Research Protocol

Examining a digital health approach for advancing schizophrenia illness self-management and provider engagement

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Summary

The effective treatment of schizophrenia is very challenging due to a number of factors. These include issues such as poor engagement with treatment plans and care providers, limited contacts with providers due to under-resourced health services, and the challenges inherent to schizophrenia symptoms. The outcomes of these problems include frequent, lengthy, and costly hospital readmissions, low quality of life, high levels of distress, and difficulties engaging in valued community roles. Digital Health technologies are a promising model to help address these problems. They are a low cost and accessible form of support and have not been substantively developed or studied for people with schizophrenia spectrum illnesses. In this study, we will test the feasibility of one such technology that is in development: App4Independence (A4i). A4i provides customized coping prompts, peer-peer networking, and a portal that facilitates better provider engagement. This research will provide critical information in the development of this new technology to address a key problem in the field - how to enhance care in a resource-limited context where provider-patient contacts are brief, infrequent, and rely on in the moment recall and self-advocacy by patients. These findings will lay the groundwork for a larger program of research and software development that will (i) validate the technology across multiple sites and, (ii) catalyze engagement with healthcare systems and caregiver networks to scale out access to this promising resource.

1. THE NEED FOR A TRIAL

1.1 What is the problem to be addressed?

Relative to the large investments in digital health strategies for conditions such as anxiety and depression, the development of technology to facilitate care for people with schizophrenia-spectrum illnesses is limited. This scenario persists despite the routine use of mobile technologies by individuals with schizophrenia. Accordingly, **the focus of this trial is on the feasibility of a schizophrenia-focused digital therapeutic**: App4Independence (A4i). A4i is a platform that uses feed, text-based, and provider portal functions to enhance provider engagement and illness self-management.

Advancing digital health (dHealth) interventions in schizophrenia is important in the Canadian health care context. Schizophrenia is responsible for 3.8% of hospital admissions in Canada and

accounts for an estimated annual cost of 6.85 billion dollars annually in healthcare and lost productivity[1]. Associated challenges include high rates of completed suicide, low quality of life, poor access to non-pharmacological interventions, and pharmacological interventions that have suboptimal effects[2]. Overall, schizophrenia has proven extremely difficult to treat as is evidenced by high relapse and re-admission rates[1]. The most common contributors to relapse in schizophrenia are medication non-adherence, social isolation, and inadequate supports[3-6].

There has been extensive commentary on the system of care problems for people suffering from schizophrenia. Within these systems, the primary point of engagement – interactions and relationships with providers – are challenged. On inpatient units, patients are frequently dissatisfied with custodial approaches to care[7-8] and in outpatient settings, the frequency and nature of contacts with providers are often inadequate. Common concerns include a lack of shared-decision making in treatment, limited support in illness self-management, and insufficient time with providers[9-11]. **Such sub-optimal provider engagement and outpatient support has been directly implicated in treatment adherence rates of 50% or less[12] and poor quality of life[13-14].** In this context, leveraging technology to enhance engagement in outpatient care and provide support with illness self-management holds considerable promise to (i) ameliorate aspects of schizophrenia that challenge provider contacts (e.g., cognition, anxiety)[15-16]; (ii) facilitate provider access to more detailed information from which to base care decisions; (iii) lead to patients feeling more empowered in the care process[17]; and (iv) lead to enhanced treatment engagement with implications for lower relapse rates[10-11,18].

1.2 What is the principal research question to be addressed?

Is the A4i digital health platform a feasible approach for improving outcomes and care engagement for individuals with schizophrenia?

1.3 Why is a trial needed now?

To date, evidence for technology-enabled approaches to enhance outcomes for individuals with severe mental illnesses is limited. In particular, feasibility has proven to be a major challenge. In-office technologies require space, infrastructure, and staffing, and have proven difficult to implement due to expense[19-20]. Web-based approaches are less expensive but have demonstrated high rates of attrition[21]. There are very few mobile applications targeting schizophrenia, in contrast with the large volume of apps for conditions such as anxiety and depression[23]. The reasons for such a gap are unclear given the observation that over 80% of individuals with schizophrenia and other psychoses routinely use mobile technology and the majority are interested in using technology to assist with illness management[24,25-27].

A number of pilot studies suggest that schizophrenia-targeted mobile and online applications in areas such as cognitive remediation are feasible and do not result in any noted risks[25,28]. Most directly relevant to this proposal is the work of Ben-Zeev and colleagues[29]. Their FOCUS app has features that include daily activity prompts, brief self-assessments, and coping strategy tips.

Preliminary investigation of this application indicated no risks associated with its use and sustained use over several months. Another dHealth approach in this area that has shown feasibility is PRIME, developed by Schlosser and colleagues[30]. The core function of PRIME is providing users with access to Masters-level clinicians who provide strategy coaching. There is, however, a paucity of trial data. One randomized trial of text-based weekly symptom monitoring showed no difference in hospitalization over a 1-year period[31]. Another randomized trial of automated text messaging (generic messaging regarding treatment adherence) did not demonstrate significant effects in re-hospitalization[32]. Lastly, the PRIME app described above was recently trialed[33] and demonstrated, compared to treatment as usual, improvement in some social engagement and depression metrics though no change in psychosis symptoms, quality of life, or functioning. Recent systematic reviews[34,35] did not identify any other randomized trials nor did our own search for the purposes of this proposal.

App4Independence (A4i)

The study proposed here, while early stage, would be one of the most rigorous trials conducted to date of a digital health approach tailored to schizophrenia. This test is needed because (i) this is a rapidly advancing area in which there are multiple calls for better feasibility and effectiveness data, (ii) if ultimately effective, A4i will provide a cost-effective approach for a major healthcare problem, and (iii) this study is an important step for the development of A4i now that we have pilot data for our prototype. A4i is different from other early-stage technologies for schizophrenia in several ways. Unlike FOCUS which relies on providers giving patients smartphones with data plans, A4i operates on the individual's own phone with or without data. This is a key consideration in under-resourced service settings. Unlike PRIME which also has involved providing phones to patients, A4i does not have as its core function the ability to connect mental health professionals in real time – another expensive feature.

Specific A4i functionality includes (see figure 1 and for a demo - https://youtu.be/GNzxIuOpPJg):

- Addressing social isolation and cognitive challenges through personalized prompts, scheduling of activities, and connections to a range of resources.
- Fostering illness self-management through evidence-informed content that makes suggestions and provides resources relevant to coping with psychosis symptoms, negative symptoms of schizophrenia, cognitive challenges, motivation and anxiety. The content concentrations are determined by an algorithm built from a short screener completed at the time of upload.
- A peer-peer engagement platform that facilitates strategy/tip sharing between users (anonymous and moderated).
- Daily wellness and goal attainment check-ins to highlight mental health trajectories.
- An ambient sound detector with an oscilloscope-type indicator that assists individuals with auditory hallucinations in the effort to separate hallucinations from real sounds (unique to A4i) with users able to rate and track their responses in terms of success with discernment.
- Passively collected data on phone use as a proxy for sleep and activity levels that in the future may prove helpful in developing predictive analytics regarding relapse (unique to A4i).

