI services for youth with psychosis using an SMS text messaging intervention. It is pragmatic in its participant eligibility criteria (broad and inclusive), comparison intervention (usual care), follow-up intensity (low), primary trial outcome (objective, meaningful and assessed under usual conditions), measurement of participant compliance and practitioner adherence to study protocol (unobtrusive), and analysis of primary outcome (inclusive, i.e. intention-to-treat).²⁷ Our study team, in addition to clinicians and researchers, includes a patient and family member with lived experience of using EPI services and key decision-makers to increase the relevance and uptake of the intervention. We will assess the effectiveness of an SMS intervention in improving attendance at the first EPI appointment, as well as longer-term service engagement, and system-level outcomes, enabled through data linkage with ICES (previously known as the Institute for Clinical Evaluative Sciences), which holds data on all hospital and physician visits for the province. We will also evaluate the cost effectiveness of the intervention and explore young people’s perspectives on its various components. Specifically, our primary objectives are to:

1. Evaluate the effect of an SMS intervention on attendance at the first consultation appointment within 30 days of study enrolment;
2. Assess indicators of longer-term service engagement 6 months following study enrolment;
3. Determine system-level outcomes, including ED visits and psychiatric hospitalizations, as a function of receiving the SMS intervention, and its cost effectiveness, factoring costs of the intervention and cost offsets of health service utilization;
4. Explore young people’s experiences of the intervention and their perspectives on its various components.

METHODS AND ANALYSIS

Study setting

The study setting will be the Gerald Sheff and Shanitha Kachan Emergency Department at CAMH, Ontario’s only 24-hour stand-alone psychiatric emergency service. The ED also houses a drop-in “Bridging Clinic” which provides care to less acute patients who are diverted after ED triage, and rapid follow-up care for patients discharged from the ED and CAMH inpatient units. Together, they serve approximately 1,200 patients each month. The EPI program at CAMH receives over 600 referrals for suspected psychosis annually, approximately 25% of which are from the ED and Bridging Clinic. Reflecting the Ontario EPI Program Standards, CAMH EPI services are delivered by multidisciplinary teams, employ strategies to promote early entry and ongoing engagement, and provide pharmacotherapy and psychosocial therapies for an average of 3 years.¹⁴ Patients are assigned to the next available and/or most appropriate psychiatrist and case manager (nurse, social worker, or occupational therapist) for a joint consultation appointment, typically within 2 weeks, and are contacted by phone by the EPI program administrator to book and confirm their appointment. After the initial appointment is confirmed, patients receive a phone call reminder the day before their scheduled appointment. As part of routine care, patients who do not attend their scheduled first appointment receive follow-up calls to reschedule an appointment for up to 30 days from the initial referral.

Eligibility criteria

Study inclusion criteria mirror the intake criteria for the CAMH EPI program. Participants will be eligible for the study if they: 1) are between 16 and 29 years old and 2) have been referred by the CAMH ED to CAMH EPI services for suspected psychosis. Our only exclusion criterion is inability to communicate in basic written English. In our pilot SMS study at CAMH, fewer than 5% of potential participants were excluded for lacking a phone; we have budgeted to offer 5% of participants access to a prepaid cellphone for the duration of the study.²⁵

Intervention procedures

Study participants will be recruited at the time of EPI referral for a trial of an SMS intervention designed to engage them during the waiting period for their consultation appointment. They will be randomized to receive either sham or active SMS intervention. Sham SMS will consist of 1 message sent just after enrolment indicating that they will be contacted for an appointment. Active SMS intervention will include the initial message sent to the control group, plus a series of subsequent messages. These will include the following content: 1) appointment reminders and instructions, 2) psychoeducational material, and 3) 2-way communication check-ins to rate distress (Figure 1). Messages sent back by participants will be monitored by the research team, and the case manager assigned to their consultation appointment will be notified and will respond accordingly if there are indicators of elevated distress. The intervention will continue until the patient attends the first consultation appointment, or for up to 30 days if the patient does not attend, which reflects the program's practice of closing referrals for non-attending patients.

Messages will be sent through CAMH's in-house Research Electronic Data Capture (REDCap) platform via a third-party plug-in, Twilio, which supports routing of SMS messages to participant devices.²⁸⁻³⁰ All data is stored securely on CAMH's REDCap servers or in a locked office and password-protected database on CAMH's secure network. The purpose of the sham intervention is to separate out the content of the intervention (i.e. reminders, psychoeducation, 2-way check-ins) from the effect of simply receiving SMS messages, decreasing participant bias.

Assignment of intervention

Immediately after informed consent, participants will be randomized by REDCap to the active or sham intervention. Generation of the randomization sequence will be managed by the study biostatistician who is not involved in enrolling participants or assigning intervention arms. Randomization will be stratified by sex (male or female) and referral source (ED or Bridging Clinic), using a computer algorithm to determine a randomized, blocked allocation of participants into intervention groups within strata. The predetermined computer algorithm is housed in REDCap, and is locked, allowing for concealed assignment before individual randomization. Once randomized, treatment assignment will be known only by the study personnel involved in managing the SMS intervention and the case manager monitoring text message responses; the principal investigator and study personnel involved in the chart review and the ICES analysis will remain blind to treatment assignment. Study personnel involved in the qualitative interviews and analysis will also be aware of treatment assignment since only individuals receiving the active intervention will participate in this component of the project.

Sample size

Our sample size calculations are based on the primary outcome of rate of attendance at the EPI program consultation appointment. The current rate of attendance at the first consultation appointment for patients referred from the ED and Bridging Clinic is 50%; we have powered our study to increase the rate of attendance to 70%, which is the average for all

referral sources other than the ED and Bridging Clinic. A total of 186 participants (93 per group) will provide >80% power to detect a change in attendance from 50% to 70% at alpha <0.05. Non-compliance and loss to follow-up are not a concern for our primary outcome since these are counted in the outcome as nonattendance at the consultation. Adjusting analyses for covariates expected to affect attendance (e.g., age, sex) is expected to further increase power. The sample sizes for secondary and exploratory outcomes will be smaller, as only some participants who attend the first appointment will be deemed eligible for, offered, and enrolled in EPI services.

Study procedures

We will recruit 186 patients consecutively referred from the CAMH ED and Bridging Clinic to the CAMH EPI program at the time of discharge. During business hours and into the evening, research staff will be on call to the ED to recruit patients as soon as they are identified for the study. Eligible participants who present after hours may be identified by ED staff and referred to the research team who will send them an e-consent form via SMS or email. Additionally, potential participants who are missed in the ED/Bridging clinic may be identified by the EPI clinic administrator who will approach them over the phone and send them an e-consent form via SMS or email. We have used the approach of having clinical and administrative staff obtain verbal consent to send e-consent forms in other studies with this population.¹⁹

As part of informed consent, participants will be asked to consent to a review of their chart, a follow-up web-based survey, and linkage of their information to data held at ICES. They will also be given the option to provide consent to be re-contacted for participation in a qualitative interview. There will be no additional in-person assessments for the quantitative component of this study. CAMH uses an electronic health record, which facilitates data abstraction from multiple clinical programs (i.e., both the ED and Bridging Clinic and EPI program). Research staff and students will be trained by the clinician principal investigators to abstract data into a structured database.

All study participants will receive a \$10 e-giftcard once the baseline e-visit is complete. Participants in the active intervention group who complete a web-based survey will receive another \$10 e-giftcard and those who complete an in-person qualitative interview will receive a \$50 e-giftcard. It will be clarified through the consent process that honoraria are to compensate participants for their time and will not be tied to clinical appointment attendance.

Outcome measures

Chart review

Outcome measures are shown in Table 1. CAMH uses many standardized assessment forms which increases the completeness of patient data. Demographic variables, clinical diagnoses, substance use, duration of untreated psychosis (measured as the period of time from first onset of psychotic symptoms to initiation of EPI services and initiation of treatment with an antipsychotic or mood-stabilizing medication), characteristics of the ED visit from which they were referred (voluntary vs. involuntary status, timing), and family involvement in care will be abstracted from the chart at the time of consultation. Additional variables will likely be available but only for patients accepted into the EPI program, and this will be reflected in the data analysis. These include several assessments that are performed routinely in the EPI program. The Service Engagement Scale (SES)³¹ is a brief validated tool designed to measure engagement with community mental health services. In 14 items, it assesses patients' availability for treatment, collaboration, help-seeking behaviours and treatment adherence on a four-point Likert scale with higher scores indicating difficulties in service engagement. The Brief Psychiatric Rating Scale (BPRS)³² is an interviewer-rated measure of psychiatric symptoms

commonly used as an outcome measure for psychotic disorders. The Clinical Global Impression (CGI)³³ is a clinician-rated measure of the patient's global severity of illness prior to and after initiating a medication. It includes subscales for Severity and Improvement. Medication and appointment nonadherence will also be assessed over 6 months of treatment. Lastly, after 6 months, current EPI enrolment status will be assessed and categorized as: not offered or enrolled in treatment (e.g., because they did not ultimately have psychosis), enrolled but disengaged prematurely, accepted for treatment but transitioned to other services, or continued in treatment.

Administrative data

Primary data collected for the study will be linked deterministically to data sources held at ICES via participants' unique health card numbers. The information available for each participant will be de-identified, stored, and analyzed onsite at ICES following procedures approved by Ontario's Information and Privacy Commissioner. The following ICES data sources will be used: the Ontario Mental Health Reporting System (OMHRS), capturing hospitalizations on adult inpatient mental health units,³⁴ the Canadian Institute of Health Information Discharge Abstract Database (CIHI-DAD), capturing all hospital admissions including hospitalizations on child and adolescent inpatient mental health units,^{35 36} National Ambulatory Care Reporting System (NACRS) which captures all ED visits,³⁷ Ontario Health Insurance Plan (OHIP) claims database, which captures outpatient physician visits,³⁵ Registered Persons Database, which contains health card numbers, demographic information, and deaths, and Ontario Drug Benefits (ODB) claims database, which provides information on all covered prescriptions (based on financial need for those under age 65 and for young people up to age 25 who lack private insurance). These data will also be used for cost effectiveness analysis. Outcomes examined in the linked ICES data are listed in Table 1.

Table 1. Summary of outcome measures and covariates

Type	Variables	Data Source
Demographic characteristics	Age	Chart review (CAMH Health Equity form and notes)
	Sex and gender	
	Sexual orientation	
	Race/ethnicity	
	Born in Canada	
	Religious/spiritual affiliation	
	Highest level of education	
	Source of income and family income	
	Number of people supported by income	
	Employment status	
	Legal history	
	Housing status	
	Living situation	

	Experience of homelessness	
	Relationship status	
Clinical characteristics	Clinical diagnoses	Chart review
	Substance use	
	DUP	
	Family involvement in care	
	BPRS ³²	
	CGI ³³	
Service engagement	Attendance at consultation appointment	Chart review
	SES ³¹	
	Medication and appointment nonadherence	
	EPI enrolment status	
System-level outcomes*	Number of ED visits	NACRS ³⁷
	Number of inpatient mental health hospitalizations	OMHRS, ³⁴ CIHI-DAD ^{35 36}
	Number of days in inpatient mental health hospitalizations	OMHRS, ³⁴ CIHI-DAD ^{35 36}
	Number of outpatient mental health visits	OHIP ³⁵
	Prescription drugs – psychiatric medications, continuously vs. noncontinuously prescribed	ODB
	Mortality	Registered Persons Database

*Administrative data held at ICES

CAMH, Centre for Addiction and Mental Health; DUP, duration of untreated psychosis; BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression; SES, Service Engagement Scale; EPI, early psychosis intervention; ED, emergency department; OMHRS, Ontario Mental Health Reporting System; CIHI-DAD, Canadian Institute of Health Information Discharge Abstract Database; NACRS, National Ambulatory Care Reporting System; OHIP, Ontario Health Insurance Plan; ODB, Ontario Drug Benefits.

Statistical analysis

Primary analysis

Descriptive and graphical statistics will be used to summarize the data on all randomized participants and to confirm that there are no group differences in baseline demographics and clinical characteristics. Distributional assumptions will be inspected and appropriate transformations or non-parametric methods will be applied as necessary. In general, generalized linear models³⁸ will be used throughout. These models account for deviation from normal assumption of the outcome variables and control for covariates.

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4 Our analysis of the primary outcome will be a logistic regression to examine the
5 likelihood of attendance at the EPI consultation with treatment assignment using risk ratios.³⁹
6 We will carefully select demographic variables and factors known to influence treatment
7 engagement (e.g., substance use, family involvement in care)⁴⁰ to be included in the model as
8 covariates. A difference in attendance between groups will be declared at a significance level of
9 0.05. Similar models will be used to address the secondary hypotheses, with specific types of
10 models appropriate to each outcome, including time-to-event analysis to examine premature
11 disengagement from services. Administrative data outcomes will be examined using generalized
12 linear models with proper distribution assumptions.
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15 Additional analyses: moderation and generalizability

16 We plan to conduct two additional exploratory analyses. First, we will run moderation
17 analyses on potential effect modifiers by adding an interaction term between the potential
18 moderator and the treatment assignment indicator in the generalized linear models. We are
19 specifically interested in the moderation effects of health equity factors including gender,
20 race/ethnicity, and housing status. A significant interaction will provide evidence that the
21 treatment effects may be different in the subgroups. A second exploratory analysis will be
22 conducted to evaluate the impact of selection bias of the study sample and estimate the
23 population average treatment effects by employing weighted analysis using propensity scores.⁴¹
24
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26 Missing data

27 The risk of missing data is mitigated through the use of chart review and analysis of
28 administrative data. While the primary outcome will not suffer from attrition, other outcomes will,
29 as some follow-up data will only be available for participants who attended their consultation
30 appointment and those who are enrolled in CAMH EPI services. For these additional outcomes,
31 we plan to use multiple imputation methods developed by Schafer to correct potential bias that
32 could be introduced by missing data.⁴²
33
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35 Economic evaluation

36 We will undertake a cost-effectiveness analysis examining attendance at the
37 consultation appointment as the outcome, adopting the perspective of the public third-party
38 payer (i.e., the Ontario Ministry of Health). We will collect data on the costs of delivering both
39 arms of the intervention. In addition, using a costing algorithm available at ICES,⁴³ we will
40 estimate all direct patient-level healthcare costs incurred by the public third-party payer for the
41 intervention and control groups, which will include costs of hospitalizations, ED visits, physician
42 services (i.e., primary care, psychiatry and other) and diagnostic tests, outpatient prescription
43 drugs for individuals covered under the provincial public drug insurance plan, and other hospital-
44 based care. Assuming that all subjects will incur (non-zero) healthcare costs, we will use a
45 generalized linear model with a gamma distribution and log link to model healthcare costs. We
46 will use a net benefit regression approach to model probabilities of cost effectiveness for each
47 additional patient referred who attends their consultation appointment in the intervention
48 compared with control group.
49

50 Understanding patient experiences: Survey and qualitative analysis

51 Participants in the active intervention group will receive a one-time survey sent as a web-
52 link to their phone or email address. Survey topics include user experience, attitudes toward the
53 SMS intervention, its perceived benefits and challenges, acceptability, and suggestions for
54 improvements. Those who consent to participate in the qualitative research component will be re-
55 contacted by phone or email to participate in semi-structured interviews to gain a more in-depth
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3 understanding of survey topics. A subsample of 10-15 participants in the active intervention group
4 will be purposively selected to maximize diversity of age, gender, and service attendance. We will
5 use critical realist theory as an underlying framework to guide our interviews, surveys, and
6 analysis.⁴⁴ Interviews will be completed until thematic saturation is achieved, estimated at 12
7 participants. Interviews will be digitally audio-recorded and transcribed verbatim. Surveys will be
8 completed and stored in REDCap. Transcriptions and survey responses will be analyzed using
9 thematic content analysis in NVivo-11. Research participants will be invited to assist with member
10 checking to confirm that themes reflect their experiences. The analysis can inform future
11 improvements to the intervention and considerations for broader implementation, privileging the
12 experiences of the patients attending these programs.
13

14 15 **PATIENT AND PUBLIC INVOLVEMENT**

16 A youth and family member who previously received EPI services have been engaged in
17 helping shape the intervention and study design from project inception. They are active
18 members of the project's Steering Committee that meets monthly to inform study design,
19 implementation, evaluation, and dissemination of results. They will have key roles in the plan to
20 spread the intervention, if successful, to other EPI programs by working with patients and
21 families to adapt the intervention to local contexts. Additional youth with lived experience of
22 receiving EPI services have been consulted on an ad hoc basis through the CAMH Youth
23 Engagement Initiative to provide detailed feedback on the SMS intervention. Patient and family
24 representatives on the research team are compensated for their time.
25

26 27 **ETHICS AND DISSEMINATION**

28 The study was approved by the Research Ethics Board (REB) at the Centre for
29 Addiction and Mental Health. The study protocol was prepared according to SPIRIT guidelines
30 (Supplemental File)⁴⁵ and registered with clinicaltrials.gov on March 6, 2020 (NCT04298450;
31 <https://clinicaltrials.gov/ct2/show/NCT04298450?term=ed+to+epi&draw=2&rank=1>). REB-
32 approved protocol amendments will be posted on the site. The principal investigators and study
33 team will meet regularly to review accrued data, data confidentiality, any adverse events,
34 adherence to protocol design, recruitment and implementation. This intervention has been
35 designed to have high likelihood of adoption and readiness for spread and scale-up because it
36 responds to a critical need, has a strong evidentiary basis, has advantages over existing
37 practice and is both low complexity and low cost.⁴⁶ This trial focuses on a particularly vulnerable
38 population—young people transitioning from adolescence to adulthood and from the ED to EPI
39 services—but the basic intervention is widely applicable. The software platform utilized to
40 coordinate this intervention is available at no charge, and the SMS functionality for sending and
41 receiving messages carries a nominal fee, supporting broad uptake.
42

43 The results of the trial will be reported in scientific journal articles and shared with key
44 stakeholders as they become available. Our study team includes the co-chair of the Early
45 Psychosis Intervention Ontario Network, a network of over 50 EPI programs across Ontario, and
46 several members of the Canadian Consortium for Early Intervention in Psychosis, providing a
47 durable and established community of practice for immediate spread. De-identified participant
48 data will be available upon reasonable request other than system-level data held at ICES.
49 Requests can be made by contacting the principal investigator Dr. Nicole Kozloff at
50 nicole.kozloff@camh.ca and will be managed by the Steering Committee.
51

52 53 **CONCLUSIONS**

54 This pragmatic randomized-controlled trial of a low-cost, low-complexity SMS
55 intervention aims to improve the transition from the ED to EPI services for young people with
56 psychosis. It targets a brief but critical period: if young people cannot even get in the door to EPI
57

services, there is no way for them to reap the many known benefits of EPI care. Improving the ED to EPI transition has the potential to result in more young people with psychosis getting appropriate treatment earlier. The proposed intervention is also likely to be easily adaptable to other referral pathways to EPI services and youth mental health services more broadly. At potentially lower cost to the health system, applying this SMS intervention to the ED to EPI transition has the potential to lead to improved short-term symptoms and functioning, long-term disease trajectories, decreased burden on patients and families, and fewer deaths among young people with psychosis.

Figures

Figure 1. Study intervention schedule*

*This figure represents a summary of the intervention schedule and is not exhaustive of text message content

SMS, short message service; Right arrow, incoming text messages received by participants; Left arrow, outgoing text messages sent by participants

Author contributions

NK is the principal investigator who conceived the original study design and obtained funding, with most of the current authors having contributed to the funding application, and all authors having participated in revisions to the study design for important intellectual content. AP and NK drafted the protocol. AA and LD consulted on patient and public involvement. WW consulted on the biostatistical analysis plan. All authors read, revised and approved the final version of the manuscript.

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Competing interests statement

The authors declare no competing interests.

Patient and public involvement

Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research.

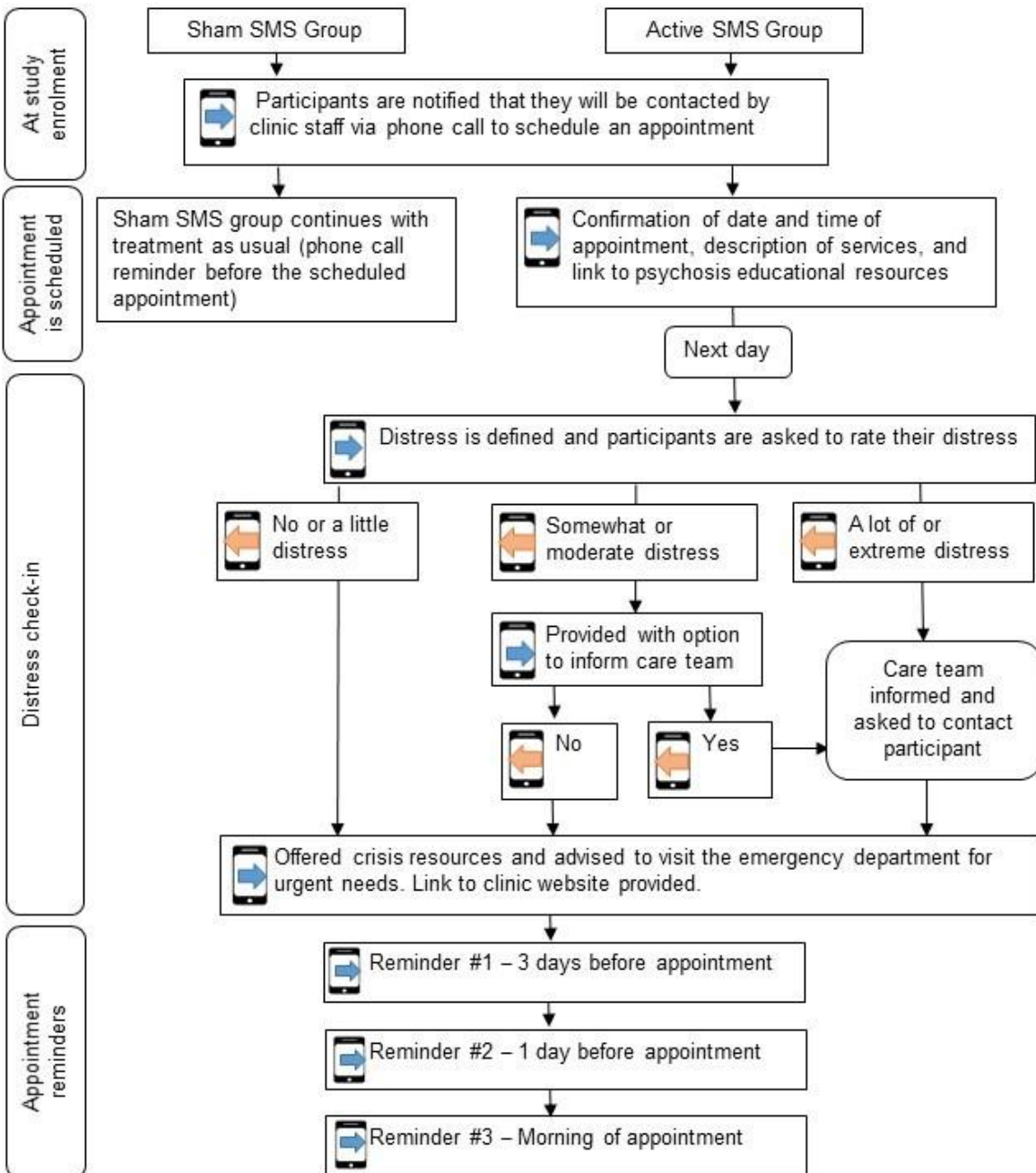
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Supplementary File 1: Protocol reporting checklist based on SPIRIT guidelines

	Reporting Item	Page Number
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
Trial registration: data set	#2b All items from the World Health Organization Trial Registration Data Set	3
Protocol version	#3 Date and version identifier	11
Funding	#4 Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a Names, affiliations, and roles of protocol contributors	12
Roles and responsibilities: sponsor contact information	#5b Name and contact information for the trial sponsor	12
Roles and responsibilities: sponsor and funder	#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	12

1	Roles and	#5d	Composition, roles, and responsibilities of the	12
2	responsibilities:		coordinating centre, steering committee, endpoint	
3	committees		adjudication committee, data management team, and	
4			other individuals or groups overseeing the trial, if	
5			applicable (see Item 21a for data monitoring committee)	
6				
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9	Introduction			
10				
11	Background and	#6a	Description of research question and justification for	4-5
12	rationale		undertaking the trial, including summary of relevant	
13			studies (published and unpublished) examining benefits	
14			and harms for each intervention	
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18	Background and	#6b	Explanation for choice of comparators	4-5
19	rationale: choice of			
20	comparators			
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23	Objectives	#7	Specific objectives or hypotheses	5
24				
25				
26	Trial design	#8	Description of trial design including type of trial (eg,	5
27			parallel group, crossover, factorial, single group),	
28			allocation ratio, and framework (eg, superiority,	
29			equivalence, non-inferiority, exploratory)	
30				
31				
32				
33	Methods:			
34	Participants,			
35	interventions, and			
36	outcomes			
37				
38				
39	Study setting	#9	Description of study settings (eg, community clinic,	5
40			academic hospital) and list of countries where data will	
41			be collected. Reference to where list of study sites can	
42			be obtained	
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46	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	5
47			applicable, eligibility criteria for study centres and	
48			individuals who will perform the interventions (eg,	
49			surgeons, psychotherapists)	
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53	Interventions:	#11a	Interventions for each group with sufficient detail to allow	6
54	description		replication, including how and when they will be	
55			administered	
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1	Interventions:	#11b	Criteria for discontinuing or modifying allocated	6
2	modifications		interventions for a given trial participant (eg, drug dose	
3			change in response to harms, participant request, or	
4			improving / worsening disease)	
5				
6				
7	Interventions:	#11c	Strategies to improve adherence to intervention	9-11
8	adherence		protocols, and any procedures for monitoring adherence	
9			(eg, drug tablet return; laboratory tests)	
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13	Interventions:	#11d	Relevant concomitant care and interventions that are	6
14	concomitant care		permitted or prohibited during the trial	
15				
16				
17	Outcomes	#12	Primary, secondary, and other outcomes, including the	7-9
18			specific measurement variable (eg, systolic blood	
19			pressure), analysis metric (eg, change from baseline,	
20			final value, time to event), method of aggregation (eg,	
21			median, proportion), and time point for each outcome.	
22			Explanation of the clinical relevance of chosen efficacy	
23			and harm outcomes is strongly recommended	
24				
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27				
28	Participant timeline	#13	Time schedule of enrolment, interventions (including any	7-9
29			run-ins and washouts), assessments, and visits for	
30			participants. A schematic diagram is highly	
31			recommended (see Figure)	
32				
33				
34				
35	Sample size	#14	Estimated number of participants needed to achieve	6-7
36			study objectives and how it was determined, including	
37			clinical and statistical assumptions supporting any	
38			sample size calculations	
39				
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41				
42	Recruitment	#15	Strategies for achieving adequate participant enrolment	7
43			to reach target sample size	
44				
45				
46	Methods:			
47	Assignment of			
48	interventions (for			
49	controlled trials)			
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52	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	6
53	generation		computer-generated random numbers), and list of any	
54			factors for stratification. To reduce predictability of a	
55			random sequence, details of any planned restriction (eg,	
56			blocking) should be provided in a separate document	
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that is unavailable to those who enrol participants or assign interventions

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4	Allocation	#16b	Mechanism of implementing the allocation sequence (eg, 6
5	concealment		central telephone; sequentially numbered, opaque,
6			sealed envelopes), describing any steps to conceal the
7	mechanism		sequence until interventions are assigned
8			
9			
10	Allocation:	#16c	Who will generate the allocation sequence, who will 6
11	implementation		enrol participants, and who will assign participants to
12			interventions
13			
14			
15	Blinding (masking)	#17a	Who will be blinded after assignment to interventions 6
16			(eg, trial participants, care providers, outcome
17			assessors, data analysts), and how
18			
19	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is 6
20	emergency unblinding		permissible, and procedure for revealing a participant's
21			allocated intervention during the trial
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26			
27	Methods: Data		
28	collection,		
29	management, and		
30	analysis		
31			
32			
33	Data collection plan	#18a	Plans for assessment and collection of outcome, 7-9
34			baseline, and other trial data, including any related
35			processes to promote data quality (eg, duplicate
36			measurements, training of assessors) and a description
37			of study instruments (eg, questionnaires, laboratory
38			tests) along with their reliability and validity, if known.
39			Reference to where data collection forms can be found,
40			if not in the protocol
41			
42			
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46	Data collection plan:	#18b	Plans to promote participant retention and complete 7, 9
47	retention		follow-up, including list of any outcome data to be
48			collected for participants who discontinue or deviate from
49			intervention protocols
50			
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53	Data management	#19	Plans for data entry, coding, security, and storage, 6, 7-8,
54			including any related processes to promote data quality 11
55			(eg, double data entry; range checks for data values).
56			
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1		Reference to where details of data management	
2		procedures can be found, if not in the protocol	
3			
4	Statistics: outcomes	#20a Statistical methods for analysing primary and secondary	9-11
5		outcomes. Reference to where other details of the	
6		statistical analysis plan can be found, if not in the	
7		protocol	
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10			
11	Statistics: additional	#20b Methods for any additional analyses (eg, subgroup and	10
12	analyses	adjusted analyses)	
13			
14			
15	Statistics: analysis	#20c Definition of analysis population relating to protocol non-	10
16	population and	adherence (eg, as randomised analysis), and any	
17	missing data	statistical methods to handle missing data (eg, multiple	
18		imputation)	
19			
20			
21	Methods: Monitoring		
22			
23			
24	Data monitoring:	#21a Composition of data monitoring committee (DMC);	11
25	formal committee	summary of its role and reporting structure; statement of	
26		whether it is independent from the sponsor and	
27		competing interests; and reference to where further	
28		details about its charter can be found, if not in the	
29		protocol. Alternatively, an explanation of why a DMC is	
30		not needed	
31			
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34			
35	Data monitoring:	#21b Description of any interim analyses and stopping	11
36	interim analysis	guidelines, including who will have access to these	
37		interim results and make the final decision to terminate	
38		the trial	
39			
40			
41			
42	Harms	#22 Plans for collecting, assessing, reporting, and managing	11
43		solicited and spontaneously reported adverse events	
44		and other unintended effects of trial interventions or trial	
45		conduct	
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49	Auditing	#23 Frequency and procedures for auditing trial conduct, if	11
50		any, and whether the process will be independent from	
51		investigators and the sponsor	
52			
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Ethics and dissemination

1	Research ethics	#24	Plans for seeking research ethics committee /	11
2	approval		institutional review board (REC / IRB) approval	
3				
4	Protocol amendments	#25	Plans for communicating important protocol	11
5			modifications (eg, changes to eligibility criteria,	
6			outcomes, analyses) to relevant parties (eg,	
7			investigators, REC / IRBs, trial participants, trial	
8			registries, journals, regulators)	
9				
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13	Consent or assent	#26a	Who will obtain informed consent or assent from	7
14			potential trial participants or authorised surrogates, and	
15			how (see Item 32)	
16				
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18	Consent or assent:	#26b	Additional consent provisions for collection and use of	7, 11
19	ancillary studies		participant data and biological specimens in ancillary	
20			studies, if applicable	
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24	Confidentiality	#27	How personal information about potential and enrolled	6
25			participants will be collected, shared, and maintained in	
26			order to protect confidentiality before, during, and after	
27			the trial	
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30	Declaration of	#28	Financial and other competing interests for principal	12
31	interests		investigators for the overall trial and each study site	
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34	Data access	#29	Statement of who will have access to the final trial	11
35			dataset, and disclosure of contractual agreements that	
36			limit such access for investigators	
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40	Ancillary and post trial	#30	Provisions, if any, for ancillary and post-trial care, and for	11
41	care		compensation to those who suffer harm from trial	
42			participation	
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44				
45	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	11
46	trial results		results to participants, healthcare professionals, the	
47			public, and other relevant groups (eg, via publication,	
48			reporting in results databases, or other data sharing	
49			arrangements), including any publication restrictions	
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53	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	11
54	authorship		professional writers	
55				
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57	Dissemination policy:	#31c	Plans, if any, for granting public access to the full	11
58	reproducible research		protocol, participant-level dataset, and statistical code	
59				
60				

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	7, 11
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	11

For peer review only

BMJ Open

ED to EPI: Protocol for a Pragmatic Randomized Controlled Trial of an SMS (Text) Messaging Intervention to Improve the Transition from the Emergency Department to Early Psychosis Intervention for Young People with Psychosis

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Manuscript ID	bmjopen-2020-042751.R1
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Complete List of Authors:	<p>Polillo, Alexia; Centre for Addiction and Mental Health, Slaight Family Centre for Youth in Transition; University of Toronto, Psychiatry Foussias, George; Centre for Addiction and Mental Health, Slaight Family Centre for Youth in Transition; University of Toronto, Psychiatry Wong, Albert; Centre for Addiction and Mental Health, Campbell Family Mental Health Research Institute; University of Toronto, Psychiatry Ampofo, Augustina; Centre for Addiction and Mental Health Stergiopoulos, Vicky; Centre for Addiction and Mental Health; University of Toronto, Psychiatry Anderson, Kelly; Western University, Epidemiology & Biostatistics Bromley, Sarah; Centre for Addiction and Mental Health, Slaight Family Centre for Youth in Transition D'Arcey, Jessica; Centre for Addiction and Mental Health, Slaight Family Centre for Youth in Transition; University of Toronto, Institute of Medical Science de Oliveira, Claire; Centre for Addiction and Mental Health, Institute for Mental Health Policy Research; University of Toronto, Institute of Health Policy, Management and Evaluation Duda, Lillian; Centre for Addiction and Mental Health Henderson, Joanna; Centre for Addiction and Mental Health, Margaret and Wallace McCain Centre for Child, Youth and Family Mental Health; University of Toronto Faculty of Medicine, Psychiatry Kidd, Sean; Centre for Addiction and Mental Health; University of Toronto, Psychiatry Kurdyak, Paul; Centre for Addiction and Mental Health, Institute for Mental Health Policy Research; University of Toronto, Psychiatry Wang, Wei; Centre for Addiction and Mental Health; University of Toronto, Psychiatry Zaheer, Juveria; Centre for Addiction and Mental Health, Institute for Mental Health Policy Research; University of Toronto, Psychiatry Voineskos, Aristotle; Centre for Addiction and Mental Health, Slaight Family Centre for Youth in Transition; University of Toronto, Psychiatry Kozloff, Nicole; Centre for Addiction and Mental Health, Slaight Family Centre for Youth in Transition; University of Toronto, Psychiatry</p>
Primary Subject Heading:	Mental health

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Title

ED to EPI: Protocol for a Pragmatic Randomized Controlled Trial of an SMS (Text) Messaging Intervention to Improve the Transition from the Emergency Department to Early Psychosis Intervention for Young People with Psychosis

Authors

Alexia Polillo, PhD, Slaight Family Centre for Youth in Transition, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

George Foussias, MD, PhD, Slaight Family Centre for Youth in Transition, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

Albert H.C. Wong, MD, PhD, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

Augustina Ampofo, BA, Centre for Addiction and Mental Health, Toronto, Canada

Vicky Stergiopoulos, MD, MHSc, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

Kelly K. Anderson, PhD, Department of Epidemiology and Biostatistics, Western University, London, Canada

Sarah Bromley, OT, Slaight Family Centre for Youth in Transition, Centre for Addiction and Mental Health, Toronto, Canada

Jessica D'Arcey, MSc (candidate), Slaight Family Centre for Youth in Transition, Centre for Addiction and Mental Health and Institute of Medical Science, University of Toronto, Toronto, Canada

Claire de Oliveira, MA, PhD, Institute for Mental Health Policy Research, Centre for Addiction and Mental Health and Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada

Lillian Duda, MPA, Centre for Addiction and Mental Health, Toronto, Canada

Joanna Henderson, PhD, Margaret and Wallace McCain Centre for Child, Youth and Family Mental Health, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

Sean A. Kidd, PhD, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

Paul Kurdyak, MD, PhD, Institute for Mental Health Policy Research, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

Wei Wang, PhD, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

1
2
3 50 Juveria Zaheer, MD, MSc, Institute for Mental Health Policy Research, Centre for Addiction and
4 51 Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

5 52
6 53 Aristotle N. Voineskos, MD, PhD, Slaight Family Centre for Youth in Transition, Centre for
7 54 Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto,
8 55 Canada

9 56
10 57 Nicole Kozloff, MD, SM, Slaight Family Centre for Youth in Transition, Centre for Addiction and
11 58 Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

13 59 14 60 **Corresponding author**

15 61 Nicole Kozloff, Centre for Addiction and Mental Health
16 62 250 College Street, 7th floor
17 63 Toronto, ON M5T 1R8
18 64 n.kozloff@mail.utoronto.ca
19 65 416-535-8501

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25 71 Schizophrenia and psychotic disorders
26 72 Early psychosis intervention
27 73 Mobile health interventions
28 74 Patient and family engagement
29 75 Pragmatic clinical trials

30 76 31 77 **ABSTRACT**

32 78 **Introduction**

33 79 Despite the overwhelming evidence supporting early intervention for psychosis, many young
34 80 people with psychosis experience long delays to treatment. While nearly half of all new
35 81 psychotic disorders are diagnosed in the emergency department (ED), most young people who
36 82 present to the ED with psychosis do not receive timely follow-up with a psychiatrist, and even
37 83 fewer with early psychosis intervention (EPI) services. We aim to test an intervention delivered
38 84 using short message service (SMS), a low-cost, low-complexity, youth-friendly approach, to
39 85 improve transitions from the ED to EPI services.

40 86 41 87 **Methods and analysis**

42 88 This is a protocol for a pragmatic randomized, single blind, controlled trial with accompanying
43 89 economic and qualitative evaluations conducted at the Centre for Addiction and Mental Health
44 90 (CAMH) in Toronto, Canada. A consecutive series of 186 participants aged 16 to 29 referred by
45 91 the CAMH ED to CAMH's EPI program will be recruited for a trial of a 2-way intervention
46 92 involving reminders, psychoeducation, and check-ins delivered via SMS. The primary outcome
47 93 will be attendance at the first consultation appointment within 30 days of study enrolment
48 94 assessed through chart reviews of routinely-collected clinic data. We will also review
49 95 participants' charts and link with provincial health administrative data to examine longer-term
50 96 service engagement and system-level outcomes, including ED visits and psychiatric
51 97 hospitalizations, 6 months and up to 2 years after baseline. A cost-effectiveness analysis of the
52 98 intervention will be performed and web-based surveys and qualitative interviews will explore
53 99 young people's perspectives on the intervention. Patients and families with lived experience will
54 100 be engaged in all aspects of the project.

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4 102 **Ethics and dissemination**
5 103 Research ethics board approval has been obtained. Findings will be reported in scientific journal
6 104 articles and shared with key stakeholders including youth, family members, knowledge users,
7 105 and decision makers.
8 106

9 107 **Trial registration number** clinicaltrials.gov #NCT04298450
10 108

11 109 **ARTICLE SUMMARY**

12 110 **Strengths and limitations of this study**

- 13 111 • Pragmatic randomized controlled trial leveraging mobile health technology, chart
14 112 reviews, routinely collected administrative data, and economic and qualitative
15 113 evaluations.
- 16 114 • Intervention well-positioned for local adoption as well as scale and spread to other EPI
17 115 programs and youth mental health services more broadly.
- 18 116 • Collaboration with health system decision-makers, clinical stakeholders, knowledge
19 117 users, team members with clinical and research expertise, people with lived experience
20 118 of psychosis, and key relationships with organizations well-positioned to support
21 119 widespread implementation.
- 22 120 • Conducting the trial at a single site will support streamlined recruitment but may limit
23 121 generalizability of our findings.
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INTRODUCTION

Psychosis, characterized by delusions and/or hallucinations, typically manifests during adolescence or early adulthood. It is the characteristic presentation of schizophrenia and schizoaffective disorder, and often occurs in bipolar disorder.¹ These disorders can cause significant dysfunction: in disability weighting surveys used to establish global disease burden, participants rated schizophrenia as the disorder most disabling for individuals.² Young people experience greater mortality by up to 24-fold in the year following a first psychotic disorder diagnosis compared to peers in the general population.³ In the long term, psychotic disorders are associated with ongoing increased mortality particularly by suicide,⁴ substance use disorders, homelessness, victimization, acts of violence,⁵ and high economic costs due to healthcare use as well as lost productivity.^{6,7} Early psychosis intervention (EPI) is a model developed to provide treatment early in the course of illness to improve patients' long-term trajectories and reduce the burden on individuals and their families. The rationale for EPI has been strengthened by consistent findings that long duration of untreated psychosis is associated with greater symptom burden, lower likelihood of remission and poor social functioning and global outcomes.⁸ Members of our team have shown that EPI service use is associated with a four-fold reduction in all-cause mortality for young people with psychosis compared to those who do not access EPI services.⁹ EPI services have also been associated with improved access to psychiatric care, reduced risk of relapse, fewer hospital readmissions, and increased employment rates.⁹⁻¹³ EPI can be a lifechanging and lifesaving intervention for young people with psychosis.