- A provider dashboard (figure 2) that, with appropriate consent, is provided to the individual's provider prior to their appointment (for this trial provided via study staff, in future will be accessible via electronic medical record). This was co-designed with psychiatrists and patients and generates a summary of day-to-day wellness ratings, responses to reminders, goal progress, self-reported medication adherence, and a 'notes for my provider' function (e.g., "Please can we discuss my medications making my mouth very dry."). (Unique to A4i).

A4i was developed by CAMH and the digital health company MEMOTEXT**.** MEMOTEXT and CAMH are collaborators in the joint venture A4i with both teams contributing their experience and expertise. MEMOTEXT concentrates on technology development and maintenance drawing from their experience in digital health interventions. The CAMH team contributes to content development, research, and commercialization through the Technology Transfer Office**.** An iterative design and development model[36] was employed to determine the requirements of A4i:
Stage 1: Literature, patent, and commercial market reviews.
Stage 2*:* Focus groups with patients, family, psychiatrists and case managers.
Stage 3: An initial test of a beta version by 5 individuals with psychosis for one week.
Stage 4: Review of initial test findings, iteration of app design.
Stage 5: Pilot testing by 38 individuals over a 1-month period followed by further iteration.

In sum, this trial is needed now as it will make a significant contribution to the evidence in this emerging area and it is a test of a unique technology. Given the high relapse rates amongst schizophrenia populations and the $1,000+/day cost of inpatient care, even modest effects for a technology such as A4i are of note given its relatively low expense and ready access. Furthermore, this line of investigation is being undertaken at a level of rigour that is rarely applied to digital health approaches[23]. Such work is essential in the larger effort to ensure that the public and service providers are not misled by unsubstantiated claims of effectiveness. Lastly, this work will bring important information forward to broaden the conversation about measurement-based care in psychiatry[37].

1.4 How will the results of this trial be used?

This trial will provide information that will be critical in determining if this technology is ready to move on to an effectiveness trial or if further iterations are needed. With these requirements established, future trials would move on to examine (i) effects observations with larger samples, (ii) comparison with a sham condition such as a generic wellness app, and (iii) sustainment of use and gains over longer periods. Knowledge exchange activities will include: (i) publication in a relevant academic journal, (ii) presentation in at least one international conference (e.g., Schizophrenia International Research Society Conference) and one e-health industry conference (BIO), and (iii) a webinar advertised through research, practice and administration networks (e.g., Health Quality Ontario, Council of Academic Hospitals of Ontario; Orygen-Australia; RAISE trial network-United States).

1.5 Are there any risks to the safety of participants involved in the trial?

None of the published work in the area of digital health approaches for schizophrenia has identified significant user risk. The only potential exception that we found was a user of FOCUS became “paranoid about their mobile phone and broke it”. We have not experienced any incidents of concern in our pilot testing of A4i. We have been, however, cognizant of potential risks surrounding the peer-peer engagement platform.

With respect to the peer-peer engagement platform, participants will craft their post on their phone in A4i. Once they submit, their post will not automatically appear in the peer-peer engagement platform feed. Their post is first reviewed by a study RA on the A4i desktop portal to confirm it is eligible for posting. If the post is eligible, the RA will approve the post from the portal and the post will appear on the peer-peer engagement platform feed. Privacy is also maintained on the peer-peer engagement platform through the use of non-identifiable avatars and nicknames in posts.

Ineligible posts contain content such as:

a) Personally identifiable information

b) A question for A4i or request for app help

c) Inappropriate content (foul language, offensive, disrespectful, advocating for med non-adherence)

d) Expressing negative thoughts (suicidal, etc.)

e) Promotion of personal items/products/etc

If an ineligible post is identified by the RA, they will reject the post so it does not appear on the peer-peer engagement platform feed. In the event of content resembling items (a), (b) and (e), the RA will connect with the participant to discuss the post and remind them of the guidelines for posting. In the event of content resembling items (c) and (d), the RA will immediately connect with the participant to discuss the post, remind them of the guidelines for posting and, if necessary, assess risk. If any risk is present, the RA will immediately inform the study PI and the individual’s care provider with the participant consent.

There is also the possibility that participants (i) find the peer-peer engagement platform feed intrusive or (ii) find the content or other functions of the app distressing if, for example, it engages some delusional interpretation.

SOP’s pertaining to adverse events and serious adverse events (HSR 206 & 207) will be followed should the nature of any of the above events qualify.

For example, there was an instance of our moderator of the peer-peer strategy network intercepting a post that might be a problem (incoherent content and statement about ceasing medication). Our response was to reach out to the individual to discuss the post and assess risk

(no association with A4i use was indicated) and inform the individual's care provider with the participant consent.

Participant privacy is another essential consideration. This risk is mitigated through tri-council protocols for data safety and storage, and MEMOTEXT only having access to phone numbers and provider dashboard data, with that information stored and managed in compliance with provincial and federal data safety and privacy requirements and approved by the CAMH Privacy Officer and Research Legal. Additionally, as mentioned above, posts submitted to the peer-peer engagement platform that contain identifying information will also be intercepted by research staff during the screening process to prevent a breach privacy. As before, we will reach out to the individual to discuss the post and remind them of the requirement to avoid posting identifying information.

Virtual Risk Mitigation Adjustments

Should a participant indicate any risk to themselves or others during a remote assessment or interview, the PI or a clinical back up will be available to join the call to ensure the participant's well-being and safety. As indicated above, the RA will also inform the individual's care provider.

2. THE PROPOSED TRIAL

Virtual Adjustment Overview

Due to the onset of COVID after the original protocol was developed, all study procedures have been adjusted to allow for phone and/or video administration. This should in most instances not pose a significant barrier as this study involves a virtual intervention and a participation requirement is ownership of a smartphone. Other procedures done virtually include all recruitment activities, screening, consent, and administration of the outcome surveys described below with some adjustments. If the study participation is not possible for any reason due to the cessation of in person engagement and assessment, we will retain the person's contact information with their consent and reconnect later in the trial if/when in person contacts can more readily be engaged in. Additionally, when contact processes/permissions return to normal we will resume in person administration of some or all of the above procedures

2.1 What is the proposed trial design?

This feasibility study[38,39] will employ a two-arm, randomized controlled trial design (see figure 3). The design will be single blind as participants will be aware of A4i exposure with the assessor blinded. Measures will be completed by both care providers and persons receiving care.

This test will determine:

1) Progression criteria including: (i) Meeting the recruitment target and assessing recruitment rate considerations that may be unique to hospital and community service sites and achieving a representative sample. (ii) Obtaining outcome data for at least 80% of those recruited. An 80%

target would seem indicated given retention in the small number of previous studies ranging from 88% (3 months of tech use - PRIME) to 94% (6 months of tech use - FOCUS). Shorter tests have yielded retention closer to 100% (e.g., the 1 month pilot of A4i). (iii) Sustained use of A4i for an average of at least 75% of the weeks in which it was installed (based on a finding of 80% for FOCUS in a 6-month test period). (iv) A lack of emergence of significant safety concerns. (v) Patient and provider satisfaction with using the provider portal in clinical contacts.