EPI programs are well-established in Ontario and provide services to young people with early psychosis across the province.¹⁴ Despite this, and the clear mandate for EPI programs to promote their services and minimize barriers to care, many youth with psychosis in Ontario either never access these services, or enter them far later than indicated.¹⁵ In Canada, nearly half of all new psychotic disorders are diagnosed in the ED.¹⁶ We recently found that among young people across Ontario presenting with psychotic disorders to the ED for the first time, 40% received no outpatient mental health follow-up within 30 days and only 45% saw a psychiatrist.¹⁷ The reasons young people with psychosis discharged from the ED did not receive follow-up were unclear in this study: both issues of access (availability and awareness of services) and engagement (youth following through on referrals) are potential explanations. Our experience at the Centre for Addiction and Mental Health (CAMH) in Toronto, where our EPI program sees referred patients for consultation within 2 weeks on average, suggests a problem of engagement: according to clinic data, 50% of the youth referred from the ED do not attend their first EPI consultation appointment (compared with approximately 30% from all other referral sources). It is clear that new approaches are required to engage this population in accessing evidence-based care that is life-saving and improves illness outcomes. In surveys of patients and families in EPI services, appointment reminders are cited as a top factor that would improve service engagement, with a preference for email and text communication.¹⁸⁻²⁰

Mobile health technologies are increasingly being tested to improve outcomes, including symptoms, appointment attendance, and medication adherence, among young people with mental illness, particularly psychosis.²¹⁻²³ Short message service (SMS) or text message is a commonly used mode of communication by adolescents and young adults: in a survey of users of community mental health services, access to mobile phones approached 100%.²⁴ SMS is associated with low user and financial burden. SMS does not require people to own a smartphone, have data plans, or have access to wireless internet. In a study of people with psychosis, participants were found to be highly engaged with an SMS intervention.²⁵ SMS reminders have been associated with improved service engagement in psychosis across studies,²² including twice the attendance rates for initial appointments in an EPI program.²⁶ An

1
2
3 175 ongoing pilot study at CAMH investigating the effect of a weekly 2-way SMS intervention on
4 176 service engagement during the first year of EPI treatment found this approach to be feasible
5 177 and valued by participants.²⁷ We are unaware of any studies examining interventions
6 178 specifically to improve the transition in care from the ED to EPI for young people with psychosis,
7 179 using mobile health technologies or otherwise.
8 180

9 181 **Objectives and Hypotheses**

10 182 “ED to EPI,” a pragmatic randomized, single blind, controlled trial²⁸ with accompanying
11 183 economic and qualitative evaluations, aims to improve the transition from the ED to EPI services
12 184 for youth with psychosis using an SMS text messaging intervention. It is pragmatic in its
13 185 participant eligibility criteria (broad and inclusive), comparison intervention (usual care), follow-
14 186 up intensity (low), primary trial outcome (objective, meaningful and assessed under usual
15 187 conditions), measurement of participant compliance and practitioner adherence to study
16 188 protocol (unobtrusive), and analysis of primary outcome (inclusive, i.e. intention-to-treat).²⁹ We
17 189 also leverage linked routinely collected data through ICES (previously known as the Institute for
18 190 Clinical Evaluative Sciences), which holds data on all hospital and physician visits for the
19 191 province. We will also evaluate the cost effectiveness of the intervention and explore young
20 192 people’s perspectives on its various components. Our study team, in addition to clinicians and
21 193 researchers, includes a patient and family member with lived experience of using EPI services
22 194 and key decision-makers to increase the relevance and uptake of the intervention. Specifically,
23 195 our primary objectives are to:
24 196

25 197 1. Evaluate the effect of an SMS intervention on attendance at the first consultation appointment
26 198 within 30 days of study enrolment;

27 199 Hypothesis 1: The SMS intervention will increase rate of attendance at the consultation
28 200 appointment.

29 201 2. Assess indicators of longer-term service engagement 6 months following study enrolment;
30 202 Hypothesis 2: The SMS intervention will lead to improved indicators of longer-term service
31 203 engagement (Service Engagement Scale scores and dropout rates).

32 204 3. Determine system-level outcomes, including ED visits and psychiatric hospitalizations, as a
33 205 function of receiving the SMS intervention, and its cost effectiveness, factoring costs of the
34 206 intervention and cost offsets of health service utilization;

35 207 Hypothesis 3: The SMS intervention will lead to decreased use of acute care services (ED visits
36 208 and psychiatric hospitalizations) and will be cost-effective relative to the control condition, based
37 209 on improved rate of transition from the ED to EPI services and anticipated reductions in use of
38 210 costly acute care services.

39 211 4. Explore young people’s experiences of the intervention and their perspectives on its various
40 212 components.

41 213 This is an exploratory research question that seeks to understand how young people experience
42 214 the SMS intervention and how they perceive its various components impact their service
43 215 engagement.
44 216

45 217 **METHODS AND ANALYSIS**

46 218 **Study setting**

47 219 The study setting will be the Gerald Sheff and Shanitha Kachan Emergency Department
48 220 at CAMH, Ontario’s only 24-hour stand-alone psychiatric emergency service. The ED also
49 221 houses a drop-in “Bridging Clinic” which provides care to less acute patients who are diverted
50 222 after ED triage, and rapid follow-up care for patients discharged from the ED and CAMH
51 223 inpatient units. Together, they serve approximately 1,200 patients each month. The EPI
52 224 program at CAMH receives over 600 referrals for suspected psychosis annually, approximately
53 225 25% of which are from the ED and Bridging Clinic. Reflecting the Ontario EPI Program
54 226

Standards, CAMH EPI services are delivered by multidisciplinary teams, employ strategies to promote early entry and ongoing engagement, and provide pharmacotherapy and psychosocial therapies for an average of 3 years.¹⁴ Patients are assigned to the next available and/or most appropriate psychiatrist and case manager (nurse, social worker, or occupational therapist) for a joint consultation appointment, typically within 2 weeks, and are contacted by phone by the EPI program administrator to book and confirm their appointment. After the initial appointment is confirmed, patients receive a phone call reminder the day before their scheduled appointment. As part of routine care, patients who do not attend their scheduled first appointment receive follow-up calls to reschedule an appointment for up to 30 days from the initial referral.

Eligibility criteria

Study inclusion criteria mirror the intake criteria for the CAMH EPI program. Participants will be eligible for the study if they: 1) are between 16 and 29 years old and 2) have been referred by the CAMH ED to CAMH EPI services for suspected psychosis. Our only exclusion criterion is inability to communicate in basic written English. In our pilot SMS study at CAMH, fewer than 5% of potential participants were excluded for lacking a phone; we have budgeted to offer 5% of participants access to a prepaid cellphone for the duration of the study.²⁷

Intervention procedures

Study participants will be recruited at the time of EPI referral for a trial of an SMS intervention designed to engage them during the waiting period for their consultation appointment. They will be randomized to receive either sham or active SMS intervention. Sham SMS will consist of 1 message sent just after enrolment indicating that they will be contacted for an appointment. The sham SMS group will not be denied any part of usual clinical care. Thus, the clinic administrator will call patients in both groups to book and remind them of the consultation appointment. Active SMS intervention will include the initial message sent to the control group, plus a series of subsequent messages. These will include the following content: 1) appointment reminders and instructions, 2) psychoeducational material, and 3) 2-way communication check-ins to rate distress (Figure 1). Intervention components were developed based on feedback from a survey of youth in the same EPI program,³⁰ as well as psychosocial interventions with evidence in early psychosis, including cognitive-behavioural therapy (psychoeducation, behavioural activation) and illness self management (reminders, distress check-in).^{31 32} See Supplementary File 1 for a comprehensive description of the intervention. Messages sent back by participants will be monitored by the research team, and the case manager assigned to their consultation appointment will be notified and will respond accordingly if there are indicators of elevated distress. The intervention will continue until the patient attends the first consultation appointment, or for up to 30 days if the patient does not attend, which reflects the program's practice of closing referrals for non-attending patients.

Messages will be sent through CAMH's in-house Research Electronic Data Capture (REDCap) platform via a third-party plug-in, Twilio, which supports routing of SMS messages to participant devices.³³⁻³⁵ All data is stored securely on CAMH's REDCap servers or in a locked office and password-protected database on CAMH's secure network. The purpose of the sham intervention is to separate out the content of the intervention (i.e. reminders, psychoeducation, 2-way check-ins) from the effect of simply receiving SMS messages, decreasing participant bias.

Assignment of intervention

Immediately after informed consent, participants will be randomized by REDCap to the active or sham intervention. Generation of the randomization sequence will be managed by the

275 study biostatistician who is not involved in enrolling participants or assigning intervention arms.
276 Randomization will be stratified by sex (male or female) and referral source (ED or Bridging
277 Clinic), using a computer algorithm to determine a randomized, blocked allocation of
278 participants into intervention groups within strata. Once randomized, treatment assignment will
279 be known only by the study personnel involved in managing the SMS intervention and the case
280 manager monitoring text message responses; the principal investigator and study personnel
281 involved in the chart review and the ICES analysis will remain blind to treatment assignment.
282 Study personnel involved in the qualitative interviews and analysis will also be aware of
283 treatment assignment since only individuals receiving the active intervention will participate in
284 this component of the project.

285 286 **Sample size**

287 Our sample size calculations are based on the primary outcome of rate of attendance at
288 the EPI program consultation appointment. The current rate of attendance at the first
289 consultation appointment for patients referred from the ED and Bridging Clinic is 50%; we have
290 powered our study to detect the treatment effect with an anticipated rate of attendance of 70%,
291 which is the average for all referral sources other than the ED and Bridging Clinic. A total of 186
292 participants (93 per group) will provide >80% power to detect a change in attendance from 50%
293 to 70% at alpha <0.05. Non-compliance and loss to follow-up are not a concern for our primary
294 outcome since these are counted in the outcome as nonattendance at the consultation.
295 Adjusting analyses for covariates expected to affect attendance (e.g., age, sex) is expected to
296 further increase power.

297 298 **Study procedures**

299 We will recruit 186 patients consecutively referred from the CAMH ED and Bridging
300 Clinic to the CAMH EPI program at the time of discharge. During business hours and into the
301 evening, research staff will be on call to the ED to recruit patients as soon as they are identified
302 for the study. Eligible participants who present after hours may be identified by ED staff and
303 referred to the research team who will send them an e-consent form via SMS or email. See
304 Supplementary File 2 for patient consent form. Additionally, potential participants who are
305 missed in the ED/Bridging clinic may be identified by the EPI clinic administrator who will
306 approach them over the phone and send them an e-consent form via SMS or email. We have
307 used the approach of having clinical and administrative staff obtain verbal consent to send e-
308 consent forms in other studies with this population.¹⁹

309
310 As part of informed consent, participants will be asked to consent to a review of their
311 chart, a follow-up web-based survey, and linkage of their information to data held at ICES. They
312 will also be given the option to provide consent to be re-contacted for participation in a
313 qualitative interview. There will be no additional in-person assessments for the quantitative
314 component of this study. CAMH uses an electronic health record, which facilitates data
315 abstraction from multiple clinical programs (i.e., both the ED and Bridging Clinic and EPI
316 program). Research staff and students will be trained by the clinician principal investigators to
317 abstract data into a structured database.

318
319 All study participants will receive a \$10 e-giftcard once the baseline e-visit is complete.
320 Participants in the active intervention group who complete a web-based survey will receive
321 another \$10 e-giftcard and those who complete a qualitative interview will receive a \$50 e-
322 giftcard. It will be clarified through the consent process that honoraria are to compensate
323 participants for their time and will not be tied to clinical appointment attendance. For the majority
324 of participants, their initial recruitment and consent will be their only interaction with the research
325 team, with a small subgroup completing qualitative interviews.

Outcome measures

Chart review

Outcome measures are shown in Table 1. CAMH uses many standardized assessment forms which increases the completeness of patient data. Demographic variables, clinical diagnoses, substance use, duration of untreated psychosis (measured as the period of time from first onset of psychotic symptoms to initiation of EPI services and initiation of treatment with an antipsychotic or mood-stabilizing medication), characteristics of the ED visit from which they were referred (urgent presentation – brought by police, involuntary status; timing of visit), and family involvement in care are routinely recorded in the clinical chart by clinicians and will be abstracted from the chart at the time of consultation. Additional variables will likely be available but only for patients accepted into the EPI program, and this will be reflected in the data analysis. These include several assessments that are performed routinely in the EPI program. The Service Engagement Scale (SES)³⁶ is a brief validated tool designed to measure engagement with community mental health services. In 14 items, it assesses patients' availability for treatment, collaboration, help-seeking behaviours and treatment adherence on a four-point Likert scale with higher scores indicating difficulties in service engagement. The Brief Psychiatric Rating Scale (BPRS)³⁷ is a clinician or interviewer-rated measure of psychiatric symptoms commonly used as an outcome measure for psychotic disorders and collected monthly in CAMH's EPI program. It includes items related to suicidality and hostility. The Clinical Global Impression (CGI)³⁸ is a clinician-rated measure of the patient's global severity of illness prior to and after initiating a medication. It includes subscales for Severity and Improvement. Medication and appointment nonadherence will also be assessed over 6 months of treatment. Lastly, after 6 months, current EPI enrolment status will be assessed and categorized as: not offered or enrolled in treatment (e.g., because they did not ultimately have psychosis), enrolled but disengaged prematurely, accepted for treatment but transitioned to other services, or continued in treatment.

Administrative data

Primary data collected for the study will be linked deterministically to data sources held at ICES via participants' unique health card numbers. The information available for each participant will be de-identified, stored, and analyzed onsite at ICES following procedures approved by Ontario's Information and Privacy Commissioner. The following ICES data sources will be used: the Ontario Mental Health Reporting System (OMHRS), capturing hospitalizations on adult inpatient mental health units,³⁹ the Canadian Institute of Health Information Discharge Abstract Database (CIHI-DAD), capturing all hospital admissions including hospitalizations on child and adolescent inpatient mental health units,^{40 41} National Ambulatory Care Reporting System (NACRS) which captures all ED visits,⁴² Ontario Health Insurance Plan (OHIP) claims database, which captures outpatient physician visits,⁴⁰ Registered Persons Database, which contains health card numbers, demographic information, and deaths, and Ontario Drug Benefits (ODB) claims database, which provides information on all covered prescriptions (based on financial need for those under age 65 and for young people up to age 25 who lack private insurance). These data will also be used for cost effectiveness analysis. Outcomes examined in the linked ICES data are listed in Table 1.

Table 1. Summary of outcome measures and covariates

Type	Variables	Data Source	Timing
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1			
2			
3	Demographic characteristics	Age	Chart review for all demographic characteristics (CAMH Health Equity form and notes)
4			Baseline ^a
5		Sex and gender	
6		Sexual orientation	
7		Race/ethnicity	
8		Born in Canada	
9		Religious/spiritual affiliation	
10		Highest level of education	
11		Source of income and family income	
12		Number of people supported by income	
13		Employment status	
14		Legal history	
15		Housing status	
16		Living situation	
17		Experience of homelessness	
18		Relationship status	
19	Clinical characteristics	Clinical diagnoses	Chart review for all clinical characteristics (consultation and progress notes)
20		Substance use	Baseline
21		DUP	Baseline
22		Family involvement in care	Baseline
23		Urgent status at ED visit (brought by police, involuntary)	
24		Timing of ED visit	
25		BPRS ³⁷	Baseline and 6 months
26		CGI ³⁸	Baseline and 6 months
27	Service engagement	Attendance at consultation appointment	Chart review for all service engagement measures
28		SES ³⁶	30 days
29			6 months (completed around 3 months in treatment)
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	Medication and appointment nonadherence		6 months
	EPI enrolment status		6 months
System-level outcomes ^b	Number of ED visits	NACRS ⁴²	6 months and up to 2 years
	Number of inpatient mental health hospitalizations	OMHRS, ³⁹ CIHI-DAD ^{40 41}	
	Number of days in inpatient mental health hospitalizations	OMHRS, ³⁹ CIHI-DAD ^{40 41}	
	Number of outpatient mental health visits	OHIP ⁴⁰	
	Prescription drugs – psychiatric medications, continuously vs. noncontinuously prescribed	ODB	
	Mortality including cause of death	Registered Persons Database	

374 ^a Items may be extracted from the ED note or EPI consultation note

375 ^bAdministrative data held at ICES

376 CAMH, Centre for Addiction and Mental Health; DUP, duration of untreated psychosis; BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression; SES, Service Engagement Scale; EPI, early psychosis intervention; ED, emergency department; OMHRS, Ontario Mental Health Reporting System; CIHI-DAD, Canadian Institute of Health Information Discharge Abstract Database; NACRS, National Ambulatory Care Reporting System; OHIP, Ontario Health Insurance Plan; ODB, Ontario Drug Benefits.

382

383 Statistical analysis

384 Primary analysis

385 Descriptive and graphical statistics will be used to summarize the data on all randomized
386 participants and to confirm that there are no group differences in baseline demographics and
387 clinical characteristics. Distributional assumptions will be inspected and appropriate
388 transformations or non-parametric methods will be applied as necessary. In general,
389 generalized linear models⁴³ will be used throughout. These models account for deviation from
390 normal assumption of the outcome variables and control for covariates.

391

392 Our analysis of the primary outcome will be a logistic regression to examine the
393 likelihood of attendance at the EPI consultation with treatment assignment using risk ratios.⁴⁴
394 We will carefully select demographic variables and factors known to influence treatment
395 engagement (e.g., substance use, family involvement in care)⁴⁵ to be included in the model as
396 covariates. A difference in attendance between groups will be declared at a significance level of
397 0.05. Similar models will be used to address the secondary hypotheses, with specific types of
398 models appropriate to each outcome, including time-to-event analysis to examine premature
399 disengagement from services. Administrative data outcomes will be examined using generalized
400 linear models with proper distribution assumptions.

401

402 Additional analyses: moderation and generalizability

403 We plan to conduct two additional exploratory analyses. First, we will run moderation
404 analyses on potential effect modifiers by adding an interaction term between the potential
405 moderator and the treatment assignment indicator in the generalized linear models. We are
406 specifically interested in the moderation effects of health equity factors including gender,
407 race/ethnicity, and housing status. A significant interaction will provide evidence that the
408 treatment effects may be different in the subgroups. A second exploratory analysis will be
409 conducted to evaluate the impact of selection bias of the study sample and estimate the
410 population average treatment effects by employing weighted analysis using propensity scores.⁴⁶

411 Missing data

412 The risk of missing data is mitigated through the use of chart review and analysis of
413 administrative data. While the primary outcome will not suffer from attrition, other outcomes will,
414 as some follow-up data will only be available for participants who attended their consultation
415 appointment and those who are enrolled in CAMH EPI services. For these additional outcomes,
416 we plan to use multiple imputation methods developed by Schafer to correct potential bias that
417 could be introduced by missing data.⁴⁷

419 Economic evaluation

420 Full details of the economic evaluation appear in Supplementary File 3. We will
421 undertake a cost-effectiveness analysis, where the outcome of interest is consultation
422 appointment attendance, adopting the perspective of the public third-party payer (i.e., the
423 Ontario Ministry of Health). We will collect data on the costs of delivering both arms of the
424 intervention. In addition, using a costing algorithm available at ICES,⁴⁸ we will estimate all direct
425 patient-level healthcare costs incurred by the public third-party payer for the intervention and
426 control groups, which will include costs of hospitalizations, ED visits, physician services (i.e.,
427 primary care, psychiatry and other) and diagnostic tests, outpatient prescription drugs for
428 individuals covered under the provincial public drug insurance plan, and other hospital-based
429 care. We will use a net benefit regression approach to model probabilities of cost effectiveness
430 for each additional patient referred who attends their consultation appointment in the
431 intervention compared with control group. In addition, we will undertake relevant sensitivity
432 analyses to test the robustness of findings by varying relevant parameters, such as the discount
433 rate. Finally, we will examine the real-world budget impact of implementing the intervention
434 across Ontario, to estimate the cost to the Ministry of Health of implementing this model of care
435 across the province and the potential cost-savings to the system associated with this.

437 Understanding patient experiences: Survey and qualitative analysis

438 Participants in the active intervention group will receive a one-time survey sent as a web-
439 link to their phone or email address. Survey topics include user experience, attitudes toward the
440 SMS intervention, its perceived benefits and challenges, acceptability, and suggestions for
441 improvements. Those who consent to participate in the qualitative research component will be re-
442 contacted by phone or email to participate in semi-structured interviews to gain a more in-depth
443 understanding of survey topics. A subsample of 10-15 participants in the active intervention group
444 will be purposively selected to maximize diversity of age, gender, and service attendance. We will
445 use critical realist theory as an underlying framework to guide our interviews, surveys, and
446 analysis.⁴⁹ Interviews will be completed until thematic saturation is achieved, estimated at 12
447 participants. Interviews will be digitally audio-recorded and transcribed verbatim. Surveys will be
448 completed and stored in REDCap. Transcriptions and survey responses will be analyzed using
449 thematic content analysis in NVivo-11. Research participants will be invited to assist with member
450 checking to confirm that themes reflect their experiences. The analysis can inform future
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3 452 improvements to the intervention and considerations for broader implementation, privileging the
4 453 experiences of the patients attending these programs.

5 454 6 455 **PATIENT AND PUBLIC INVOLVEMENT**

7 456 A youth and family member who previously received EPI services have been engaged in
8 457 helping shape the intervention and study design from project inception. They are active
9 458 members of the project's Steering Committee that meets monthly to inform study design,
10 459 implementation, evaluation, and dissemination of results. They will have key roles in the plan to
11 460 spread the intervention, if successful, to other EPI programs by working with patients and
12 461 families to adapt the intervention to local contexts. Additional youth with lived experience of
13 462 receiving EPI services have been consulted on an ad hoc basis through the CAMH Youth
14 463 Engagement Initiative to provide detailed feedback on the SMS intervention. Patient and family
15 464 representatives on the research team are compensated for their time.

16 465 17 466 **ETHICS AND DISSEMINATION**

18 467 The study was approved by the Research Ethics Board (REB) at the Centre for
19 468 Addiction and Mental Health. The study protocol was prepared according to SPIRIT guidelines⁵⁰
20 469 and registered with clinicaltrials.gov on March 6, 2020 (NCT04298450;
21 470 <https://clinicaltrials.gov/ct2/show/NCT04298450?term=ed+to+epi&draw=2&rank=1>). REB-
22 471 approved protocol amendments will be posted on the site. The principal investigators and study
23 472 team will meet regularly to review accrued data, data confidentiality, any adverse events,
24 473 adherence to protocol design, recruitment and implementation. This intervention has been
25 474 designed to have high likelihood of adoption and readiness for spread and scale-up because it
26 475 responds to a critical need, has a strong evidentiary basis, has advantages over existing
27 476 practice and is both low complexity and low cost.⁵¹ The study team is well-positioned to support
28 477 widespread implementation of the intervention if successful. We have used an integrated
29 478 knowledge translation approach that leverages input from stakeholders, including patients,
30 479 clinicians (both from the ED and EPI services), policymakers, and relevant organizations
31 480 throughout the study to champion the spread of the intervention to other EPI programs and
32 481 youth mental health services more broadly. This trial focuses on a particularly vulnerable
33 482 population—young people transitioning from adolescence to adulthood and from the ED to EPI
34 483 services—but the basic intervention is widely applicable. The software platform utilized to
35 484 coordinate this intervention is available at no charge, and the SMS functionality for sending and
36 485 receiving messages carries a nominal fee, supporting broad uptake.

37 486
38 487 The results of the trial will be reported in scientific journal articles and shared with key
39 488 stakeholders as they become available. Our study team includes the co-chair of the Early
40 489 Psychosis Intervention Ontario Network, a network of over 50 EPI programs across Ontario, and
41 490 several members of the Canadian Consortium for Early Intervention in Psychosis, providing a
42 491 durable and established community of practice for immediate spread. De-identified participant
43 492 data will be available upon reasonable request other than system-level data held at ICES.
44 493 Requests can be made by contacting the principal investigator Dr. Nicole Kozloff at
45 494 nicole.kozloff@camh.ca and will be managed by the Steering Committee.

46 495
47 496 This pragmatic randomized-controlled trial of a low-cost, low-complexity SMS
48 497 intervention aims to improve the transition from the ED to EPI services for young people with
49 498 psychosis. It targets a brief but critical period: if young people cannot even get in the door to EPI
50 499 services, there is no way for them to reap the many known benefits of EPI care. Improving the
51 500 ED to EPI transition has the potential to result in more young people with psychosis getting
52 501 appropriate treatment earlier. The proposed intervention is also likely to be easily adaptable to

502 other referral pathways to EPI services and youth mental health services more broadly. At
 503 potentially lower cost to the health system, applying this SMS intervention to the ED to EPI
 504 transition has the potential to lead to improved short-term symptoms and functioning, long-term
 505 disease trajectories, decreased burden on patients and families, and fewer deaths among
 506 young people with psychosis.

507 **Figures**

508 **Figure 1.** Study intervention schedule*

509 *This figure represents a summary of the intervention schedule and is not exhaustive of text
 510 message content

511 SMS, short message service; Right arrow, incoming text messages received by participants;
 512 Left arrow, outgoing text messages sent by participants

513

514 **Author contributions**

515 NK is the principal investigator who conceived the original study design and obtained funding,
 516 with most of the current authors having contributed to the funding application, and all authors
 517 having participated in revisions to the study design for important intellectual content. AP, GF,
 518 AW, AA, VS, JD'A, LD, ANV, and NK sit on the project's Steering Committee. AP, GF, JD'A,
 519 and NK form the Data Management Committee. AP leads the survey and qualitative analysis.
 520 GF, AW, SB, and ANV have administrative roles in the clinical programs and will support the
 521 acquisition and interpretation of data. AA and LD act as patient and public consultants. VS acts
 522 as a Health System Decision-Maker on the project. KKA, CdO, PK, and NK consult on the ICES
 523 analysis. CdO is a health economist who consults on the economic analysis. VS, JH and SK
 524 provide knowledge translation expertise. JZ provides consultation on the qualitative interviews
 525 and analysis. WW acts as the biostatistical consultant. AP and NK drafted the protocol. All
 526 authors read, revised and approved the final version of the manuscript.

527

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 531 Applicable). The funders were not involved in study design; collection, management, analysis,
 532 and interpretation of data; writing of the report; and the decision to submit the report for
 533 publication, including whether they will have ultimate authority over any of these activities.

534

535 **Competing interests statement**

536 The authors declare no competing interests.

537

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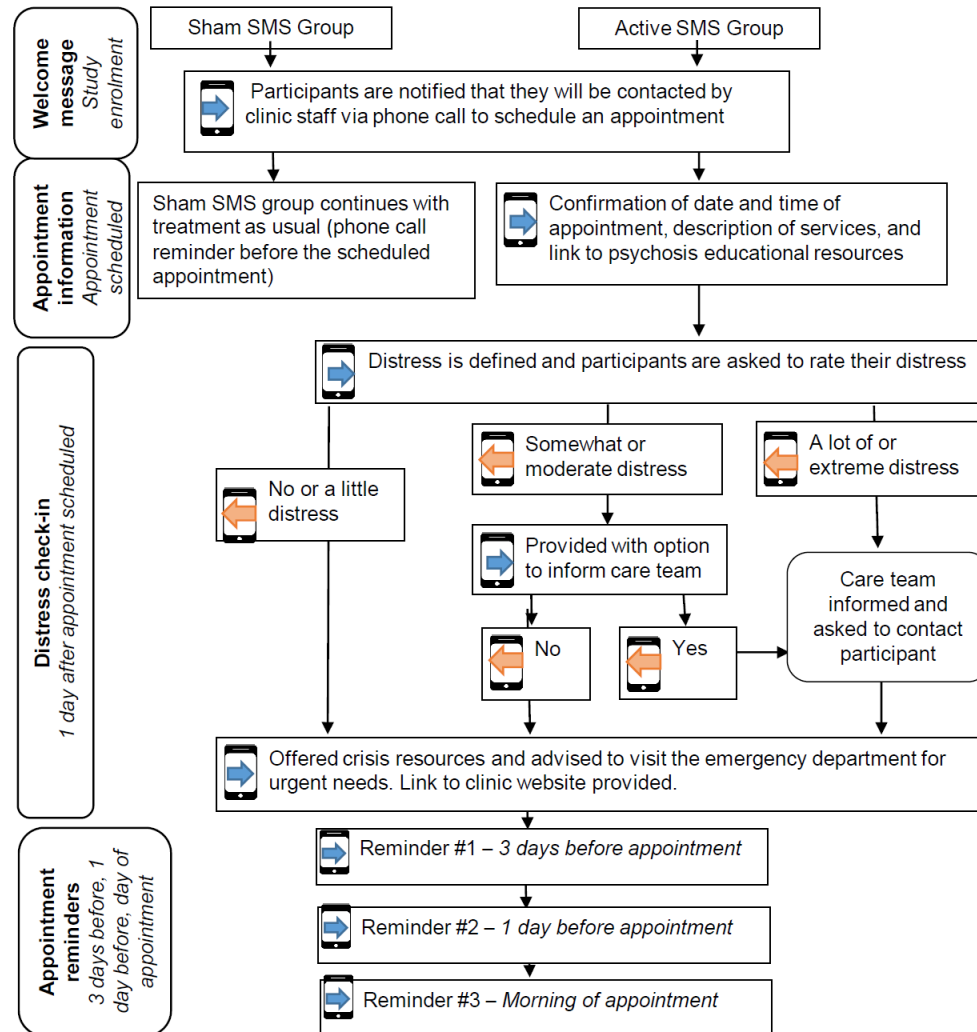
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Figure 1. SMS intervention schedule*



*This figure represents a summary of the intervention schedule and is not exhaustive of text message content

SMS, short message service; Right arrow, incoming text messages received by participants; Left arrow, outgoing text messages sent by participants

Hi [First Name], this is [Clinic]. If you haven't yet been given an appointment, one of our clinic staff will contact you in the next few days. Just so you're aware, our number comes up as private. Please text '1' to confirm you received this message.

(If 1 texted back): Thanks for confirming!

ACTIVE GROUP

Hi [First Name], thank you for booking your first visit with [Clinic] on [date] at [time]. If you need to reschedule, please call [Clinic Phone]. At your appointment, you will meet with a psychiatrist and a case manager who will work with you to figure out how we can best support you. Experiencing psychosis can be difficult and knowing more about mental health may help you cope. If you'd like to learn more about mental health and psychosis, please visit: www.camh.ca/psychosis

Next day**

Hi [First Name], while you wait for your upcoming appointment with us at [Clinic], we wanted to check in! How are you doing this week? Please send back '1' for well, '2' for okay, or '3' for bad.

If response = 1

Thanks for letting us know. Here are some resources if you're experiencing a crisis: www.camh.ca/crisis-resources. If you need urgent support, please see your nearest emergency department. Please text '1' to confirm you received this message.

If response = 1

If response = 2 or 3

We say people are experiencing distress when they are feeling anxious, depressed, worried, or hopeless. Can you please rate your distress for us? '0' for no distress, '1' for a little distressed, '2' for somewhat distressed, '3' for moderately distressed, '4' for a lot of distress, or '5' for extreme distress (urgent).

If response = 2-3

Thanks for letting us know. Here are some resources if you're experiencing a crisis: www.camh.ca/crisis-resources. If you need urgent support, please see your nearest emergency department. Would you like us to pass this information on to your care team? They may reach out to you during business hours. Please text back: '1' for yes, or '2' for no. We won't pass this information on unless you text back '1'.

If response = 1: Thanks for letting us know. We have passed this onto your care team who may reach out during business hours. If you need urgent support, please see your nearest emergency department. Please text '1' to confirm you received this message.
If response = 2: Thanks for letting us know. We won't pass this information on. If you need urgent support, please see your nearest emergency department. Please text '1' to confirm you received this message.

If response = 4

Thanks for letting us know, we have passed this information on to your care team, who may reach out during business hours. Here are some resources if you're experiencing a crisis: www.camh.ca/crisis-resources. If you need urgent support, please see your nearest emergency department. Please text '1' to confirm you received this message.

If response = 5

Thanks for letting us know. We have passed this information on to your care team, who may reach out during business hours. We urge you to consider trying these resources: www.camh.ca/crisis-resources. If you need urgent support, please see your nearest emergency department. Please text '1' to confirm you received this message.

If response = 1

Thanks for confirming! For more information about our services, please visit: www.camh.ca/sceis.

3 days pre-appointment**

Hi, this is a reminder that your appointment at [Clinic] is coming up on [date] at [time].

1 day pre-appointment

Hi, this is a reminder of your appointment tomorrow at [time]. The care team is looking forward to meeting you. If you need to reschedule, call [Clinic Phone].

Morning of appointment

Hi, your appointment with [Clinic] is today at [time]. Please call us at [Clinic Phone] if you need any assistance.

If participant does not show, they receive the following message, and then the process starts over from the check-in until participant shows up or 30 days have passed:

If 30 days have passed and participant has not attended

Hi, we understand you didn't make it to your [Clinic] appointment. To reschedule, please call [Clinic Phone].

Hi, you have now finished receiving text messages from the research study. Thank you for your participation!

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At Time of Enrollment
After appointment scheduled via phone
Two-way distress check-in
Reminder #1
Reminder #2
Reminder #3

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**ED to EPI: Using SMS (Text) Messaging to Improve the Transition from the
Emergency Department to Early Psychosis Intervention for Young People
with Psychosis**

Online Version - Informed Consent Form

Principal Investigator: Dr. Nicole Kozloff
Dr. George Foussias
Dr. Vicky Stergiopoulos
Dr. Aristotle Voineskos

Co-Investigators: Augustina Ampofo Dr. Sean Kidd
Dr. Kelly Anderson Dr. Paul Kurdyak
Sarah Bromley Dr. Alexia Polillo
Jessica D'Arcey Dr. Brittany Poynter
Dr. Jeff Daskalakis Dr. Wei Wang
Dr. Claire de Oliveira Dr. Albert Wong
Lillian Duda Dr. Juveria Zaheer
Dr. Joanna Henderson

Sponsor: Canadian Institutes of Health Research, CAMH Foundation

Purpose of the Study:

We invite you to participate in this study because you have been referred to the Slight Centre for Early Intervention Services. The Slight Centre is an outpatient program for young people experiencing a first episode of psychosis and their families. In this study we will examine if text messaging can improve the transition from the emergency department to early intervention services for youth. We hope that this study will eventually lead to young people getting appropriate treatment earlier and improve their long-term outcomes. Your participation in this study is voluntary. The following information is provided to help you make an informed decision whether or not to participate.

What will I be asked to do as part of this study?

If you decide to participate in this study, you will be asked to do the following:

- 1) **Intervention:** You are being invited to take part in a study. If you consent to participate, you will be randomly assigned to receive one of two types of text messages. Random assignment means that you have an equal chance of being assigned to each text message group. If you are assigned to the text message intervention, you will receive text messages at a time of your choosing (e.g., morning, evening). You will be sent text messages with information about appointment details, education about psychosis, an opportunity to rate your distress, and appointment reminders. These text messages will continue until you attend your first consultation appointment, or for up to 30 days if you did not attend. If you are assigned to the other group, you will receive a one-time text message. If you do not have a phone, one will be offered to you for the duration of the study with the expectation that it is returned at your first consultation appointment.



Please note that text messages are NOT being monitored constantly and if you are experiencing an urgent issue, this information should not be sent by text message. Instead, please visit your nearest emergency department. Additionally, this is not a direct line of communication with your care team and it is not a secure form of communication. You should not send any personal health information that is not requested by the text messages.

- 2) **Collection of data:** We will also review your medical chart to obtain additional information about you. Information collected through this study will be transferred to the Institute for Clinical Evaluative Sciences (ICES). ICES is an organization that holds routinely collected data on health care use in Ontario. ICES is committed to protecting the privacy and security of health information. ICES is an approved unit under Ontario's Personal Health Information Protection Act and follows the policies and procedures for privacy protection and data security approved by Ontario's Information and Privacy Commissioner. Linking the data will involve using personal identifiers such as your name, date of birth, and OHIP number to identify your health service use. These identifiers will be removed as soon as the data is connected to ICES. The data will then be replaced by a scrambled code in order to decrease the likelihood of a data breach (when people get access to private information without permission)
- 3) **Follow up survey:** You may be asked to complete a brief survey following your participation in the text message intervention. Your participation in the survey is voluntary. If you consent to study participation, you may receive a link to the online survey at the contact information of your choice (text message or email). The survey takes approximately 5 to 10 minutes to complete. If you complete the survey, you will be compensated with a \$10 e-gift card sent to you by email or text message from your choice of a list of retailers. The survey contains questions about your experiences with the text message intervention.

Are there risks involved?

There are no known harms associated with participation in this study. If your text messaging plan does not include unlimited texting, you may incur additional charges on your cell phone bill. The study will not reimburse you for these charges. You may also feel emotional discomfort and fatigue from receiving recurrent text messages with appointment reminders and questions about how you are feeling. If you do feel this way, you may refuse to answer any question, or terminate your participation in this study at any point in time. You may be asked some questions during the survey that might make you feel somewhat uncomfortable. If you do feel uncomfortable, you may indicate this in the comments or skip the question. You can also pause the survey and continue at another time. Please be advised that if the researcher or study personnel sees that there is a risk to your safety or the safety of others, then steps will be taken to ensure your safety and the safety of others. Lastly, the security of information sent by email/text cannot be guaranteed.

Are there benefits involved?

No direct benefits to your health will likely result from this study. It is possible that the results of this study will increase engagement in early intervention services and may benefit other people now or



in the future. You will also receive compensation for your time and participation in the study. The investigators responsible for this study or CAMH are not conducting this study to receive commercial benefit. However, if this research produces financial returns from a commercialization of the results in the future, you will not receive any benefit from these returns.

Can participation in this study end early?

Participation in any research study is voluntary. Your decision whether or not to participate will not interfere with your right to healthcare or other services to which you are otherwise entitled. You can contact the research team through email or phone to withdraw from the study at any time. After data is anonymized your responses cannot be withdrawn, however, no new data will be collected. Throughout your participation in this study, you will continue to receive usual care as agreed upon by you and your treatment team. In the event of research-related harm, you have not waived any legal rights/rights to legal recourse.

Are study participants paid to participate in this study?

Everyone who participates in the text messaging intervention will receive a \$10 e-gift card by email or text message from your choice of a list of retailers. If you decide to withdraw before study end, you will still be paid for your time and participation. Those participants selected to participate in the follow up survey will receive another \$10 e-gift card by email or text message from their choice of retailers for completing the survey.

Will personal information about me be kept confidential?