2) Preliminary outcome data in domains hypothesized to be relevant to the likely effects of A4i including symptomatology, treatment engagement, clinical alliance, and quality of life as compared with TAU. These data will help to inform and refine A4i treatment target hypotheses, assist with sample size determination and outcome timeframes for effectiveness trials.

2.2 What are the planned trial interventions?

In the treatment condition A4i (as described above) will be installed on participant phones following screening and baseline assessment completion. Should participants (i) show no interactions with the app in the first two weeks or, (ii) respond to an app prompt regarding A4i utility that there is a problem, they will receive a phone call from a research assistant uninvolved in assessments to coach through and trouble shoot challenges. Both control and experimental condition participants will be receiving standard outpatient care (TAU) for psychosis involving routine (at least monthly) contacts with a care provider. The centralized recruitment process at CAMH facilitates tracking and control over participation in other treatment studies that may confound the findings. For community sites, participants will be asked about their involvement in any other trials (less likely than CAMH) with study implementation adjusted to address potential confounds. Note that those assigned to TAU will be provided with access to A4i after their 6-month evaluation for a period of 6 months if they are interested in this option.

2.3 What are the proposed practical arrangements for allocating participants to trial groups?

Blocked randomization, stratified by gender, will be employed to ensure balance in sample size between treatment and control groups and gender representation. Stratification by study site (CAMH versus community agency) will also be undertaken to determine feasibility questions that may differ as a function of same. REDCap will be employed and will allocate based on the computer-generated randomization list. Allocation concealment will be achieved since the person making the assignment will have no awareness or control over the randomization schedule.

2.4 What are the proposed methods for protecting against sources of bias? Comparison with TAU is single blind as it is not possible for participants to have adequate information to consent without knowing that they are or are not using the technology. Randomization will be secure as noted above. Statistical analyses will be performed by a biostatistician uninvolved in study operations and kept blind to treatment conditions. During all operational meetings steps will be taken to ensure that participant identifiers are managed such that the risk of unblinding to assessors is minimized. Finally, participants will be asked to not discuss with the assessor whether or not they used A4i.

2.5 What are the planned inclusion/exclusion criteria?

Inclusion Criteria (participants with schizophrenia):

1) Participants will be adults, 18 years of age or older, with a chart diagnosis of a DSM-5 schizophrenia spectrum illness confirmed by a structured diagnostic interview (SCID-5)[40].
2) All participants will be engaged in outpatient psychiatric treatment.
3) Proficiency in English.
4) Own and use an Android or iOS smartphone.

Exclusion Criteria

1) Lack of capacity with no identified substitute decision maker.
2) Intellectual disability.
3) Not currently residing in Canada

Criteria (service providers): Service providers will be psychiatrists and case managers engaged in the care of the participants.

2.6 What is the proposed duration of treatment period?

Evaluations will be completed at baseline and 6 months, which is the time period used in tests of other comparable dHealth approaches[29]in which signals in key metrics were observed. Participants in the TAU group will be offered an a4i app account following the 6-month follow-up visit. The only difference between the active A4i app accounts and the TAU app accounts is the involvement of clinicians. We will not onboard clinicians for the TAU group should they choose to try out the app after study participation. At the 6-month follow-up, active group participants will be asked if they would like to continue on the app, and if so informed that their clinician may not choose to continue to use the app and to communicate with clinicians through typically modes of contact. No app-use metrics will be collected from this period of time for the purposes of the RCT and there will be no further measures collected after the 6-month follow-up. Remaining A4i accounts will be deactivated at the end of the study. If at any point in the study (including after the 6-month visit), participants no longer wish to participate/have an app account, they will be instructed that they can delete the app and we will deactivate their account.

2.7 What is the proposed frequency and duration of follow up?

For the purposes of this trial only pre-post measures will be completed. It is also of note that follow up data is less relevant for dHealth approaches for which ongoing use is anticipated rather than clear end dates as are the case with other clinical interventions.

2.8 What are the proposed primary and secondary outcome measures?

Feasibility Indicators: (1) Assessment of numbers approached, successfully screened, consented, and numbers assessed at both time points to evaluate recruitment and retention. Additionally, recruitment rates will be compared between CAMH and collaborating community sites. (2) Objective A4i use metrics will be collected including information on the time,

frequency, and nature of use for each participant. (3) An unblinded RA will contact treatment arm providers and participants to complete a brief semi-structured interview assessing strengths (generally and in clinical interactions) and limitations of A4i and any risks not otherwise reported or observed during study operations. For participants who switch care providers (i.e., due to factors unrelated to the study, clinical care changes decided by the care team) part way through the study, we will confirm verbally with the participant whether they consent to their new care providers participating or if they withdraw their consent for the participation of care providers. This does not impact the participant's ability to participate as they do not need to have a clinician participate with them to be eligible for the study. If the participant is agreeable to have their new clinician participate, we will contact and consent the new care provider to the study. On a case-by-case basis based on participant preference, how often they see each care provider, and how far into the study the change in provider occurs, we may collect data from both care providers in order to accurately capture the user experience of the participant and their care providers. Use of A4i generated summaries for providers will be assessed both in terms of provider and participant reports of quality in clinical interactions and also frequency and duration of use in a given clinical interaction. Patient satisfaction will also be examined with the 26-item scale used by Ben-Zeev and colleagues[28]. (4) Safety will be assessed through information gathered via all study-related interactions with significant safety concerns operationalized as one or more critical incidents occurring in which there is evidence of an association between the incident and A4i use. Worsening in one or more outcome areas as compared with TAU would be another domain that would be flagged.

Virtual Assessment and Interview Administration Adjustment

A4i Installation

Installation of A4i will be scheduled via email and/or telephone by the study RA shortly after the consent discussion. Installations will be conducted via WebEx using either the teleconferencing or videoconferencing features depending on the participant's preference. Participants will be provided with the meeting link or phone number to join the WebEx call. Participants will be guided by the RA through installation using vocal instructions. The study RA will also use screen sharing to show the participant images of what a phone screens should display at each step during installation.

Dashboard Summaries

Summaries of the dashboard data will be sent to providers once per month via CAMH Secure File Transfer and will be password protected.

First Month Check-ins

During the first month, participants will be contacted via telephone for a brief check in about their experience with the app to see if they are having any challenges using the technology.

Problems will be addressed by study staff as soon as possible. In addition, if participants report technical difficulties to the research team, the research team will follow-up dependent on level of participant need or by participant request. Number of follow-up touch points will be recorded for each participant.