- The research data will be kept confidential from the inception of the study.
- Any information about you obtained from this research will be kept as confidential (private) as possible unless disclosure is required by law. It is important to note that confidentiality will be protected to the extent permitted by law. However, there are 3 exceptions to our confidentiality policy. In any of the following situations, we are obligated by law to contact authorities: 1) if there is a serious possibility that you may harm yourself or others; 2) if you have been involved in any form of child abuse or neglect; 3) if you have been the victim of abuse by a healthcare worker
- All data obtained from this research will be kept in a locked office and secured password database with limited access only to study personnel and authorized CAMH personnel.
- To protect your identity and confidentiality, all personal identifiers (such as your name, birth date) will be removed (de-identified and replaced with a specific code number; the research records and data will be indicated by a case number rather than your name, and the information linking these case numbers with your identity will be kept separate from the research records. This information will be kept in a separate, secure location and will only be accessible to study personnel.
- Study personnel may also access your health records for research purposes; your medical records will be kept confidential.
- All electronic files will be stored on CAMH's secure hospital or institutional network and will be password protected.

- Other Canadian research centres (other than CAMH) may be involved in analyzing the data, and if so this will be confidential, and your name will not be given out.
- Following the completion of the study, the researchers intend to publish the results in scientific journals. You will not be identified in any of these reports. A report of the results of this project will be given to you if you request it.
- The information you provide will not affect the usual care that you receive.
- The investigators on this study will keep the data as long as necessary to fulfill the research purposes and in accordance with the applicable laws and regulations and will use enhanced security measures to store it.
- De-identified data from this study may be shared with the research community at large to advance science and health. We will remove or code any personal information that could identify you before files are shared with other researchers to ensure that, by current scientific standards and known methods, no one will be able to identify you from the information we share.
- Your de-identified research data (information about your diagnosis, symptoms, and study evaluations) may be shared with investigators at other Canadian research centres (other than CAMH).

Will this research study involve the use or disclosure of my identifiable medical information?

- Study personnel will retrieve information about your demographics and clinical care from your medical chart. This will be stored in a secure database with a case number rather than your personal identifiers.

Who will have access to identifiable information related to my participation in this research study?

Personal Health Information (PHI) is information about your physical or mental health or the health care that you receive that could identify you. In addition to the investigators listed on the first page of this consent form and their research staff, the following individual and/or programs will or may have access to identifiable information (which may include your identifiable medical information):

- a. Institute for Clinical Evaluative Sciences (ICES) is a prescribed entity under Ontario's Personal Health Information Protection Act and adheres to policies and procedures for privacy protection and data security approved by Ontario's Information and Privacy Commissioner.
- b. *As part of the Research Services Quality Assurance Program, this study may be monitored and/or audited by a member of the Quality Assurance Team. Your research records and CAMH records may be reviewed during which confidentiality will be maintained as per CAMH policies and extent permitted by law.*
- c. As a part of continuing review of the research, your study records may be assessed on behalf of the Research Ethics Board. A person from the research ethics team may contact you (if your contact information is available) to ask you questions about the research study and your consent



to participate. The person assessing your file or contacting you must maintain their confidentiality to the extent permitted by law.

Offer to Answer Questions

We have used some technical terms in this form. Please feel free to ask about anything that you do not understand. Consider this research and the consent form carefully as long as you feel necessary before you make a decision.

Dr. Nicole Kozloff is responsible for this study. If you have any questions, please contact Dr. Nicole Kozloff at 416-535-8501 x 30769.

If you have any questions about your rights as a participant in a research study, you may contact Dr. Robert Levitan, Chair, Research Ethics Board, Centre for Addiction and Mental Health, at 416-535-8501 x 34020.

Consent to Participate: My signature below indicates that:

- I acknowledge that the research study described above has been explained to me and that any questions that I have asked have been answered to my satisfaction.
- I have been informed of the alternatives to participation in this study, including the right not to participate and the right to withdraw without compromising the quality of medical care for me and for other members of my family.
- I have been informed of the potential risks/harms and discomforts and I also understand the benefits of participating in this study.
- I know that I may ask now, or in the future, any questions that I may have about the study or the research procedures.
- I have been assured that records relating to my research participation and to me will be kept confidential and that no information will be printed that would disclose my identity without my permission, unless required by law.
- I have been given sufficient time to read and understand the above information
- I understand and consent that my records and research data may also be shared with other investigators for analysis and future projects (this would include only de-identified data).

Please check one:

- Yes, I consent to participating in this study**
- No, I do not consent to participating in this study**

Optional – Future Contact:

Do you agree to be re-contacted by our study team for an in-person interview or other follow up? You will be compensated for your participation.



- Yes, I agree to be contacted about study follow-up
- No, I do not wish to be contacted about study follow-up

Texting Preferences:

If you agreed to participate in the study:

At what phone number would you like to receive text messages?

At what phone number or email address would you like to receive other links related to the study (e.g., your e-giftcard, the survey, and future communications)?

What time of day would you prefer to receive text messages?

- Morning Afternoon Evening

What first name would you like us to call you in your text messages?

Compensation Preferences:

Which e-giftcard would you like to receive as compensation for participating? It may take up to 10 business days to receive your compensation.

- Tim Hortons Amazon

Please contact 416-535-8501 x 30677 if you do not receive a text message from us within 24 hours.

The security of information sent by e-mail/text cannot be guaranteed. Please do not communicate personal sensitive information by e-mail/text. Let the research team know if you do not want to be contacted by e-mail/text. Email/Text is not routinely monitored outside of work hours. Please do not use e-mail/text to communicate emergency or urgent health matters – please contact your clinician or family doctor. If it is a medical emergency, call 911.

Supplementary File 3

We will undertake a cost-effectiveness analysis, where the outcome of interest is consultation appointment attendance, adopting the perspective of the public third-party payer (i.e., the Ontario Ministry of Health). Using a costing algorithm developed in SAS and available at ICES,¹ we will be able to estimate all direct patient-level healthcare costs incurred by the public third-party payer for both the intervention and control groups. In particular, we will include costs of hospitalizations, ED visits, physician services (i.e. primary care, psychiatry and other) and diagnostic tests, outpatient prescription drugs for individuals covered under the provincial public drug insurance plan, home care, long-term care, and other hospital-based care (which includes rehabilitation and complex continuing care). The costing methodology used in the algorithm includes a bottom-up/micro-costing approach to cost services at the individual level. This makes use of individual episodes of care or utilization in the healthcare system and their associated prices (or costs or amounts paid). A top-down approach, which allocates corporate aggregate (i.e. institutional) costs to individual visits or cases/episodes of care, will be applied in cases where individual unit costs are not available (e.g., for institutional care settings). In addition, we will include all costs associated with delivering both arms of the intervention. Costs will be reported in 2023 using the Consumer Price Index for Health and personal care (Statistics Canada). All costs and outcomes will be discounted at a rate of 1.5% per year, in line with the Canadian Agency for Drugs and Technologies in Health guidelines.² The incremental cost-effectiveness ratio (ICER) will be calculated as the difference in discounted mean costs between the intervention and control groups divided by the difference in attendance rates. We will use a net benefit regression approach to model probabilities of cost-effectiveness for each additional patient referred who attends their consultation appointment in the intervention compared with control group. In addition, we will undertake relevant sensitivity analyses to test the robustness of findings by varying relevant parameters, such as the discount rate. Finally, we will examine the real-world budget impact of implementing the intervention across Ontario, to estimate the cost to the Ministry of Health of implementing this model of care across the province and the potential cost-savings to the system associated with this.

REFERENCES

1. Wodchis WP, Austin PC, Henry DA. A 3-year study of high-cost users of health care. *CMAJ* 2016;188(3):182-88. doi: 10.1503/cmaj.150064 [published Online First: 2016/01/13]
2. Guidelines for the Economic Evaluation of Health Technologies. 4th ed. Ottawa, ON, 2017.

Supplementary File 1: Protocol reporting checklist based on SPIRIT guidelines

		Page
	Reporting Item	Number
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
Trial registration: data set	#2b All items from the World Health Organization Trial Registration Data Set	3
Protocol version	#3 Date and version identifier	12
Funding	#4 Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a Names, affiliations, and roles of protocol contributors	13

1	Roles and	#5b	Name and contact information for the trial sponsor	13
2				
3	responsibilities:			
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5	sponsor contact			
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7	information			
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11	Roles and	#5c	Role of study sponsor and funders, if any, in study	13
12				
13	responsibilities:		design; collection, management, analysis, and	
14				
15	sponsor and funder		interpretation of data; writing of the report; and the	
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17			decision to submit the report for publication, including	
18			whether they will have ultimate authority over any of	
19			these activities	
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25	Roles and	#5d	Composition, roles, and responsibilities of the	13
26				
27	responsibilities:		coordinating centre, steering committee, endpoint	
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29	committees		adjudication committee, data management team, and	
30				
31			other individuals or groups overseeing the trial, if	
32			applicable (see Item 21a for data monitoring committee)	
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37	Introduction			
38				
39				
40				
41	Background and	#6a	Description of research question and justification for	4-5
42				
43	rationale		undertaking the trial, including summary of relevant	
44				
45			studies (published and unpublished) examining benefits	
46				
47			and harms for each intervention	
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51	Background and	#6b	Explanation for choice of comparators	4-5
52				
53	rationale: choice of			
54				
55	comparators			
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1	Objectives	#7	Specific objectives or hypotheses	5
2				
3				
4	Trial design	#8	Description of trial design including type of trial (eg,	5
5			parallel group, crossover, factorial, single group),	
6			allocation ratio, and framework (eg, superiority,	
7			equivalence, non-inferiority, exploratory)	
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14	Methods:			
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16	Participants,			
17	interventions, and			
18	outcomes			
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24	Study setting	#9	Description of study settings (eg, community clinic,	5-6
25			academic hospital) and list of countries where data will be	
26			collected. Reference to where list of study sites can be	
27			obtained	
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34	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	6
35			applicable, eligibility criteria for study centres and	
36			individuals who will perform the interventions (eg,	
37			surgeons, psychotherapists)	
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44	Interventions:	#11a	Interventions for each group with sufficient detail to allow	6-7
45			replication, including how and when they will be	
46	description		administered	
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51	Interventions:	#11b	Criteria for discontinuing or modifying allocated	6-7
52			interventions for a given trial participant (eg, drug dose	
53	modifications			
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1		change in response to harms, participant request, or	
2		improving / worsening disease)	
3			
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5			
6	Interventions:	#11c Strategies to improve adherence to intervention protocols,	8-11
7			
8	adherence	and any procedures for monitoring adherence (eg, drug	
9		tablet return; laboratory tests)	
10			
11			
12			
13	Interventions:	#11d Relevant concomitant care and interventions that are	6-7
14			
15	concomitant care	permitted or prohibited during the trial	
16			
17			
18	Outcomes	#12 Primary, secondary, and other outcomes, including the	8-10
19			
20		specific measurement variable (eg, systolic blood	
21		pressure), analysis metric (eg, change from baseline, final	
22		value, time to event), method of aggregation (eg, median,	
23		proportion), and time point for each outcome. Explanation	
24		of the clinical relevance of chosen efficacy and harm	
25		outcomes is strongly recommended	
26			
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35	Participant timeline	#13 Time schedule of enrolment, interventions (including any	7-10
36			
37		run-ins and washouts), assessments, and visits for	
38		participants. A schematic diagram is highly recommended	
39		(see Figure)	
40			
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45	Sample size	#14 Estimated number of participants needed to achieve	7
46			
47		study objectives and how it was determined, including	
48		clinical and statistical assumptions supporting any sample	
49		size calculations	
50			
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55	Recruitment	#15 Strategies for achieving adequate participant enrolment to	7-8
56			
57		reach target sample size	
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1 **Methods:**

2 **Assignment of**
3
4 **interventions (for**
5
6 **controlled trials)**
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10	11 Allocation: sequence	12 #16a	13 Method of generating the allocation sequence (eg, 14 generation computer-generated random numbers), and list of any 15 factors for stratification. To reduce predictability of a 16 random sequence, details of any planned restriction (eg, 17 blocking) should be provided in a separate document that 18 is unavailable to those who enrol participants or assign 19 interventions 20 21 22 23 24 25 26	27 7
28	29 Allocation	30 #16b	31 Mechanism of implementing the allocation sequence (eg, 32 concealment central telephone; sequentially numbered, opaque, 33 mechanism sealed envelopes), describing any steps to conceal the 34 sequence until interventions are assigned 35 36 37	38 7
39	40 Allocation:	41 #16c	42 Who will generate the allocation sequence, who will enrol 43 implementation participants, and who will assign participants to 44 interventions 45 46 47	48 7
49	50 Blinding (masking)	51 #17a	52 Who will be blinded after assignment to interventions (eg, 53 trial participants, care providers, outcome assessors, data 54 analysts), and how 55 56 57	58 7
59	60 Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7

1 **Methods: Data**

2
3 **collection,**

4
5 **management, and**

6
7 **analysis**

<p>8 9 10 11 Data collection plan</p>	<p>12 #18a</p>	<p>13 Plans for assessment and collection of outcome, 14 baseline, and other trial data, including any related 15 processes to promote data quality (eg, duplicate 16 measurements, training of assessors) and a description 17 of study instruments (eg, questionnaires, laboratory tests) 18 along with their reliability and validity, if known. Reference 19 to where data collection forms can be found, if not in the 20 protocol</p>	<p>21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60</p> <p>7-10</p>
<p>Data collection plan: retention</p>	<p>#18b</p>	<p>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</p>	<p>7-10</p>
<p>Data management</p>	<p>#19</p>	<p>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</p>	<p>7-9, 12</p>
<p>Statistics: outcomes</p>	<p>#20a</p>	<p>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</p>	<p>10-12</p>

1	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and	11
2			adjusted analyses)	
3	analyses			
4				
5				
6	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	11
7			adherence (eg, as randomised analysis), and any	
8	population and		statistical methods to handle missing data (eg, multiple	
9	missing data		imputation)	
10				
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15				
16	Methods: Monitoring			
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19	Data monitoring:	#21a	Composition of data monitoring committee (DMC);	12
20			summary of its role and reporting structure; statement of	
21	formal committee		whether it is independent from the sponsor and	
22			competing interests; and reference to where further	
23			details about its charter can be found, if not in the	
24			protocol. Alternatively, an explanation of why a DMC is	
25			not needed	
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36	Data monitoring:	#21b	Description of any interim analyses and stopping	12
37			guidelines, including who will have access to these	
38	interim analysis		interim results and make the final decision to terminate	
39			the trial	
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46	Harms	#22	Plans for collecting, assessing, reporting, and managing	12
47			solicited and spontaneously reported adverse events and	
48			other unintended effects of trial interventions or trial	
49			conduct	
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1	Auditing	#23	Frequency and procedures for auditing trial conduct, if	12
2			any, and whether the process will be independent from	
3			investigators and the sponsor	
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8	Ethics and			
9	dissemination			
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14	Research ethics	#24	Plans for seeking research ethics committee / institutional	12
15	approval		review board (REC / IRB) approval	
16				
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19	Protocol	#25	Plans for communicating important protocol modifications	12
20	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
21			relevant parties (eg, investigators, REC / IRBs, trial	
22			participants, trial registries, journals, regulators)	
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29	Consent or assent	#26a	Who will obtain informed consent or assent from potential	7-8
30			trial participants or authorised surrogates, and how (see	
31			Item 32)	
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37	Consent or assent:	#26b	Additional consent provisions for collection and use of	7-8, 12
38	ancillary studies		participant data and biological specimens in ancillary	
39			studies, if applicable	
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45	Confidentiality	#27	How personal information about potential and enrolled	7-8
46			participants will be collected, shared, and maintained in	
47			order to protect confidentiality before, during, and after	
48			the trial	
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54	Declaration of	#28	Financial and other competing interests for principal	13
55	interests		investigators for the overall trial and each study site	
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1	Data access	#29	Statement of who will have access to the final trial	13
2			dataset, and disclosure of contractual agreements that	
3			limit such access for investigators	
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9	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	12-13
10	trial care		compensation to those who suffer harm from trial	
11			participation	
12				
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14				
15				
16	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	12-13
17	trial results		results to participants, healthcare professionals, the	
18			public, and other relevant groups (eg, via publication,	
19			reporting in results databases, or other data sharing	
20			arrangements), including any publication restrictions	
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29	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	12-13
30	authorship		professional writers	
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34	Dissemination policy:	#31c	Plans, if any, for granting public access to the full	12-13
35	reproducible		protocol, participant-level dataset, and statistical code	
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39	research			
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42	Appendices			
43				
44				
45	Informed consent	#32	Model consent form and other related documentation	7-8, 12
46	materials		given to participants and authorised surrogates	
47				
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50	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	12
51			biological specimens for genetic or molecular analysis in	
52			the current trial and for future use in ancillary studies, if	
53			applicable	
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For peer review only

BMJ Open

ED to EPI: Protocol for a Pragmatic Randomized Controlled Trial of an SMS (Text) Messaging Intervention to Improve the Transition from the Emergency Department to Early Psychosis Intervention for Young People with Psychosis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-042751.R2
Article Type:	Protocol
Date Submitted by the Author:	19-Nov-2020
Complete List of Authors:	<p>Polillo, Alexia; Centre for Addiction and Mental Health, Slaight Family Centre for Youth in Transition; University of Toronto, Psychiatry Foussias, George; Centre for Addiction and Mental Health, Slaight Family Centre for Youth in Transition; University of Toronto, Psychiatry Wong, Albert; Centre for Addiction and Mental Health, Campbell Family Mental Health Research Institute; University of Toronto, Psychiatry Ampofo, Augustina; Centre for Addiction and Mental Health Stergiopoulos, Vicky; Centre for Addiction and Mental Health; University of Toronto, Psychiatry Anderson, Kelly; Western University, Epidemiology & Biostatistics Bromley, Sarah; Centre for Addiction and Mental Health, Slaight Family Centre for Youth in Transition D'Arcey, Jessica; Centre for Addiction and Mental Health, Slaight Family Centre for Youth in Transition; University of Toronto, Institute of Medical Science de Oliveira, Claire; Centre for Addiction and Mental Health, Institute for Mental Health Policy Research; University of Toronto, Institute of Health Policy, Management and Evaluation Duda, Lillian; Centre for Addiction and Mental Health Henderson, Joanna; Centre for Addiction and Mental Health, Margaret and Wallace McCain Centre for Child, Youth and Family Mental Health; University of Toronto Faculty of Medicine, Psychiatry Kidd, Sean; Centre for Addiction and Mental Health; University of Toronto, Psychiatry Kurdyak, Paul; Centre for Addiction and Mental Health, Institute for Mental Health Policy Research; University of Toronto, Psychiatry Wang, Wei; Centre for Addiction and Mental Health; University of Toronto, Psychiatry Zaheer, Juveria; Centre for Addiction and Mental Health, Institute for Mental Health Policy Research; University of Toronto, Psychiatry Voineskos, Aristotle; Centre for Addiction and Mental Health, Slaight Family Centre for Youth in Transition; University of Toronto, Psychiatry Kozloff, Nicole; Centre for Addiction and Mental Health, Slaight Family Centre for Youth in Transition; University of Toronto, Psychiatry</p>
Primary Subject Heading:	Mental health

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Secondary Subject Heading:	Health services research
Keywords:	Schizophrenia & psychotic disorders < PSYCHIATRY, Clinical trials < THERAPEUTICS, Child & adolescent psychiatry < PSYCHIATRY, Information technology < BIOTECHNOLOGY & BIOINFORMATICS





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Title

ED to EPI: Protocol for a Pragmatic Randomized Controlled Trial of an SMS (Text) Messaging Intervention to Improve the Transition from the Emergency Department to Early Psychosis Intervention for Young People with Psychosis

Authors

Alexia Polillo, PhD, Slaight Family Centre for Youth in Transition, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

George Foussias, MD, PhD, Slaight Family Centre for Youth in Transition, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

Albert H.C. Wong, MD, PhD, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

Augustina Ampofo, BA, Centre for Addiction and Mental Health, Toronto, Canada

Vicky Stergiopoulos, MD, MHSc, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

Kelly K. Anderson, PhD, Department of Epidemiology and Biostatistics, Western University, London, Canada

Sarah Bromley, OT, Slaight Family Centre for Youth in Transition, Centre for Addiction and Mental Health, Toronto, Canada

Jessica D'Arcey, MSc (candidate), Slaight Family Centre for Youth in Transition, Centre for Addiction and Mental Health and Institute of Medical Science, University of Toronto, Toronto, Canada

Claire de Oliveira, MA, PhD, Institute for Mental Health Policy Research, Centre for Addiction and Mental Health and Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada

Lillian Duda, MPA, Centre for Addiction and Mental Health, Toronto, Canada

Joanna Henderson, PhD, Margaret and Wallace McCain Centre for Child, Youth and Family Mental Health, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

Sean A. Kidd, PhD, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

Paul Kurdyak, MD, PhD, Institute for Mental Health Policy Research, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

Wei Wang, PhD, Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

1
2
3 50 Juveria Zaheer, MD, MSc, Institute for Mental Health Policy Research, Centre for Addiction and
4 51 Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

5 52
6 53 Aristotle N. Voineskos, MD, PhD, Slight Family Centre for Youth in Transition, Centre for
7 54 Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto,
8 55 Canada

9 56
10 57 Nicole Kozloff, MD, SM, Slight Family Centre for Youth in Transition, Centre for Addiction and
11 58 Mental Health and Department of Psychiatry, University of Toronto, Toronto, Canada

59 60 **Corresponding author**

61 Nicole Kozloff, Centre for Addiction and Mental Health
62 250 College Street, 7th floor
63 Toronto, ON M5T 1R8
64 n.kozloff@mail.utoronto.ca
65 416-535-8501

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75 Pragmatic clinical trials

76 77 **ABSTRACT**

78 **Introduction**

79 While nearly half of all new psychotic disorders are diagnosed in the emergency department
80 (ED), most young people who present to the ED with psychosis do not receive timely follow-up
81 with a psychiatrist, and even fewer with evidence-based early psychosis intervention (EPI)
82 services. We aim to test an intervention delivered using short message service (SMS), a low-
83 cost, low-complexity, youth-friendly approach, to improve transitions from the ED to EPI
84 services.

85 86 **Methods and analysis**

87 This is a protocol for a pragmatic randomized, single blind, controlled trial with accompanying
88 economic and qualitative evaluations conducted at the Centre for Addiction and Mental Health
89 (CAMH) in Toronto, Canada. A consecutive series of 186 participants aged 16 to 29 referred by
90 the ED to CAMH's EPI program will be recruited for a trial of a 2-way intervention involving
91 reminders, psychoeducation, and check-ins delivered via SMS. The primary outcome will be
92 attendance at the first consultation appointment within 30 days of study enrolment assessed
93 through chart reviews in the electronic health record. We will also extract routine clinical
94 measures, including the Brief Psychiatric Rating Scale, Clinical Global Impression, and Service
95 Engagement Scale, and link with provincial health administrative data to examine system-level
96 outcomes, including ED visits and psychiatric hospitalizations, 6 months and up to 2 years after
97 baseline. We will perform a cost-effectiveness analysis of the primary study outcome and costs
98 incurred, calculating an incremental cost effectiveness ratio. Web-based surveys and qualitative
99 interviews will explore intervention user experience. Patients and families with lived experience
100 will be engaged in all aspects of the project.

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4 102 **Ethics and dissemination**
5 103 Research ethics board approval has been obtained. Findings will be reported in scientific journal
6 104 articles and shared with key stakeholders including youth, family members, knowledge users,
7 105 and decision makers.
8 106

9 107 **Trial registration number** clinicaltrials.gov #NCT04298450
10 108

11 109 **ARTICLE SUMMARY**

12 110 **Strengths and limitations of this study**

- 14 111 • Pragmatic randomized controlled trial leveraging mobile health technology, chart
15 112 reviews, routinely collected administrative data, and economic and qualitative
16 113 evaluations.
- 17 114 • Intervention well-positioned for local adoption as well as scale and spread to other EPI
18 115 programs and youth mental health services more broadly.
- 19 116 • Collaboration with health system decision-makers, clinical stakeholders, knowledge
20 117 users, team members with clinical and research expertise, people with lived experience
21 118 of psychosis, and key relationships with organizations well-positioned to support
22 119 widespread implementation.
- 23 120 • Conducting the trial at a single site will support streamlined recruitment but may limit
24 121 generalizability of our findings.
- 25 122 • The pragmatic data collection methods being utilized, particularly chart review, may be
26 123 subject to unreliable extraction and missing data.
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INTRODUCTION

Psychosis, characterized by delusions and/or hallucinations, typically manifests during adolescence or early adulthood. It is the characteristic presentation of schizophrenia and schizoaffective disorder, and often occurs in bipolar disorder.¹ These disorders can cause significant dysfunction: in disability weighting surveys used to establish global disease burden, participants rated schizophrenia as the disorder most disabling for individuals.² Young people experience greater mortality by up to 24-fold in the year following a first psychotic disorder diagnosis compared to peers in the general population.³ In the long term, psychotic disorders are associated with ongoing increased mortality particularly by suicide,⁴ substance use disorders, homelessness, victimization, acts of violence,⁵ and high economic costs due to healthcare use as well as lost productivity.^{6,7} Early psychosis intervention (EPI) is a model developed to provide treatment early in the course of illness to improve patients' long-term trajectories and reduce the burden on individuals and their families. The rationale for EPI has been strengthened by consistent findings that long duration of untreated psychosis is associated with greater symptom burden, lower likelihood of remission and poor social functioning and global outcomes.⁸ Members of our team have shown that EPI service use is associated with a four-fold reduction in all-cause mortality for young people with psychosis compared to those who do not access EPI services.⁹ EPI services have also been associated with improved access to psychiatric care, reduced risk of relapse, fewer hospital readmissions, and increased employment rates.⁹⁻¹³ EPI can be a lifechanging and lifesaving intervention for young people with psychosis.

EPI programs are well-established in Ontario and provide services to young people with early psychosis across the province.¹⁴ Despite this, and the clear mandate for EPI programs to promote their services and minimize barriers to care, many youth with psychosis in Ontario either never access these services, or enter them far later than indicated.¹⁵ In Canada, nearly half of all new psychotic disorders are diagnosed in the ED.¹⁶ We recently found that among young people across Ontario presenting with psychotic disorders to the ED for the first time, 40% received no outpatient mental health follow-up within 30 days and only 45% saw a psychiatrist.¹⁷ The reasons young people with psychosis discharged from the ED did not receive follow-up were unclear in this study: both issues of access (availability and awareness of services) and engagement (youth following through on referrals) are potential explanations. Our experience at the Centre for Addiction and Mental Health (CAMH) in Toronto, where our EPI program sees referred patients for consultation within 2 weeks on average, suggests a problem of engagement: according to clinic data, 50% of the youth referred from the ED do not attend their first EPI consultation appointment (compared with approximately 30% from all other referral sources). It is clear that new approaches are required to engage this population in accessing evidence-based care that is life-saving and improves illness outcomes. In surveys of patients and families in EPI services, appointment reminders are cited as a top factor that would improve service engagement, with a preference for email and text communication.¹⁸⁻²⁰

Mobile health technologies are increasingly being tested to improve outcomes, including symptoms, appointment attendance, and medication adherence, among young people with mental illness, particularly psychosis.²¹⁻²³ Short message service (SMS) or text message is a commonly used mode of communication by adolescents and young adults: in a survey of users of community mental health services, access to mobile phones approached 100%.²⁴ SMS is associated with low user and financial burden. SMS does not require people to own a smartphone, have data plans, or have access to wireless internet. In a study of people with psychosis, participants were found to be highly engaged with an SMS intervention.²⁵ SMS reminders have been associated with improved service engagement in psychosis across studies,²² including twice the attendance rates for initial appointments in an EPI program.²⁶ An

ongoing pilot study at CAMH investigating the effect of a weekly 2-way SMS intervention on service engagement during the first year of EPI treatment found this approach to be feasible and valued by participants.²⁷ We are unaware of any studies examining interventions specifically to improve the transition in care from the ED to EPI for young people with psychosis, using mobile health technologies or otherwise.

Objectives and Hypotheses

“ED to EPI,” a pragmatic randomized, single blind, controlled trial²⁸ with accompanying economic and qualitative evaluations, aims to improve the transition from the ED to EPI services for youth with psychosis using an SMS text messaging intervention. It is pragmatic in its participant eligibility criteria (broad and inclusive), comparison intervention (usual care), follow-up intensity (low), primary trial outcome (objective, meaningful and assessed under usual conditions), measurement of participant compliance and practitioner adherence to study protocol (unobtrusive), and analysis of primary outcome (inclusive, i.e. intention-to-treat).²⁹ We also leverage linked routinely collected data through ICES (previously known as the Institute for Clinical Evaluative Sciences), which holds data on all hospital and physician visits for the province. We will also evaluate the cost effectiveness of the intervention and explore young people’s perspectives on its various components. Our study team, in addition to clinicians and researchers, includes a patient and family member with lived experience of using EPI services and key decision-makers to increase the relevance and uptake of the intervention. Specifically, our primary objectives are to:

1. Evaluate the effect of an SMS intervention on attendance at the first consultation appointment within 30 days of study enrolment;

Hypothesis 1: The SMS intervention will increase rate of attendance at the consultation appointment.

2. Assess indicators of longer-term service engagement 6 months following study enrolment; Hypothesis 2: The SMS intervention will lead to improved indicators of longer-term service engagement (Service Engagement Scale scores and dropout rates).

3. Determine system-level outcomes, including ED visits and psychiatric hospitalizations, as a function of receiving the SMS intervention, and its cost effectiveness, factoring costs of the intervention and cost offsets of health service utilization;

Hypothesis 3: The SMS intervention will lead to decreased use of acute care services (ED visits and psychiatric hospitalizations) and will be cost-effective relative to the control condition, based on improved rate of transition from the ED to EPI services and anticipated reductions in use of costly acute care services.

4. Explore young people’s experiences of the intervention and their perspectives on its various components.

This is an exploratory research question that seeks to understand how young people experience the SMS intervention and how they perceive its various components impact their service engagement.

METHODS AND ANALYSIS

Study setting

The study setting will be the Gerald Sheff and Shanitha Kachan Emergency Department at CAMH, Ontario’s only 24-hour stand-alone psychiatric emergency service. The ED also houses a drop-in “Bridging Clinic” which provides care to less acute patients who are diverted after ED triage, and rapid follow-up care for patients discharged from the ED and CAMH inpatient units. Together, they serve approximately 1,200 patients each month. The EPI program at CAMH receives over 600 referrals for suspected psychosis annually, approximately 25% of which are from the ED and Bridging Clinic. Reflecting the Ontario EPI Program

Standards, CAMH EPI services are delivered by multidisciplinary teams, employ strategies to promote early entry and ongoing engagement, and provide pharmacotherapy and psychosocial therapies for an average of 3 years.¹⁴ Patients are assigned to the next available and/or most appropriate psychiatrist and case manager (nurse, social worker, or occupational therapist) for a joint consultation appointment, typically within 2 weeks, and are contacted by phone by the EPI program administrator to book and confirm their appointment. After the initial appointment is confirmed, patients receive a phone call reminder the day before their scheduled appointment. As part of routine care, patients who do not attend their scheduled first appointment receive follow-up calls to reschedule an appointment for up to 30 days from the initial referral.

Eligibility criteria

Study inclusion criteria mirror the intake criteria for the CAMH EPI program. Participants will be eligible for the study if they: 1) are between 16 and 29 years old and 2) have been referred by the CAMH ED to CAMH EPI services for suspected psychosis. Our only exclusion criterion is inability to communicate in basic written English. In our pilot SMS study at CAMH, fewer than 5% of potential participants were excluded for lacking a phone; we have budgeted to offer 5% of participants access to a prepaid cellphone for the duration of the study.²⁷

Intervention procedures

Study participants will be recruited at the time of EPI referral for a trial of an SMS intervention designed to engage them during the waiting period for their consultation appointment. They will be randomized to receive either sham or active SMS intervention. Sham SMS will consist of 1 message sent just after enrolment indicating that they will be contacted for an appointment. The sham SMS group will not be denied any part of usual clinical care. Thus, the clinic administrator will call patients in both groups to book and remind them of the consultation appointment. Active SMS intervention will include the initial message sent to the control group, plus a series of subsequent messages. These will include the following content: 1) appointment reminders and instructions, 2) psychoeducational material, and 3) 2-way communication check-ins to rate distress (Figure 1). Intervention components were developed based on feedback from a survey of youth in the same EPI program,³⁰ as well as psychosocial interventions with evidence in early psychosis, including cognitive-behavioural therapy (psychoeducation, behavioural activation) and illness self management (reminders, distress check-in).^{31 32} See Supplementary File 1 for a comprehensive description of the intervention. Messages sent back by participants will be monitored by the research team, and the case manager assigned to their consultation appointment will be notified and will respond accordingly if there are indicators of elevated distress. The intervention will continue until the patient attends the first consultation appointment, or for up to 30 days if the patient does not attend, which reflects the program's practice of closing referrals for non-attending patients.

Messages will be sent through CAMH's in-house Research Electronic Data Capture (REDCap) platform via a third-party plug-in, Twilio, which supports routing of SMS messages to participant devices.³³⁻³⁵ All data is stored securely on CAMH's REDCap servers or in a locked office and password-protected database on CAMH's secure network. The purpose of the sham intervention is to separate out the content of the intervention (i.e. reminders, psychoeducation, 2-way check-ins) from the effect of simply receiving SMS messages, decreasing participant bias.

Assignment of intervention

Immediately after informed consent, participants will be randomized by REDCap to the active or sham intervention. Generation of the randomization sequence will be managed by the

277 study biostatistician who is not involved in enrolling participants or assigning intervention arms.
278 Randomization will be stratified by sex (male or female) and referral source (ED or Bridging
279 Clinic), using a computer algorithm to determine a randomized, blocked allocation of
280 participants into intervention groups within strata. Once randomized, treatment assignment will
281 be known only by the study personnel involved in managing the SMS intervention and the case
282 manager monitoring text message responses; the principal investigator and study personnel
283 involved in the chart review and the ICES analysis will remain blind to treatment assignment.
284 Study personnel involved in the qualitative interviews and analysis will also be aware of
285 treatment assignment since only individuals receiving the active intervention will participate in
286 this component of the project.

287 288 **Sample size**

289 Our sample size calculations are based on the primary outcome of rate of attendance at
290 the EPI program consultation appointment. The current rate of attendance at the first
291 consultation appointment for patients referred from the ED and Bridging Clinic is 50%; we have
292 powered our study to detect the treatment effect with an anticipated rate of attendance of 70%,
293 which is the average for all referral sources other than the ED and Bridging Clinic. A total of 186
294 participants (93 per group) will provide >80% power to detect a change in attendance from 50%
295 to 70% at alpha <0.05. Non-compliance and loss to follow-up are not a concern for our primary
296 outcome since these are counted in the outcome as nonattendance at the consultation.
297 Adjusting analyses for covariates expected to affect attendance (e.g., age, sex) is expected to
298 further increase power.

299 300 **Study procedures**

301 We will recruit 186 patients consecutively referred from the CAMH ED and Bridging
302 Clinic to the CAMH EPI program at the time of discharge. During business hours and into the
303 evening, research staff will be on call to the ED to recruit patients as soon as they are identified
304 for the study. Eligible participants who present after hours may be identified by ED staff and
305 referred to the research team who will send them an e-consent form via SMS or email. See
306 Supplementary File 2 for patient consent form. Additionally, potential participants who are
307 missed in the ED/Bridging clinic may be identified by the EPI clinic administrator who will
308 approach them over the phone and send them an e-consent form via SMS or email. We have
309 used the approach of having clinical and administrative staff obtain verbal consent to send e-
310 consent forms in other studies with this population.¹⁹

311
312 As part of informed consent, participants will be asked to consent to a review of their
313 chart, a follow-up web-based survey, and linkage of their information to data held at ICES. They
314 will also be given the option to provide consent to be re-contacted for participation in a
315 qualitative interview. There will be no additional in-person assessments for the quantitative
316 component of this study. CAMH uses an electronic health record, which facilitates data
317 abstraction from multiple clinical programs (i.e., both the ED and Bridging Clinic and EPI
318 program). Research staff and students will be trained by the clinician principal investigators to
319 abstract data into a structured database.

320
321 All study participants will receive a \$10 e-giftcard once the baseline e-visit is complete.
322 Participants in the active intervention group who complete a web-based survey will receive
323 another \$10 e-giftcard and those who complete a qualitative interview will receive a \$50 e-
324 giftcard. It will be clarified through the consent process that honoraria are to compensate
325 participants for their time and will not be tied to clinical appointment attendance. For the majority
326 of participants, their initial recruitment and consent will be their only interaction with the research
327 team, with a small subgroup completing qualitative interviews.

Outcome measures

Chart review

Outcome measures are shown in Table 1. CAMH uses many standardized assessment forms which increases the completeness of patient data. Demographic variables, clinical diagnoses, substance use, duration of untreated psychosis (measured as the period of time from first onset of psychotic symptoms to initiation of EPI services and initiation of treatment with an antipsychotic or mood-stabilizing medication), characteristics of the ED visit from which they were referred (urgent presentation – brought by police, involuntary status; timing of visit), and family involvement in care are routinely recorded in the clinical chart by clinicians and will be abstracted from the chart at the time of consultation. Additional variables will likely be available but only for patients accepted into the EPI program, and this will be reflected in the data analysis. These include several assessments that are performed routinely in the EPI program. The Service Engagement Scale (SES)³⁶ is a brief validated tool designed to measure engagement with community mental health services. In 14 items, it assesses patients' availability for treatment, collaboration, help-seeking behaviours and treatment adherence on a four-point Likert scale with higher scores indicating difficulties in service engagement. The Brief Psychiatric Rating Scale (BPRS)³⁷ is a clinician or interviewer-rated measure of psychiatric symptoms commonly used as an outcome measure for psychotic disorders and collected monthly in CAMH's EPI program. It includes items related to suicidality and hostility. The Clinical Global Impression (CGI)³⁸ is a clinician-rated measure of the patient's global severity of illness prior to and after initiating a medication. It includes subscales for Severity and Improvement. Medication and appointment nonadherence will also be assessed over 6 months of treatment. Lastly, after 6 months, current EPI enrolment status will be assessed and categorized as: not offered or enrolled in treatment (e.g., because they did not ultimately have psychosis), enrolled but disengaged prematurely, accepted for treatment but transitioned to other services, or continued in treatment. Data abstractors will undergo rigorous training and monitoring, use standardized extraction forms, and calculate inter-rater reliability.

Administrative data

Primary data collected for the study will be linked deterministically to data sources held at ICES via participants' unique health card numbers. The information available for each participant will be de-identified, stored, and analyzed onsite at ICES following procedures approved by Ontario's Information and Privacy Commissioner. The following ICES data sources will be used: the Ontario Mental Health Reporting System (OMHRS), capturing hospitalizations on adult inpatient mental health units,³⁹ the Canadian Institute of Health Information Discharge Abstract Database (CIHI-DAD), capturing all hospital admissions including hospitalizations on child and adolescent inpatient mental health units,^{40 41} National Ambulatory Care Reporting System (NACRS) which captures all ED visits,⁴² Ontario Health Insurance Plan (OHIP) claims database, which captures outpatient physician visits,⁴⁰ Registered Persons Database, which contains health card numbers, demographic information, and deaths, and Ontario Drug Benefits (ODB) claims database, which provides information on all covered prescriptions (based on financial need for those under age 65 and for young people up to age 25 who lack private insurance). These data will also be used for cost effectiveness analysis. Outcomes examined in the linked ICES data are listed in Table 1.