Assessments

Assessments will be scheduled via email and/or telephone by the study RA. All assessments will be conducted via WebEx using either the teleconferencing or videoconferencing features depending on the participant's preference. Participants will be provided with the meeting link and phone number to join the WebEx call. The study RA will also use screen sharing to show the participant the questionnaires to assist with completing the assessment. Participants will be given the option to complete self-reports as surveys sent to their email should there be any challenges with scheduling and availability. Email addresses will not be stored with the assessment data in REDCap, and will be deleted from the survey invitation log after data has been collected.

If using phone administration, the non-verbal ratings in the PANSS scale will be left blank. This aspect of the PANSS is a minor component and is not anticipated to have a substantial impact on scale integrity. The SANS scale will not be scored given its behavioural observation emphasis with it not being possible to complete by phone and, with video, administration would lead to serious concerns about a valid and reliable administration. This will not substantially impact the trial as this is a secondary, exploratory outcome. When contact processes/permissions return to normal we will resume in person administration of some or all of the above procedures including re-initiating SANS administration.

Interviews

Semi-structured qualitative interviews and the phone surveys regarding app feasibility and usability will be audio-recorded (audio only) and transcribed verbatim by a study RA. No clinical interviews/assessments will be recorded.

Clinical Outcome Metrics:

1. Given the observation of improvement in psychiatric symptomatology in pilot testing and the importance of symptom severity for the quality of life and other key outcomes for people with schizophrenia[41], symptom severity is considered the primary outcome. General symptomatology will be assessed using the 53-item, 5-point likert scale Brief Symptom Inventory[42]. Schizophrenia-specific symptomatology will be assessed with the Positive and Negative Syndrome Scale[43] with negative symptoms assessed with the Scale for the Assessment of Negative Symptoms[44].
2. *Treatment Engagement* was not fulsomely tested in the A4i pilot study due to its short duration, though is of critical important to considerations such as rehospitalization[3]. Accordingly, Treatment adherence will be measured using (i) the 4-item Brief Adherence Rating Scale[45] with

responses obtained by both providers and participants to assess medication adherence, (ii) the 5-item, 6-point likert scale Medical Outcomes Study general adherence scale[46] to capture broader adherence to treatment recommendations (again triangulated with provider responses) and (iii) the percentage of scheduled appointments attended through EMR audit at CAMH or provider report at non-CAMH sites. This broader approach to assessing adherence is necessary, as it is a construct that captures both medication regimen adherence and care team engagement.

3. *Provider-Patient Clinical Alliance* will be assessed with STAR[47]. This 12-item measure employing a 5-point likert scale has been used extensively in studies of outpatient care for severe mental illness. This measure supports patient and provider versions.
4. The Heinrichs-Carpenter *Quality of Life Scale*, has 21 items, is well validated for schizophrenia[48], and captures sense of purpose, motivation, emotional and social interaction, role functioning, and engagement in regular activities.
5. *Descriptive Measures* include core demographics (ethnicity, sexual orientation, age, education, etc.; assessed at time 1 and service use history (hospitalization) assessed at both time points and triangulated by providers and schizophrenia participants. Gender, specifically, will be determined through baseline self-report of female, male, transgender (male-female or female-male), non-binary, or other.
6. *Substance Use* will be measured using the substance use subscale of the Global Appraisal of Independent Needs, Short Screener (GAIN-SS). This subscale is a brief (5-item) self-report questionnaire which captures the frequency of challenges related to substance use. This is a validated screening tool[49]. The scoring of this subscale will be minimally altered to include an additional anchor from 2-6 months and 7-12 months in order to match our intervention length and better understand changes within the intervention period. Scores will be pooled to match the manualized scoring.

2.9 How will the outcome measures be measured at follow up?

As noted above.

2.10 What is the proposed sample size and what is the justification for the assumptions underlying the power calculations?

We propose to recruit in total 160 participants, i.e. 80 per group. The sample size determination was guided by two underlying power considerations driven by our aims. First, we expect to establish feasibility of the trial by obtaining reliable estimates of feasibility indicators, for example retention rate and completion rate of key measurements[50]. With 160 participants we would achieve a small margin of error of 2.8% for an expected retention rate (85%). The margin of error increases to 3.7% for estimating the minimum proposed completion rate of measurement (expected at 80%) with attrition taken into account. Second, while we don't anticipate to have full power to detect treatment effect compared to TAU given feasibility test objective of this trial, the proposed sample size will give us a reasonable chance (64%) to detect a small to moderate effect (ES = 0.40). The small to moderate effect size is in line with some of the findings in the pilot study – with the caveat that the pilot was an uncontrolled test of outcome. With longer treatment period, we expect to see larger effects as well. The power calculation assumed a level of significance of 0.05 and accounted for 15% attrition.

2.11 If applicable, are health service research issues be addressed?

As noted above, several health service engagement metrics will be captured. Economic analyses would be optimal in future trials and the potential effects on quality of life are probed here.

2.12 What is the planned recruitment rate? How will the recruitment be organized? Over what time period will recruitment take place? What evidence is there that the planned recruitment rate is achievable?

Recruitment will occur through two primary sources. First, recruitment will occur through a centralized CAMH referral process located in the psychosis early intervention service and the schizophrenia division, as well as advertisements and contacts with clinicians in other CAMH schizophrenia services. Across these two sets of CAMH services approximately 3-4000 patients are annually registered. In the pilot study of 1 month of use (not including an early beta test, recruitment period was September 2017-March 2018) the centralized early psychosis recruitment process was the primary referral route and yielded a rate of 5.5 study completers/month. In the proposed trial, along with this centralized early intervention recruitment process, a greater emphasis will also be placed on recruitment through general schizophrenia services at CAMH.

For non-centralized recruitment process participants, case managers will provide an initial introduction to the study using the script in Appendix 1. A trained research personnel will obtain informed consent. Participants will be provided with a clear explanation of the objectives, procedures, risks and benefits of the study and all questions will be answered. Questions will be asked of subjects to ensure that they understand the nature of the research, the risks and potential benefits of study participation, and their rights as research subjects prior to obtaining their signature on the informed consent document. Because consent is an ongoing process, we will continue to educate participants about the nature of the research and address any questions that may arise throughout the course of the study. If a participant is incapable of providing written informed consent, a member of the research team will connect with them and their Substitute Decision Maker (SDM) and provide the same briefing prior to obtaining the SDM's consent.

For centralized recruitment, as part of the CLEARR (Clinical Engagement and Research Recruitment) initiative, a CLEARR Coordinator will identify potential participants and notify the research team and the participant's clinician about the participant's eligibility to participate in the study. The clinician will then ask the participant if they would be willing to meet with a study team member about participating. Only with participants' agreement will they be approached by research personnel (the RA). For participants who are recruited through the Slaight Centre for Youth in Transition's (SCFYT) centralized recruitment process, they will then be pre-screened with the REB approved "pre-screen form" that is implemented across all Slaight studies to allow for alignment and data sharing and recruitment; this data will be entered into a password protected and restricted pre-screen tracking database. For participants who are not recruited through the SCFYT centralized recruitment process, the study RA will still then use the Slaight pre-screen form mentioned above to pre-screen the participant. Once a participant has completed

the ICF, the RA will inform the CLEARR Coordinator and clinician of the participant's enrollment into the study. All CLEARR procedures will adhere to SOP HSR228.