Table 1. Summary of outcome measures and covariates

Type	Variables	Data Source	Timing
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1			
2			
3	Demographic characteristics	Age	Chart review for all demographic characteristics (CAMH Health Equity form and notes)
4		Sex and gender	
5		Sexual orientation	
6		Race/ethnicity	
7		Born in Canada	
8		Religious/spiritual affiliation	
9		Highest level of education	
10		Source of income and family income	
11		Number of people supported by income	
12		Employment status	
13		Legal history	
14		Housing status	
15		Living situation	
16		Experience of homelessness	
17		Relationship status	
18	Clinical characteristics	Clinical diagnoses	Chart review for all clinical characteristics (consultation and progress notes)
19		Substance use	
20		DUP	
21		Family involvement in care	
22		Urgent status at ED visit (brought by police, involuntary)	
23		Timing of ED visit	
24		BPRS ³⁷	Baseline and 6 months
25		CGI ³⁸	Baseline and 6 months
26	Service engagement	Attendance at consultation appointment	Chart review for all service engagement measures
27		SES ³⁶	30 days
28			6 months (completed around 3 months in treatment)
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	Medication and appointment nonadherence		6 months
	EPI enrolment status		6 months
System-level outcomes ^b	Number of ED visits	NACRS ⁴²	6 months and up to 2 years
	Number of inpatient mental health hospitalizations	OMHRS, ³⁹ CIHI-DAD ^{40 41}	
	Number of days in inpatient mental health hospitalizations	OMHRS, ³⁹ CIHI-DAD ^{40 41}	
	Number of outpatient mental health visits	OHIP ⁴⁰	
	Prescription drugs – psychiatric medications, continuously vs. noncontinuously prescribed	ODB	
	Mortality including cause of death	Registered Persons Database	

377 ^a Items may be extracted from the ED note or EPI consultation note

378 ^b Administrative data held at ICES

379 CAMH, Centre for Addiction and Mental Health; DUP, duration of untreated psychosis; BPRS,
380 Brief Psychiatric Rating Scale; CGI, Clinical Global Impression; SES, Service Engagement
381 Scale; EPI, early psychosis intervention; ED, emergency department; OMHRS, Ontario Mental
382 Health Reporting System; CIHI-DAD, Canadian Institute of Health Information Discharge
383 Abstract Database; NACRS, National Ambulatory Care Reporting System; OHIP, Ontario Health
384 Insurance Plan; ODB, Ontario Drug Benefits.

385

386 **Statistical analysis**

387 **Primary analysis**

388 Descriptive and graphical statistics will be used to summarize the data on all randomized
389 participants and to confirm that there are no group differences in baseline demographics and
390 clinical characteristics. Distributional assumptions will be inspected and appropriate
391 transformations or non-parametric methods will be applied as necessary. In general,
392 generalized linear models⁴³ will be used throughout. These models account for deviation from
393 normal assumption of the outcome variables and control for covariates.

394

395 Our analysis of the primary outcome will be a logistic regression to examine the
396 likelihood of attendance at the EPI consultation with treatment assignment using risk ratios.⁴⁴
397 We will carefully select demographic variables and factors known to influence treatment
398 engagement (e.g., substance use, family involvement in care)⁴⁵ to be included in the model as
399 covariates. A difference in attendance between groups will be declared at a significance level of
400 0.05. Similar models will be used to address the secondary hypotheses, with specific types of
401 models appropriate to each outcome, including time-to-event analysis to examine premature
402 disengagement from services. Administrative data outcomes will be examined using generalized
403 linear models with proper distribution assumptions.

404

405 Additional analyses: moderation and generalizability

406 We plan to conduct two additional exploratory analyses. First, we will run moderation
407 analyses on potential effect modifiers by adding an interaction term between the potential
408 moderator and the treatment assignment indicator in the generalized linear models. We are
409 specifically interested in the moderation effects of health equity factors including gender,
410 race/ethnicity, and housing status. A significant interaction will provide evidence that the
411 treatment effects may be different in the subgroups. A second exploratory analysis will be
412 conducted to evaluate the impact of selection bias of the study sample and estimate the
413 population average treatment effects by employing weighted analysis using propensity scores.⁴⁶

414 Missing data

415 The risk of missing data is mitigated through the use of chart review and analysis of
416 administrative data. While the primary outcome will not suffer from attrition, other outcomes will,
417 as some follow-up data will only be available for participants who attended their consultation
418 appointment and those who are enrolled in CAMH EPI services. For these additional outcomes,
419 we plan to use multiple imputation methods developed by Schafer to correct potential bias that
420 could be introduced by missing data.⁴⁷

423 Economic evaluation

424 Full details of the economic evaluation appear in Supplementary File 3. We will
425 undertake a cost-effectiveness analysis, where the outcome of interest is consultation
426 appointment attendance, adopting the perspective of the public third-party payer (i.e., the
427 Ontario Ministry of Health). We will collect data on the costs of delivering both arms of the
428 intervention. In addition, using a costing algorithm available at ICES,⁴⁸ we will estimate all direct
429 patient-level healthcare costs incurred by the public third-party payer for the intervention and
430 control groups, which will include costs of hospitalizations, ED visits, physician services (i.e.,
431 primary care, psychiatry and other) and diagnostic tests, outpatient prescription drugs for
432 individuals covered under the provincial public drug insurance plan, and other hospital-based
433 care. We will calculate the incremental cost-effectiveness ratio (ICER) as the difference in
434 discounted mean costs between the intervention and control group divided by the difference in
435 attendance rates. We will use a net benefit regression approach to model probabilities of cost
436 effectiveness for each additional patient referred who attends their consultation appointment in
437 the intervention compared with control group. In addition, we will undertake relevant sensitivity
438 analyses to test the robustness of findings by varying relevant parameters, such as the discount
439 rate. Finally, we will examine the real-world budget impact of implementing the intervention
440 across Ontario, to estimate the cost to the Ministry of Health of implementing this model of care
441 across the province and the potential cost-savings to the system associated with this.

443 Understanding patient experiences: Survey and qualitative analysis

444 Participants in the active intervention group will receive a one-time survey sent as a web-
445 link to their phone or email address. Survey topics include user experience, attitudes toward the
446 SMS intervention, its perceived benefits and challenges, acceptability, and suggestions for
447 improvements. Those who consent to participate in the qualitative research component will be re-
448 contacted by phone or email to participate in semi-structured interviews to gain a more in-depth
449 understanding of survey topics. A subsample of 10-15 participants in the active intervention group
450 will be purposively selected to maximize diversity of age, gender, and service attendance. We will
451 use critical realist theory as an underlying framework to guide our interviews, surveys, and
452 analysis.⁴⁹ Interviews will be completed until thematic saturation is achieved, estimated at 12
453 participants. Interviews will be digitally audio-recorded and transcribed verbatim. Surveys will be
454 completed and stored in REDCap. Transcriptions and survey responses will be analyzed using

thematic content analysis in NVivo-11. Research participants will be invited to assist with member checking to confirm that themes reflect their experiences. The analysis can inform future improvements to the intervention and considerations for broader implementation, privileging the experiences of the patients attending these programs.

PATIENT AND PUBLIC INVOLVEMENT

A youth and family member who previously received EPI services have been engaged in helping shape the intervention and study design from project inception. They are active members of the project's Steering Committee that meets monthly to inform study design, implementation, evaluation, and dissemination of results. They will have key roles in the plan to spread the intervention, if successful, to other EPI programs by working with patients and families to adapt the intervention to local contexts. Additional youth with lived experience of receiving EPI services have been consulted on an ad hoc basis through the CAMH Youth Engagement Initiative to provide detailed feedback on the SMS intervention. Patient and family representatives on the research team are compensated for their time.

ETHICS AND DISSEMINATION

The study was approved by the Research Ethics Board (REB) at the Centre for Addiction and Mental Health. The study protocol was prepared according to SPIRIT guidelines⁵⁰ and registered with clinicaltrials.gov on March 6, 2020 (NCT04298450; <https://clinicaltrials.gov/ct2/show/NCT04298450?term=ed+to+epi&draw=2&rank=1>). REB-approved protocol amendments will be posted on the site. The principal investigators and study team will meet regularly to review accrued data, data confidentiality, any adverse events, adherence to protocol design, recruitment and implementation. This intervention has been designed to have high likelihood of adoption and readiness for spread and scale-up because it responds to a critical need, has a strong evidentiary basis, has advantages over existing practice and is both low complexity and low cost.⁵¹ The study team is well-positioned to support widespread implementation of the intervention if successful. We have used an integrated knowledge translation approach that leverages input from stakeholders, including patients, clinicians (both from the ED and EPI services), policymakers, and relevant organizations throughout the study to champion the spread of the intervention to other EPI programs and youth mental health services more broadly. This trial focuses on a particularly vulnerable population—young people transitioning from adolescence to adulthood and from the ED to EPI services—but the basic intervention is widely applicable. The software platform utilized to coordinate this intervention is available at no charge, and the SMS functionality for sending and receiving messages carries a nominal fee, supporting broad uptake.

The results of the trial will be reported in scientific journal articles and shared with key stakeholders as they become available. Our study team includes the co-chair of the Early Psychosis Intervention Ontario Network, a network of over 50 EPI programs across Ontario, and several members of the Canadian Consortium for Early Intervention in Psychosis, providing a durable and established community of practice for immediate spread. De-identified participant data will be available upon reasonable request other than system-level data held at ICES. Requests can be made by contacting the principal investigator Dr. Nicole Kozloff at nicole.kozloff@camh.ca and will be managed by the Steering Committee.

This pragmatic randomized-controlled trial of a low-cost, low-complexity SMS intervention aims to improve the transition from the ED to EPI services for young people with psychosis. It targets a brief but critical period: if young people cannot even get in the door to EPI services, there is no way for them to reap the many known benefits of EPI care. Improving the

ED to EPI transition has the potential to result in more young people with psychosis getting appropriate treatment earlier. The proposed intervention is also likely to be easily adaptable to other referral pathways to EPI services and youth mental health services more broadly. At potentially lower cost to the health system, applying this SMS intervention to the ED to EPI transition has the potential to lead to improved short-term symptoms and functioning, long-term disease trajectories, decreased burden on patients and families, and fewer deaths among young people with psychosis.

Figures

Figure 1. Study intervention schedule*

*This figure represents a summary of the intervention schedule and is not exhaustive of text message content

SMS, short message service; Right arrow, incoming text messages received by participants; Left arrow, outgoing text messages sent by participants

Author contributions

NK is the principal investigator who conceived the original study design and obtained funding, with most of the current authors having contributed to the funding application, and all authors having participated in revisions to the study design for important intellectual content. AP, GF, AW, AA, VS, JD'A, LD, ANV, and NK sit on the project's Steering Committee. AP, GF, JD'A, and NK form the Data Management Committee. AP leads the survey and qualitative analysis. GF, AW, SB, and ANV have administrative roles in the clinical programs and will support the acquisition and interpretation of data. AA and LD act as patient and public consultants. VS acts as a Health System Decision-Maker on the project. KKA, CdO, PK, and NK consult on the ICES analysis. CdO is a health economist who consults on the economic analysis. VS, JH and SK provide knowledge translation expertise. JZ provides consultation on the qualitative interviews and analysis. WW acts as the biostatistical consultant. AP and NK drafted the protocol. All authors read, revised and approved the final version of the manuscript.

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Competing interests statement

The authors declare no competing interests.

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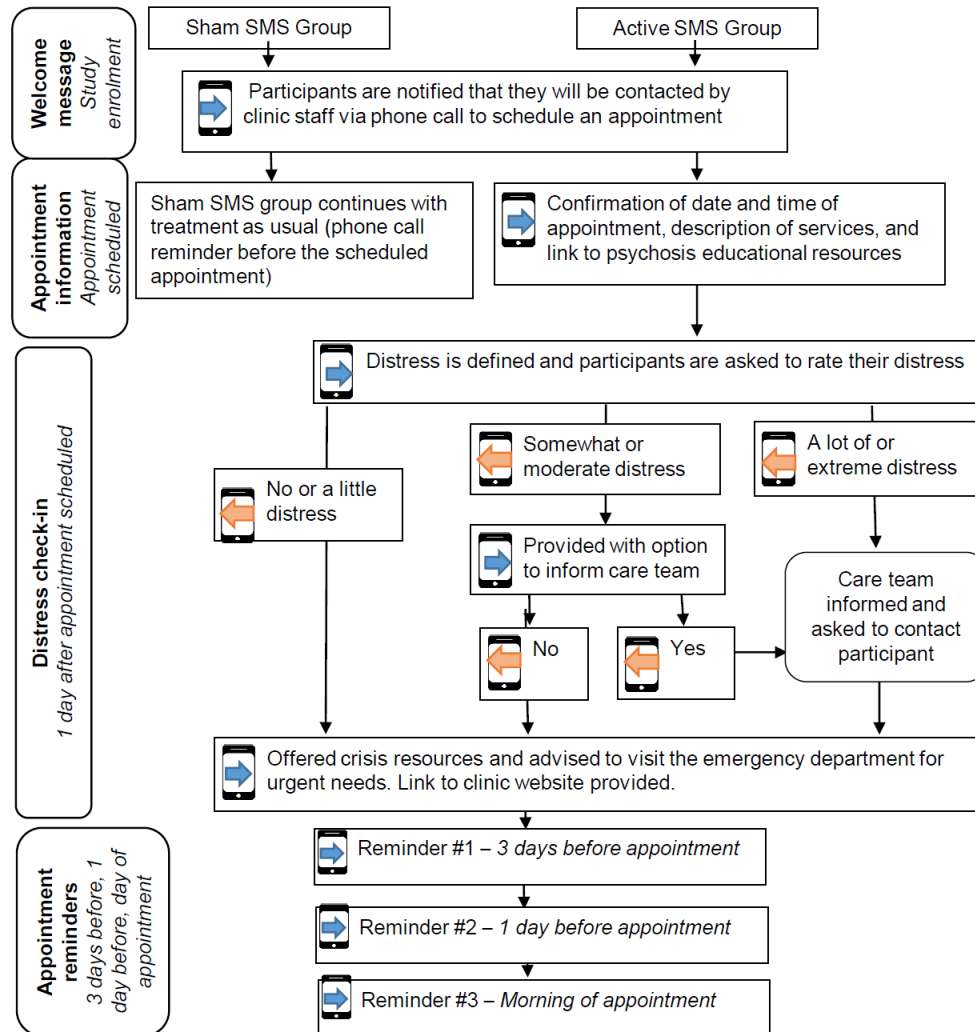
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Figure 1. SMS intervention schedule*



*This figure represents a summary of the intervention schedule and is not exhaustive of text message content

SMS, short message service; Right arrow, incoming text messages received by participants; Left arrow, outgoing text messages sent by participants

Hi [First Name], this is [Clinic]. If you haven't yet been given an appointment, one of our clinic staff will contact you in the next few days. Just so you're aware, our number comes up as private. Please text '1' to confirm you received this message.

(If 1 texted back): Thanks for confirming!

ACTIVE GROUP

Hi [First Name], thank you for booking your first visit with [Clinic] on [date] at [time]. If you need to reschedule, please call [Clinic Phone]. At your appointment, you will meet with a psychiatrist and a case manager who will work with you to figure out how we can best support you. Experiencing psychosis can be difficult and knowing more about mental health may help you cope. If you'd like to learn more about mental health and psychosis, please visit: www.camh.ca/psychosis

Next day**

Hi [First Name], while you wait for your upcoming appointment with us at [Clinic], we wanted to check in! How are you doing this week? Please send back '1' for well, '2' for okay, or '3' for bad.

If response = 1

Thanks for letting us know. Here are some resources if you're experiencing a crisis: www.camh.ca/crisis-resources. If you need urgent support, please see your nearest emergency department. Please text '1' to confirm you received this message.

If response = 1

If response = 2 or 3

We say people are experiencing distress when they are feeling anxious, depressed, worried, or hopeless. Can you please rate your distress for us? '0' for no distress, '1' for a little distressed, '2' for somewhat distressed, '3' for moderately distressed, '4' for a lot of distress, or '5' for extreme distress (urgent).

If response = 2-3

Thanks for letting us know. Here are some resources if you're experiencing a crisis: www.camh.ca/crisis-resources. If you need urgent support, please see your nearest emergency department. Would you like us to pass this information on to your care team? They may reach out to you during business hours. Please text back: '1' for yes, or '2' for no. We won't pass this information on unless you text back '1'.

If response = 1: Thanks for letting us know. We have passed this onto your care team who may reach out during business hours. If you need urgent support, please see your nearest emergency department. Please text '1' to confirm you received this message.
If response = 2: Thanks for letting us know. We won't pass this information on. If you need urgent support, please see your nearest emergency department. Please text '1' to confirm you received this message.

If response = 4

Thanks for letting us know, we have passed this information on to your care team, who may reach out during business hours. Here are some resources if you're experiencing a crisis: www.camh.ca/crisis-resources. If you need urgent support, please see your nearest emergency department. Please text '1' to confirm you received this message.

If response = 5

Thanks for letting us know. We have passed this information on to your care team, who may reach out during business hours. We urge you to consider trying these resources: www.camh.ca/crisis-resources. If you need urgent support, please see your nearest emergency department. Please text '1' to confirm you received this message.

If response = 1

Thanks for confirming! For more information about our services, please visit: www.camh.ca/sceis.

3 days pre-appointment**

Hi, this is a reminder that your appointment at [Clinic] is coming up on [date] at [time].

1 day pre-appointment

Hi, this is a reminder of your appointment tomorrow at [time]. The care team is looking forward to meeting you. If you need to reschedule, call [Clinic Phone].

Morning of appointment

Hi, your appointment with [Clinic] is today at [time]. Please call us at [Clinic Phone] if you need any assistance.

If participant does not show, they receive the following message, and then the process starts over from the check-in until participant shows up or 30 days have passed:

If 30 days have passed and participant has not attended

Hi, we understand you didn't make it to your [Clinic] appointment. To reschedule, please call [Clinic Phone].

Hi, you have now finished receiving text messages from the research study. Thank you for your participation!

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At Time of Enrollment
After appointment scheduled via phone
Two-way distress check-in
Reminder #1
Reminder #2
Reminder #3

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**ED to EPI: Using SMS (Text) Messaging to Improve the Transition from the
Emergency Department to Early Psychosis Intervention for Young People
with Psychosis**

Online Version - Informed Consent Form

Principal Investigator: Dr. Nicole Kozloff
Dr. George Foussias
Dr. Vicky Stergiopoulos
Dr. Aristotle Voineskos

Co-Investigators: Augustina Ampofo Dr. Sean Kidd
Dr. Kelly Anderson Dr. Paul Kurdyak
Sarah Bromley Dr. Alexia Polillo
Jessica D'Arcey Dr. Brittany Poynter
Dr. Jeff Daskalakis Dr. Wei Wang
Dr. Claire de Oliveira Dr. Albert Wong
Lillian Duda Dr. Juveria Zaheer
Dr. Joanna Henderson

Sponsor: Canadian Institutes of Health Research, CAMH Foundation

Purpose of the Study:

We invite you to participate in this study because you have been referred to the Slight Centre for Early Intervention Services. The Slight Centre is an outpatient program for young people experiencing a first episode of psychosis and their families. In this study we will examine if text messaging can improve the transition from the emergency department to early intervention services for youth. We hope that this study will eventually lead to young people getting appropriate treatment earlier and improve their long-term outcomes. Your participation in this study is voluntary. The following information is provided to help you make an informed decision whether or not to participate.

What will I be asked to do as part of this study?

If you decide to participate in this study, you will be asked to do the following:

- 1) **Intervention:** You are being invited to take part in a study. If you consent to participate, you will be randomly assigned to receive one of two types of text messages. Random assignment means that you have an equal chance of being assigned to each text message group. If you are assigned to the text message intervention, you will receive text messages at a time of your choosing (e.g., morning, evening). You will be sent text messages with information about appointment details, education about psychosis, an opportunity to rate your distress, and appointment reminders. These text messages will continue until you attend your first consultation appointment, or for up to 30 days if you did not attend. If you are assigned to the other group, you will receive a one-time text message. If you do not have a phone, one will be offered to you for the duration of the study with the expectation that it is returned at your first consultation appointment.



Please note that text messages are NOT being monitored constantly and if you are experiencing an urgent issue, this information should not be sent by text message. Instead, please visit your nearest emergency department. Additionally, this is not a direct line of communication with your care team and it is not a secure form of communication. You should not send any personal health information that is not requested by the text messages.

- 2) **Collection of data:** We will also review your medical chart to obtain additional information about you. Information collected through this study will be transferred to the Institute for Clinical Evaluative Sciences (ICES). ICES is an organization that holds routinely collected data on health care use in Ontario. ICES is committed to protecting the privacy and security of health information. ICES is an approved unit under Ontario's Personal Health Information Protection Act and follows the policies and procedures for privacy protection and data security approved by Ontario's Information and Privacy Commissioner. Linking the data will involve using personal identifiers such as your name, date of birth, and OHIP number to identify your health service use. These identifiers will be removed as soon as the data is connected to ICES. The data will then be replaced by a scrambled code in order to decrease the likelihood of a data breach (when people get access to private information without permission)
- 3) **Follow up survey:** You may be asked to complete a brief survey following your participation in the text message intervention. Your participation in the survey is voluntary. If you consent to study participation, you may receive a link to the online survey at the contact information of your choice (text message or email). The survey takes approximately 5 to 10 minutes to complete. If you complete the survey, you will be compensated with a \$10 e-gift card sent to you by email or text message from your choice of a list of retailers. The survey contains questions about your experiences with the text message intervention.

Are there risks involved?

There are no known harms associated with participation in this study. If your text messaging plan does not include unlimited texting, you may incur additional charges on your cell phone bill. The study will not reimburse you for these charges. You may also feel emotional discomfort and fatigue from receiving recurrent text messages with appointment reminders and questions about how you are feeling. If you do feel this way, you may refuse to answer any question, or terminate your participation in this study at any point in time. You may be asked some questions during the survey that might make you feel somewhat uncomfortable. If you do feel uncomfortable, you may indicate this in the comments or skip the question. You can also pause the survey and continue at another time. Please be advised that if the researcher or study personnel sees that there is a risk to your safety or the safety of others, then steps will be taken to ensure your safety and the safety of others. Lastly, the security of information sent by email/text cannot be guaranteed.

Are there benefits involved?

No direct benefits to your health will likely result from this study. It is possible that the results of this study will increase engagement in early intervention services and may benefit other people now or



Centre for Addiction and Mental Health

in the future. You will also receive compensation for your time and participation in the study. The investigators responsible for this study or CAMH are not conducting this study to receive commercial benefit. However, if this research produces financial returns from a commercialization of the results in the future, you will not receive any benefit from these returns.

Can participation in this study end early?

Participation in any research study is voluntary. Your decision whether or not to participate will not interfere with your right to healthcare or other services to which you are otherwise entitled. You can contact the research team through email or phone to withdraw from the study at any time. After data is anonymized your responses cannot be withdrawn, however, no new data will be collected. Throughout your participation in this study, you will continue to receive usual care as agreed upon by you and your treatment team. In the event of research-related harm, you have not waived any legal rights/rights to legal recourse.

Are study participants paid to participate in this study?

Everyone who participates in the text messaging intervention will receive a \$10 e-gift card by email or text message from your choice of a list of retailers. If you decide to withdraw before study end, you will still be paid for your time and participation. Those participants selected to participate in the follow up survey will receive another \$10 e-gift card by email or text message from their choice of retailers for completing the survey.

Will personal information about me be kept confidential?

- The research data will be kept confidential from the inception of the study.
- Any information about you obtained from this research will be kept as confidential (private) as possible unless disclosure is required by law. It is important to note that confidentiality will be protected to the extent permitted by law. However, there are 3 exceptions to our confidentiality policy. In any of the following situations, we are obligated by law to contact authorities: 1) if there is a serious possibility that you may harm yourself or others; 2) if you have been involved in any form of child abuse or neglect; 3) if you have been the victim of abuse by a healthcare worker
- All data obtained from this research will be kept in a locked office and secured password database with limited access only to study personnel and authorized CAMH personnel.
- To protect your identity and confidentiality, all personal identifiers (such as your name, birth date) will be removed (de-identified and replaced with a specific code number; the research records and data will be indicated by a case number rather than your name, and the information linking these case numbers with your identity will be kept separate from the research records. This information will be kept in a separate, secure location and will only be accessible to study personnel.
- Study personnel may also access your health records for research purposes; your medical records will be kept confidential.
- All electronic files will be stored on CAMH's secure hospital or institutional network and will be password protected.
- Other Canadian research centres (other than CAMH) may be involved in analyzing the data,



Centre for Addiction and Mental Health

and if so this will be confidential, and your name will not be given out.

- Following the completion of the study, the researchers intend to publish the results in scientific journals. You will not be identified in any of these reports. A report of the results of this project will be given to you if you request it.
- The information you provide will not affect the usual care that you receive.
- The investigators on this study will keep the data as long as necessary to fulfill the research purposes and in accordance with the applicable laws and regulations and will use enhanced security measures to store it.
- De-identified data from this study may be shared with the research community at large to advance science and health. We will remove or code any personal information that could identify you before files are shared with other researchers to ensure that, by current scientific standards and known methods, no one will be able to identify you from the information we share.
- Your de-identified research data (information about your diagnosis, symptoms, and study evaluations) may be shared with investigators at other Canadian research centres (other than CAMH).

Will this research study involve the use or disclosure of my identifiable medical information?

- Study personnel will retrieve information about your demographics and clinical care from your medical chart. This will be stored in a secure database with a case number rather than your personal identifiers.

Who will have access to identifiable information related to my participation in this research study?

Personal Health Information (PHI) is information about your physical or mental health or the health care that you receive that could identify you. In addition to the investigators listed on the first page of this consent form and their research staff, the following individual and/or programs will or may have access to identifiable information (which may include your identifiable medical information):

- a. Institute for Clinical Evaluative Sciences (ICES) is a prescribed entity under Ontario's Personal Health Information Protection Act and adheres to policies and procedures for privacy protection and data security approved by Ontario's Information and Privacy Commissioner.
- b. *As part of the Research Services Quality Assurance Program, this study may be monitored and/or audited by a member of the Quality Assurance Team. Your research records and CAMH records may be reviewed during which confidentiality will be maintained as per CAMH policies and extent permitted by law.*
- c. As a part of continuing review of the research, your study records may be assessed on behalf of the Research Ethics Board. A person from the research ethics team may contact you (if your contact information is available) to ask you questions about the research study and your consent to participate. The person assessing your file or contacting you must maintain their confidentiality to the extent permitted by law.



Offer to Answer Questions

We have used some technical terms in this form. Please feel free to ask about anything that you do not understand. Consider this research and the consent form carefully as long as you feel necessary before you make a decision.

Dr. Nicole Kozloff is responsible for this study. If you have any questions, please contact Dr. Nicole Kozloff at 416-535-8501 x 30769.

If you have any questions about your rights as a participant in a research study, you may contact Dr. Robert Levitan, Chair, Research Ethics Board, Centre for Addiction and Mental Health, at 416-535-8501 x 34020.

Consent to Participate: My signature below indicates that:

- I acknowledge that the research study described above has been explained to me and that any questions that I have asked have been answered to my satisfaction.
- I have been informed of the alternatives to participation in this study, including the right not to participate and the right to withdraw without compromising the quality of medical care for me and for other members of my family.
- I have been informed of the potential risks/harms and discomforts and I also understand the benefits of participating in this study.
- I know that I may ask now, or in the future, any questions that I may have about the study or the research procedures.
- I have been assured that records relating to my research participation and to me will be kept confidential and that no information will be printed that would disclose my identity without my permission, unless required by law.
- I have been given sufficient time to read and understand the above information
- I understand and consent that my records and research data may also be shared with other investigators for analysis and future projects (this would include only de-identified data).

Please check one:

- Yes, I consent to participating in this study**
- No, I do not consent to participating in this study**

Optional – Future Contact:

Do you agree to be re-contacted by our study team for an in-person interview or other follow up? You will be compensated for your participation.

- Yes, I agree to be contacted about study follow-up**



No, I do not wish to be contacted about study follow-up

Texting Preferences:

If you agreed to participate in the study:

At what phone number would you like to receive text messages?

At what phone number or email address would you like to receive other links related to the study (e.g., your e-giftcard, the survey, and future communications)?

What time of day would you prefer to receive text messages?

Morning Afternoon Evening

What first name would you like us to call you in your text messages?

Compensation Preferences:

Which e-giftcard would you like to receive as compensation for participating? It may take up to 10 business days to receive your compensation.

Tim Hortons Amazon

Please contact 416-535-8501 x 30677 if you do not receive a text message from us within 24 hours.

The security of information sent by e-mail/text cannot be guaranteed. Please do not communicate personal sensitive information by e-mail/text. Let the research team know if you do not want to be contacted by e-mail/text. Email/Text is not routinely monitored outside of work hours. Please do not use e-mail/text to communicate emergency or urgent health matters – please contact your clinician or family doctor. If it is a medical emergency, call 911.

Supplementary File 3

We will undertake a cost-effectiveness analysis, where the outcome of interest is consultation appointment attendance, adopting the perspective of the public third-party payer (i.e., the Ontario Ministry of Health). Using a costing algorithm developed in SAS and available at ICES,¹ we will be able to estimate all direct patient-level healthcare costs incurred by the public third-party payer for both the intervention and control groups. In particular, we will include costs of hospitalizations, ED visits, physician services (i.e. primary care, psychiatry and other) and diagnostic tests, outpatient prescription drugs for individuals covered under the provincial public drug insurance plan, home care, long-term care, and other hospital-based care (which includes rehabilitation and complex continuing care). The costing methodology used in the algorithm includes a bottom-up/micro-costing approach to cost services at the individual level. This makes use of individual episodes of care or utilization in the healthcare system and their associated prices (or costs or amounts paid). A top-down approach, which allocates corporate aggregate (i.e. institutional) costs to individual visits or cases/episodes of care, will be applied in cases where individual unit costs are not available (e.g., for institutional care settings). In addition, we will include all costs associated with delivering both arms of the intervention. Costs will be reported in 2023 using the Consumer Price Index for Health and personal care (Statistics Canada). All costs and outcomes will be discounted at a rate of 1.5% per year, in line with the Canadian Agency for Drugs and Technologies in Health guidelines.² The incremental cost-effectiveness ratio (ICER) will be calculated as the difference in discounted mean costs between the intervention and control groups divided by the difference in attendance rates. We will use a net benefit regression approach to model probabilities of cost-effectiveness for each additional patient referred who attends their consultation appointment in the intervention compared with control group. In addition, we will undertake relevant sensitivity analyses to test the robustness of findings by varying relevant parameters, such as the discount rate. Finally, we will examine the real-world budget impact of implementing the intervention across Ontario, to estimate the cost to the Ministry of Health of implementing this model of care across the province and the potential cost-savings to the system associated with this.

REFERENCES

1. Wodchis WP, Austin PC, Henry DA. A 3-year study of high-cost users of health care. *CMAJ* 2016;188(3):182-88. doi: 10.1503/cmaj.150064 [published Online First: 2016/01/13]
2. Guidelines for the Economic Evaluation of Health Technologies. 4th ed. Ottawa, ON, 2017.

Supplementary File 1: Protocol reporting checklist based on SPIRIT guidelines

		Page
	Reporting Item	Number
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
Trial registration: data set	#2b All items from the World Health Organization Trial Registration Data Set	3
Protocol version	#3 Date and version identifier	12
Funding	#4 Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a Names, affiliations, and roles of protocol contributors	13

1	Roles and	#5b	Name and contact information for the trial sponsor	13
2				
3	responsibilities:			
4				
5	sponsor contact			
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7	information			
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10				
11	Roles and	#5c	Role of study sponsor and funders, if any, in study	13
12				
13	responsibilities:		design; collection, management, analysis, and	
14				
15	sponsor and funder		interpretation of data; writing of the report; and the	
16				
17			decision to submit the report for publication, including	
18			whether they will have ultimate authority over any of	
19			these activities	
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24				
25	Roles and	#5d	Composition, roles, and responsibilities of the	13
26				
27	responsibilities:		coordinating centre, steering committee, endpoint	
28				
29	committees		adjudication committee, data management team, and	
30				
31			other individuals or groups overseeing the trial, if	
32			applicable (see Item 21a for data monitoring committee)	
33				
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37	Introduction			
38				
39				
40				
41	Background and	#6a	Description of research question and justification for	4-5
42				
43	rationale		undertaking the trial, including summary of relevant	
44				
45			studies (published and unpublished) examining benefits	
46			and harms for each intervention	
47				
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51	Background and	#6b	Explanation for choice of comparators	4-5
52				
53	rationale: choice of			
54				
55	comparators			
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1	Objectives	#7	Specific objectives or hypotheses	5
2				
3				
4	Trial design	#8	Description of trial design including type of trial (eg,	5
5			parallel group, crossover, factorial, single group),	
6			allocation ratio, and framework (eg, superiority,	
7			equivalence, non-inferiority, exploratory)	
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10				
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14	Methods:			
15				
16	Participants,			
17				
18	interventions, and			
19				
20	outcomes			
21				
22				
23				
24	Study setting	#9	Description of study settings (eg, community clinic,	5-6
25			academic hospital) and list of countries where data will be	
26			collected. Reference to where list of study sites can be	
27			obtained	
28				
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34	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	6
35			applicable, eligibility criteria for study centres and	
36			individuals who will perform the interventions (eg,	
37			surgeons, psychotherapists)	
38				
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44	Interventions:	#11a	Interventions for each group with sufficient detail to allow	6-7
45			replication, including how and when they will be	
46	description		administered	
47				
48				
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51	Interventions:	#11b	Criteria for discontinuing or modifying allocated	6-7
52			interventions for a given trial participant (eg, drug dose	
53	modifications			
54				
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1		change in response to harms, participant request, or	
2		improving / worsening disease)	
3			
4			
5			
6	Interventions:	#11c Strategies to improve adherence to intervention protocols,	8-11
7			
8	adherence	and any procedures for monitoring adherence (eg, drug	
9		tablet return; laboratory tests)	
10			
11			
12			
13	Interventions:	#11d Relevant concomitant care and interventions that are	6-7
14			
15	concomitant care	permitted or prohibited during the trial	
16			
17			
18			
19	Outcomes	#12 Primary, secondary, and other outcomes, including the	8-10
20		specific measurement variable (eg, systolic blood	
21		pressure), analysis metric (eg, change from baseline, final	
22		value, time to event), method of aggregation (eg, median,	
23		proportion), and time point for each outcome. Explanation	
24		of the clinical relevance of chosen efficacy and harm	
25		outcomes is strongly recommended	
26			
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35	Participant timeline	#13 Time schedule of enrolment, interventions (including any	7-10
36		run-ins and washouts), assessments, and visits for	
37		participants. A schematic diagram is highly recommended	
38		(see Figure)	
39			
40			
41			
42			
43			
44			
45	Sample size	#14 Estimated number of participants needed to achieve	7
46		study objectives and how it was determined, including	
47		clinical and statistical assumptions supporting any sample	
48		size calculations	
49			
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55	Recruitment	#15 Strategies for achieving adequate participant enrolment to	7-8
56		reach target sample size	
57			
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60			

1 **Methods:**

2 **Assignment of**
3
4 **interventions (for**
5
6 **controlled trials)**
7
8
9

10	11 Allocation: sequence	12 #16a	13 Method of generating the allocation sequence (eg, 14 generation computer-generated random numbers), and list of any 15 factors for stratification. To reduce predictability of a 16 random sequence, details of any planned restriction (eg, 17 blocking) should be provided in a separate document that 18 is unavailable to those who enrol participants or assign 19 interventions 20 21 22 23 24 25 26	27 7
28	29 Allocation	30 #16b	31 Mechanism of implementing the allocation sequence (eg, 32 concealment central telephone; sequentially numbered, opaque, 33 mechanism sealed envelopes), describing any steps to conceal the 34 sequence until interventions are assigned 35 36 37	38 7
39	40 Allocation:	41 #16c	42 Who will generate the allocation sequence, who will enrol 43 implementation participants, and who will assign participants to 44 interventions 45 46 47	48 7
49	50 Blinding (masking)	51 #17a	52 Who will be blinded after assignment to interventions (eg, 53 trial participants, care providers, outcome assessors, data 54 analysts), and how 55 56 57	58 7
59	60 Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7

1 **Methods: Data**

2
3 **collection,**

4
5 **management, and**

6
7 **analysis**

<p>8 9 10 11 Data collection plan</p>	<p>12 #18a</p>	<p>13 Plans for assessment and collection of outcome, 14 baseline, and other trial data, including any related 15 processes to promote data quality (eg, duplicate 16 measurements, training of assessors) and a description 17 of study instruments (eg, questionnaires, laboratory tests) 18 along with their reliability and validity, if known. Reference 19 to where data collection forms can be found, if not in the 20 protocol</p>	<p>21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60</p> <p>7-10</p>
<p>Data collection plan:</p>	<p>#18b</p>	<p>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</p>	<p>7-10</p>
<p>Data management</p>	<p>#19</p>	<p>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</p>	<p>7-9, 12</p>
<p>Statistics: outcomes</p>	<p>#20a</p>	<p>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</p>	<p>10-12</p>

1	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and	11
2			adjusted analyses)	
3	analyses			
4				
5				
6	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	11
7			adherence (eg, as randomised analysis), and any	
8	population and		statistical methods to handle missing data (eg, multiple	
9	missing data		imputation)	
10				
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16	Methods: Monitoring			
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18				
19	Data monitoring:	#21a	Composition of data monitoring committee (DMC);	12
20			summary of its role and reporting structure; statement of	
21	formal committee		whether it is independent from the sponsor and	
22			competing interests; and reference to where further	
23			details about its charter can be found, if not in the	
24			protocol. Alternatively, an explanation of why a DMC is	
25			not needed	
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36	Data monitoring:	#21b	Description of any interim analyses and stopping	12
37			guidelines, including who will have access to these	
38	interim analysis		interim results and make the final decision to terminate	
39			the trial	
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46	Harms	#22	Plans for collecting, assessing, reporting, and managing	12
47			solicited and spontaneously reported adverse events and	
48			other unintended effects of trial interventions or trial	
49			conduct	
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1	Auditing	#23	Frequency and procedures for auditing trial conduct, if	12
2			any, and whether the process will be independent from	
3			investigators and the sponsor	
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9	Ethics and			
10				
11	dissemination			
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13				
14	Research ethics	#24	Plans for seeking research ethics committee / institutional	12
15			review board (REC / IRB) approval	
16	approval			
17				
18				
19	Protocol	#25	Plans for communicating important protocol modifications	12
20			(eg, changes to eligibility criteria, outcomes, analyses) to	
21	amendments		relevant parties (eg, investigators, REC / IRBs, trial	
22			participants, trial registries, journals, regulators)	
23				
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29	Consent or assent	#26a	Who will obtain informed consent or assent from potential	7-8
30			trial participants or authorised surrogates, and how (see	
31			Item 32)	
32				
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37	Consent or assent:	#26b	Additional consent provisions for collection and use of	7-8, 12
38			participant data and biological specimens in ancillary	
39	ancillary studies		studies, if applicable	
40				
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44				
45	Confidentiality	#27	How personal information about potential and enrolled	7-8
46			participants will be collected, shared, and maintained in	
47			order to protect confidentiality before, during, and after	
48			the trial	
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55	Declaration of	#28	Financial and other competing interests for principal	13
56			investigators for the overall trial and each study site	
57	interests			
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1	Data access	#29	Statement of who will have access to the final trial	13
2			dataset, and disclosure of contractual agreements that	
3			limit such access for investigators	
4				
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9	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	12-13
10	trial care		compensation to those who suffer harm from trial	
11			participation	
12				
13				
14				
15				
16	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	12-13
17	trial results		results to participants, healthcare professionals, the	
18			public, and other relevant groups (eg, via publication,	
19			reporting in results databases, or other data sharing	
20			arrangements), including any publication restrictions	
21				
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29	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	12-13
30	authorship		professional writers	
31				
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34	Dissemination policy:	#31c	Plans, if any, for granting public access to the full	12-13
35	reproducible		protocol, participant-level dataset, and statistical code	
36				
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39	research			
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41				
42	Appendices			
43				
44				
45	Informed consent	#32	Model consent form and other related documentation	7-8, 12
46	materials		given to participants and authorised surrogates	
47				
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49				
50	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	12
51			biological specimens for genetic or molecular analysis in	
52			the current trial and for future use in ancillary studies, if	
53			applicable	
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For peer review only