In addition, this study will utilize centralized efforts in the Schizophrenia Division. The Schizophrenia Division Centralized Recruitment Procedure will be used to recruit participants for this study. The Centralized Research Personnel will prescreen patients for eligibility to participate using minimal inclusion/exclusion criteria outlined in REB #036/2020. Once a patient has been identified, the Centralized Research Personnel will send preferred contact information to the Study Specific Research personnel who will reach out to the patient to further explain the study. No information will be passed to the Study Specific Research Personnel prior to the patient's verbal consent.

We will request the participant inform anyone on the research team if they would not like their pre-screen data shared with the SFCYT/ Schizophrenia Division teams and any other secondary investigator.

We will also contact former research participants who participated in previous studies and provided informed written or verbal consent for future contact. Recruitment script for participants who previously expressed interest in future studies is located in Appendix 2.

Following provision of written informed consent, all participants will be assessed for suitability for inclusion in the study based on the inclusion and exclusion criteria. If it is deemed necessary, research staff may review participants' CAMH medical charts [for CAMH participants] to obtain additional information to confirm their eligibility or to obtain clinically relevant information for research purposes.

All clients will be given the option to participate. Participation in the study is voluntary. The decision to participate will not affect patients' receipt of treatment or clinical services. Participants will be informed that they have the option of terminating their participation at any time, without consequence and that no new data will be collected on them. Any existing data will be anonymized.

The second major source of recruitment will be community provider sites in Toronto. These three sites, all with high rates of contact with the target population, are CMHA Toronto, the Schizophrenia Society of Ontario, and Progress Place. At community sites, engagement strategies will include presentations by the PI and research staff, posters distributed electronically, and introductions to clients by providers oriented to A4i. These methods of recruitment will be expanded provincially, and nationally. Specifically, we will be targeting professional networks and organizations that are relevant to schizophrenia populations and treatment. These will include CMHA and Schizophrenia Society sites and associated networks.

Additionally, our approved poster advertisement will be displayed on on the A4i website (https://www.a4i.me/), as well as we will advertise the study on CAMH's 'Find a Study' website.

Key differences between the pilot and this trial are the longer duration of A4i use (6 mos vs 1 mos) which may slow recruitment and the longer duration of the study which, for some aspects of the strategy, may improve recruitment as providers become better oriented and refer more routinely. Accordingly, it is conservatively estimated that we should be able to obtain a recruitment rate of 7-8 participants per month on average. Recruitment would occur over a period of 21 months.

Participants will receive a total of $80 as honourarium to compensate for their time. $40 will be provided for the baseline assessment and another $40 will be provided for the 6-month follow-up. Participants will also be provided with transit fare if needed. Participants will have a choice between cash, or e-gift card selection for the same amount. If the participant chooses an e-gift card, the card code is emailed to them right away and is redeemable online. Care providers participating in the study will not receive financial compensation.

Participants will be notified both verbally and in the consent form that using A4i will consume some of their cellular data package, and will be offered $25 as compensation for a data top-up to mitigate the chance of data overages.

Virtual Recruitment Adjustment

Informed consent of all participants (clients and care providers) will be documented using the REDCap e-Consent Framework and in compliance with SOP HSR229.

Clients

CLEARR, non-centralized and community organizations outside of CAMH will maintain their procedures for recruiting participants up until the first contact between the study RA and the client. At that point, if the prospective participant is interested, the clinician or case manger will provide the participant's phone number to the study RA with the prospective participant's consent. The RA will then connect with the prospective participant via telephone using the Initial Telephone Contact Script–Client in order to introduce the study and gauge interest in participating. Alternatively, with the permission of all involved, a member of the research team may schedule to call the provider at the client's next appointment time. As part of the Initial Telephone Contact Script–Client, if they are interested in participating, the member of the research team will obtain the prospective participant's consent for use of email to communicate and confirm their preferred method for a consent discussion – telephone or WebEx.

The prospective participant will then be provided via email with a read-only copy of the ICF via REDCAP prior to conducting the consent discussion. The link may be used by the prospective

participant as many times as they wish (it is not single-use). Upon clicking the link, the prospective participant will review the landing page, and continue on to the ICF text. The entire contents of the ICF will be displayed according to the current REB approved consent form, minus the signature/attestation page(s). If they are still interested in participating, a consent discussion will be scheduled via email to be conducted using the method they specified in the initial telephone contact. The informed consent discussion will be documented using the Informed Consent Process Checklist & Note.

At the time of the consent discussion, if the potential participant is a Slaight Centre client, the study RA will administer the Slaight Pre-Screen form. Following the consent discussion, the prospective participant will be sent a link to the e-consent via email or the chat feature in WebEx. The participant will complete the e-consent and be provided with the option to download and/or email themselves the signed ICF. If email is chosen, the email will only be used for this purpose (it is not retained by REDCap).

Following the participant signature, the person conducting the consent discussion will complete the Person Conducting Consent Discussion Attestation Page. PDF copies of the signed ICFs and Attestation pages will be retained in the REDCap File Repository. The research team will provide the participant with a copy of the fully signed ICF via Secure File Transfer.

SDM

If a prospective participant has an SDM, as part of the Initial Telephone Contact Script – Client with an SDM, the RA will also request the SDM's telephone number or consent from the prospective participant to request the SDM's telephone number from their case manager.

The study RA will then connect with the SDM over telephone using the Initial Telephone Contact Script for SDMs. If they are interested in the client participating, the member of the research team will obtain the SDM's consent for use of email to communicate and confirm their preferred method for a consent discussion aligns with the prospective participant.

Both the SDM and the prospective participant will then be provided via email with a read-only copy of the ICF via REDCAP prior to conducting the consent discussion. The link may be used by the SDM and prospective participant as many times as they wish (it is not single-use). Upon clicking the link, they will review the landing page, and continue on to the ICF text. The entire contents of the ICF will be displayed according to the current REB approved consent form, minus the signature/attestation page(s). If both the SDM and the prospective participant are still interested in participating, a consent discussion will be scheduled via email to be conducted using the method agreed upon in the initial telephone contact. The consent discussion may be scheduled individually or as a group with both the SDM and prospective participant so long as

both are comfortable with that. The informed consent discussion will be documented using the Informed Consent Process Checklist & Note.

For Slaight Centre clients, at the time of the consent discussion the study RA will administer the Slaight Pre-Screen form. Following the consent discussion, the SDM will be sent a link to the e-consent via email or the chat feature in WebEx. The SDM will complete the e-consent and be provided with the option to download and/or email themselves the signed ICF. If email is chosen, the email will only be used for this purpose (it is not retained by REDCap).

Following the SDM signature, the person conducting the consent discussion will complete the Person Conducting Consent Discussion Attestation Page. PDF copies of the signed ICFs and Attestation pages will be retained in the REDCap File Repository. The research team will provide the participant and SDM with a copy of the fully signed ICF via Secure File Transfer.

Providers
Providers will be consented via the same virtual method as clients outlined above after their client has consented into the study. The study RA will use the telephone number the care provider used to call and inform the RA about their prospective participant. If participants were not referred to the study by their care provider, contact information will be collected from the client. The study RA will use the Initial Telephone Contact Script for Providers. If the care provider does not consent to being part of the study the participant will be informed of this. Participants are also trained on the use of the app and that this is not a means of communication with their care providers and to use regular means of communication to contact them.

Compensation
Compensation will be delivered to the participants by mail while operations remain offsite, or via email in the form of e-gift cards (depending on participant preference). The study RA will follow up with the participant via telephone and email to ensure they received the compensation. Once they have, we will request they send an email confirming it has been received. Participants who are required to reconsent in the study will be offered an additional $10.00 to reimburse them for their time, compensation is not dependent on them signing the consent addendum.

2.13 Are there likely to be any problems with compliance? On what evidence are the compliance figures based?
Engagement in the use of A4i once uploaded is expected to be good. In our feasibility testing, out of 38 users, 4% (primarily attributed to forgetfulness) could be considered non-compliant with minimal app use over a 1-month period. This is consistent with findings from Ben-Zeev's group[28-29]. To define compliance, the rolling retention and churn rates of app usage were considered with 2/38 not returning to the app up to or after 20 days of use. It is to be expected, however, that this might be higher over a 6-month period. App features that assist with

engagement include: the personalization of the peer-to-peer social feed based on the user's intake profile; daily wellness check ins that are accompanied by motivational content; an escalation of medication and appointment in-app reminders where the reminder will be delivered directly through SMS if no response is provided within an hour of receiving it; and provider engagement about the app. As well, as noted, indication of initial challenges with app use will prompt a call from an RA which might assist with engagement.

2.14 What is the likely rate of loss to follow up? On what evidence is the loss to follow-up based?

We experienced no loss to follow up in feasibility testing. This is similar to other studies in this area[28-29] though, again, this will probably be higher over a 6-month period hence our attrition estimate of 15%.

2.15 How many centers will be involved: CAMH would be the centre though recruitment would take place across several Toronto organizations, and potentially organizations across the province and Canada.

2.16 What is the proposed type of analyses?

The data analysis strategy is as follows: (1) A4i use and satisfaction, along with feasibility metrics, will be examined descriptively with comparisons by gender and study site (CAMH vs community) completed using Non-parametric Kruskal Wallis H test (continuous variables) and $\chi 2$ analysis (categorical variables) to detect differences. (2) Qualitative data collected from A4i users and providers will be analysed using qualitative content analysis procedures[51]. (3) Descriptive statistics will be used to summarize the data on all participants to understand the uni- and multi-dimensional characteristics of data distribution and confirm the balance between the two groups. To evaluate the treatment effects on the primary and secondary outcomes, we will employ the intent-to-treat approach and use generalized linear models as the primary analytic approach, of which the baseline to 6-month change score will be treated as the response variable and treatment assignment, regardless of compliance, as the primary predictor with the corresponding baseline outcome measure, key demographic variables and study site being controlled as covariates. The generalized linear model could accommodate potential deviation from normality of the outcome variables. The multiple imputation method[52] will be used to handle missing responses and account for potential bias. Three additional analyses will be conducted in addition to the primary analysis. First, we will conduct a sensitivity analysis by including the number of contacts with the psychiatrist in the model as an additional covariate to be controlled. Second, we will explore moderation of the treatment effect of baseline symptom severity and key demographic variables by adding their interaction with the treatment assignment in the model. This may provide suggestive evidence of differentiated treatment effects. Third, we will look at the impact of compliance by correlating the change score of the outcomes with the app use for the subjects under the treatment condition. Additionally, if more than 10% of the

subjects show no app use, a sensitivity analysis will be conducted with only subjects who used the app at least once.

2.17 What is the proposed frequency of analyses?
We will complete the analysis upon completion of the post-intervention assessments.

2.18 Are there any planned subgroup analyses?
Given the possible importance of gender (female, male and non-binary) as a moderation factor, we will test if it has any effect on the magnitude of change in the outcomes. This will be done by adding an interaction between gender and treatment assignment indictor to the model described in 2.16.

2.19 Has any pilot study been carried out using this design?
Following a preliminary 1-week beta test by 5 individuals to address technical issues, analysis of qualitative and quantitative A4i outcome data from 38 individuals was conducted – assessing feasibility over a 1-month period. The paper describing these findings can be found here: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0219491. The mean number of interactions with the app per day as 4.21 and, by day 20, a 4% churn rate was observed (rates of individuals who ceased app use). Considering outcomes (noting a lack of a control group), small to medium effect changes were observed in several symptom domains: a significant decrease in the depression domain of the Brief Symptom Inventory with a medium effect size (ES = .42) was observed, along with decreases in paranoid ideation (ES = .29), psychoticism (ES = .22), obsessive compulsive symptoms (ES = .38), phobic anxiety (ES = .38) and interpersonal sensitivity (ES = .18) with depression, obsessive compulsive, and paranoid ideation findings the most robust. Signals of improvement were also seen in medication adherence and ratings of personal recovery, though changes in these areas were limited. Frequency of use did not appear to be related to outcomes, though those who used the app more frequently were more unwell in several symptom areas including depression. With disagree, neutral and agree options on satisfaction scale items the mean average 'agree' response was 68% (with agree being positive). Qualitative feedback was primarily positive: "easily reminding me about the next time I need to take my meds"; "[it helps me] redefine my daily thoughts…for people to feel mentally healthy"; "helps you focus on something when your thoughts are racing". Critical feedback was largely in the realm of minor enhancements. Only one participant noted that the texts made him/her anxious though also noted that they would 'definitely' use A4i in the future if available.

3. Trial Management
3.1 What are the arrangements for day to day management of the trial?
The day to day management of the trial will happen under the leadership of the PI (Kidd), the RAs, and the student trainee. The RAs and student will enter data into REDCap, with the RAs conducting routine audits of data entry against forms and the study research ethics binder. Along with ad hoc communications this team will meet weekly. The PI/RA designate also will attend

weekly meetings with the CAMH Slaight Centre (which serves the early psychosis population) and the Schizophrenia Division (which serves a more chronic/mature population) to facilitate recruitment.

3.2 Describe the trial steering committee/data safety and monitoring committee: A data monitoring committee will be established for this trial due to both some of the potential risks identified above and the possibility of a perceived conflict of interest should A4i move into commercialization and revenue generation in the future. The committee composition will include two clinicians with expertise in schizophrenia, a scientist with trials and severe mental illness expertise, a dHealth expert, a biostatistician, and two individuals with lived experience of schizophrenia. The committee will meet every 6 months and ad hoc pending need and will operate per established guidelines[54].

3.3 Addressing Conflict of Interest

Dr. Kidd will comply with the requirements of the management plan outlined by the CAMH Compliance Office. This includes:

- Disclosing the relationship to A4i and management plan to the REB
- Disclosing the relationship to A4i to all research personnel involved in the study, including fellows/students
- Disclosing the relationship with A4i to research participants during informed consent
- Remaining uninvolved in recruitment, consenting, and data collection/recording
- Arranging independent data analysis and DSMB/C analysis to be carried out by a non-conflicted party external to CAMH
- Ensuring the research data set will be made publicly available either in a repository or sup file (as flagged by CIHR reviewers)

3.4 Data Management and Integrity

The basic protection against risk in this study will be provided by Dr. Sean Kidd (study PI). The PI will have primary responsibility for monitoring of participants during the entire time they participate in the study. The PI will meet regularly with study personnel to review accrued data, data confidentiality, and adherence to protocol design, recruitment, and participant complaints. During meetings the Study PI will also review the enrollment data, the accrual and integrity of clinical data, and any adverse event associated with the various components of the study. If a serious adverse event occurs during the study, it will be reported to REB.

Any hard copy data pertaining to a participant's involvement in this study will be coded and stored in locked offices. This information will only be accessible to the research team. In unusual cases, a participant's research records may be released in response to a court order. If the research team learns that a participant or someone with whom the participant is involved with is in serious danger or harm, an investigator will inform the appropriate agencies as per legal or regulatory requirements.

The hard data are stored in a locked filing cabinet stored in a locked office to further protect participant anonymity. Data auditing, entry and quality control will be carried out regularly. Regularly scheduled, and as needed, communications between the study team and the Study PI will clarify any inconsistencies and ambiguities in the data.

At point-of-entry, study data values will undergo consistency edits (e.g., ID validation, range verification, duplicate detection) and personnel will be required to correct errors. Data management staff will run logic error programs to check for accuracy and irregularities within and across data structures and within and across sites. Quality assurance checks will be conducted daily and weekly by site personnel, as well as by data management staff.

3.5 Confidentiality

There is a potential risk of breach of confidentiality that is inherent in all research protocols. Breach of confidentiality will be minimized by the staff who will maintain research data (identified only by participant code number not related to name, or date of birth) in separate charts and a dedicated password protected electronic database. A list of participant names, their ID numbers, and information about how they can be reached will be kept in a separate locked cabinet with access only to study personnel authorized by the PI. Procedures have been established, and will be followed, to minimize the risk of breach of confidentiality. Procedures to maintain confidentially include: (1) formal training sessions for all research staff emphasizing the importance of confidentiality; (2) specific procedures developed to protect participants' confidentiality, and (3) formal mechanisms limiting access to information that can link data to individual participants. All information obtained from participants will be kept as confidential as possible. Computer based files/data will be entered into password-secured databases and paper-based files will be stored in a secure location. These data will only be accessible to personnel involved in the study and they will abide by confidentiality regulations of the REB. The ethics committee will be granted direct access to the study participants' original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the participants, to the extent permitted by the law and regulations.

Research and recruitment data gathered as part of this study may be shared and provided to other investigators affiliated with the Slaight Family Centre for Youth in Transition (SFCYT) at CAMH, for the purpose of data sharing and recruitment. If participants are enrolled in multiple studies, their research data (which may include identifiable information) will be shared across studies to reduce participant burden and avoid duplication of procedures/processes. Only investigators/research teams affiliated with the Slaight Centre will have access to secured files and/or research/recruitment data and will be well-informed regarding the protection of participants' rights to confidentiality.

Furthermore, investigators collaborating with SFCYT Centre (or other secondary investigators) will have access to the research data collected during the study (which may include identifiable medical information, including gender, diagnosis etc) for the purposes of conducting secondary analyses about mental illnesses, such as autism spectrum disorder, depressive disorders, psychotic disorders, bipolar disorders, anxiety disorders, sleep disorders, or dementia (e.g., Alzheimer's disease). 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 a participant before files are shared with other researchers to ensure that by current scientific standards and known methods, no one will be able to identify a participant from the information we share.

Participants will not be identified by name in any publication of research results. Results will be published as group data without the use of characteristics that would identify individual participants.

Virtual Adjustments to Data Management and Protecting Confidentiality

Recruitment

Names and emails of prospective participants as well as their preferred method for a consent discussion will be stored in a password protected Excel recruitment tracking database on the CAMH secure server. Should the initial recruitment call be conducted offsite, and the participant be a Slaight Centre client, the Slaight Pre-Screen Form, for each prospective participant will be safely stored in a locked cabinet at the research personnel's residence and will be transported every 2 weeks to CAMH as per Slaight Centre procedures. If there are earlier safe opportunities to directly transport the documents to CAMH property, they will be transported by the study RA and/or PI. If the initial recruitment call is conducted offsite for non-Slaight Center clients, the information collected as part of the Initial Telephone Script, will be stored in a password protected recruitment log located on secure CAMH servers. Consent forms, consent process checklists, and attestation notes will be housed on REDCap on secure CAMH servers and stored according to SOP # HSR 229. Copies of the consent forms will be stored on REDCap. The consents will also be downloaded, password protected and stored in the study folder on the CAMH secure server until it is safe to resume work on site. At that time, consents will be printed and stored in a locked filing cabinet in a locked office at CAMH separate from any assessment materials. Only the PI and study RA will have keys to the filing cabinet.

To verify the potential participant's identity at the consent discussion they will be asked to state their full name and date of birth which can be confirmed against their Slaight Pre-Screen Form information for Slaight Centre clients, and for non-Slaight clients' information will be checked against the study recruitment log. Documentation of verifying potential participant identification will be recorded in the Excel recruitment tracking database.

Study Enrollment

All participant data will be de-identified using a randomly generated numeric code as soon as possible after the participant has consented into the study. When a participant is enrolled into the study, typically a hard copy of the Participant Contact Information and Identification Form will be completed in order to obtain source documentation, however because we are working remotely information usually captured on the form will be transcribed into the aforementioned password protected Excel master identification log located on the CAMH server. The identification log linking participants to their numeric identifier will only be accessed by research team members. This identification log will include their name, PPT ID, date of birth, telephone number, email and an alternate contact's name, relationship and telephone number. This log will be password protected and will be kept in the project folder on the CAMH secure server. This log will be used to confirm identification at each subsequent research visit, and documentation that identification and location has been confirmed will be tracked in the study visit tracking log. Once onsite procedures resume, hardcopies may be printed and stored with consent forms as source documentation. At that time, the documents will be stored in a locked filing cabinet in a locked office at CAMH.

Assessment, Interview, and First Month Check-In

All study specific documents (hard copy and electronic measures stored in REDCap) will use a participant study identifier when it is required. The minimum PHI necessary will be collected. No participant names or other identifying information will be used in the dissemination of study findings.

If offsite, the check-ins, assessment and interview will be conducted from a clear, private space at the interviewer's residence. If onsite, a private office will be booked. Participants will be encouraged to attend the interview in a private space as well.

Prior to the check-in, assessments and interviews, the study RA will verify the participant's identity using full name and date of birth; advise the participant to avoid sharing personally identifying information outside the context of the questions asked; remind the participant the feasibility and use qualitative interview portion at the last study visit will be audio-recorded; confirm they are in a fixed location; and obtain an emergency contact number in case the call ends inadvertently. Participants will have the option to take breaks, pause and resume the assessment and/or interview on another date as well as stop the assessment and/or interview entirely based on their preference. Participants will be reminded that they do not need to disclose or discuss any information about their experiences they do not feel comfortable sharing.

For the follow-up session, the assessment data will be conducted first so as not to be collected during the audio-recorded interview.

While working offsite, information collected through assessments, interviews, and the first-month check-in will be entered directly into REDCap, so that no hardcopy source documents are required. RAs will not record any PII in REDCap and will only include minimal PHI required to

make a rating. Hardcopy assessments and interviews will only be used in the event that REDCap is unavailable (e.g., due to scheduled maintenance or server issues). While working offsite, any hard copies of the monthly check-ins, assessments and transcriptions that were used will count as source documents and will be safely stored in a locked secure area with the RA at their residence. When it is safe and reasonable to resume work on site, all hard copies of participant data will be brought to a secure office at a CAMH site where they will be stored in a locked filing cabinet that can only be accessed by the study RA's and PI. If there are earlier safe opportunities to directly transport the documents to CAMH property, they will be done by the study RA and/or PI. Hard copies of assessment data and consent forms will be stored in separate locked filing cabinets in a locked office at CAMH. Only the Principal Investigator and study RAs will have keys to the filing cabinet. As well, a master hard copy list indicating participant names and linking numbers will be kept in a separate file from the data and stored as noted above. An electronic, password protected identification log and study visit log will be kept in the project folder on the CAMH secure server and stored separately.

First Month Check-Ins

Any problems during the first-month check-in will be recorded in a REDCap form (or if unavailable, a hard copy form) of the First Month Check-Ins document. This REDCap form is only accessible by non-blinded study personnel.

Assessments

The assessment data collected will be recorded in a REDCap assessment form (or if unavailable, a hard copy form) with the participant ID and date. Electronic data will be stored in REDCap, which is a password protected online data capture system located on CAMH secure servers. The project REDCap database is only accessible by study personnel.

When the study RA shares their screen to assist with installation and completing the questionnaires, all documents or windows containing PHI will be closed. No personal photographs will be saved their background. The questionnaires will be open and ready for sharing with the participant. Email and other windows will be closed as well.

Feasibility and Usability Qualitative Interviews

Audio recording is beneficial to the procedures since it allows the interviewer to remain engaged with the participant without their attention directed elsewhere. The member of the research team who scheduled the interview will be the one audio-recording the interview. Using the CAMH-approved WebEx platform is the necessary approach for audio-recording since other CAMH-approved external audio recordings devices may not capture the audio as well and would require more steps to securely transfer the audio recording to the project folder.

Audio-recordings will be reviewed for quality and then securely transferred from the research team member's WebEx account to the study-specific folder on the secure CAMH server within

30 days of the recording. Once transferred the audio-recording will be deleted from the WebEx account. Once the audio-recording is transcribed and verified it will be deleted from the study-specific folder on the CAMH secure server. Transcription will aim to be completed within 30 days of the interview. The study RA's and PI will be the only research personnel able to access the audio-recordings.

The electronic version of the transcription will be in a password protected Word document saved and stored on the secure CAMH server. Transcriptions and audio recordings will be labeled as follows: [Participant ID], [Interview Date]. After an RA transcribes the interview, the Word document will be printed, the participant ID will be added and then signed and dated by the person who transcribed the interview with the following statement written on the first page, "I certify and have verified that the information on this page (s) is an exact copy having all of the same attributes and information as the original audio recordings."

3.6 For what reasons might a participant be withdrawn from the study?

Reasons for withdrawing individual participants from the study may include one or more of the following:

a) Major protocol violation

b) Participant lost to follow-up

c) Withdrawal of consent

Any participant may be discontinued from the study at the discretion of the investigators if this is deemed to be in the best interest of the participant. The decision may be made either to protect the participant's health and safety, or because it is part of the research plan that people who develop certain conditions may not continue to participate.

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Appendix 1 – Case Manager Script

I'd like to tell you about a project that is happening that involves testing of a cellphone application designed to assist people with schizophrenia in a range of areas – focusing on improving coping and improving social engagement. It would involve installing the app on your phone, you using it for a few months and completing some surveys about your wellness, general functioning and how your care is going. You would get paid for your involvement. It is completely fine to say no to this – doing that will not affect the services you receive in any way. If you are interested, I would pass your name and phone number along to the research assistant

for the project who would tell you more about it. No need to decide right now. Just let me know when you like if you are interested.

Appendix 2 – Recruitment Script for Re-contact

Thank you for your past participation in research studies at CAMH.

We are reaching out to see if you would be interested in taking part in another study. Would you like to hear more?

This is an opportunity for to participate in a research study testing a mobile mental health application called App for Independence or A4i. This app is designed for use by people with a diagnosis in the schizophrenia spectrum and experience auditory hallucinations and who are engaged with a CAMH case manager or psychiatrist.

Here is what is involved:

1) Completing a consent to take part where you would receive more information.

2) Using A4i for a few months and completing some assessments before and after using A4i on your phone.

3) To take part you would need to speak and read English, be 18 years of age or older, own and use an Android or iPhone smartphone with a data and talk plan, and be engaged in outpatient treatment.

4) You would be reimbursed for your time spent being assessed.

Would you like to come in and learn more about the study and possibly take part?

If yes – book.

If no – Thanks for your time then. Are you okay with others still reaching out to you to tell you about studies? If no – flag with Slaight as no longer approach. If yes, discontinue contact only.

Appendices – Table 1 – Assessment Timelines

Clinical Metrics Timeline (Noting COVID related changes regarding the PANSS and the SANS)

Assessment	Baseline	6 Month Follow-Up	Collected From
Brief Symptom Inventory	X	X	Client
Positive and Negative Syndrome Scale	X	X	Client
Scale for the Assessment of Negative Symptoms	X	X	Client
Brief Adherence Rating Scale	X	X	Client and Care Provider
Medical Outcomes Study General Adherence Scale	X	X	Client and Care Provider
% of Schedule Appointments Attended	X	X	EMR Audit or Care Provider
STAR	X	X	Client and Care Provider

Quality of Life Scale	X	X	Client
Demographics	X		Client
Service Use History	X	X	Client and Care Provider
Global Assessment of Individual Need – Substance Use Scale	X	X	Client

Feasibility Indicators Timeline

Assessment	Baseline	6 Month Follow-Up	Collected From
Semi-Structured Interview assessing Strengths, Limitations & Risks		X	Client and Care Provider
Phone survey assessing Quality of Clinical Interactions + Frequency & Use of A4i Summary in clinical interactions		X	Client and Care Provider
Patient Satisfaction (26-item scale by Ben Zeev and Colleagues)		X	Client