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Evaluating the utility of digital phenotyping to predict health outcomes in schizophrenia: Protocol for the HOPE-S observational study

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ABSTRACT

INTRODUCTION: The course of schizophrenic illness is characterized by recurrent relapses which are associated with adverse clinical outcomes such as treatment-resistance, functional and cognitive decline. Early identification is essential and relapse prevention remains a primary treatment goal for long-term management of schizophrenia. With the ubiquity of devices such as smartphones, objective digital biomarkers can be harnessed and may offer alternative means for symptom monitoring and relapse prediction. The acceptability of digital sensors (smartphone and wrist-wearable device) and the association between the captured digital data with clinical and health outcomes in individuals with schizophrenia will be examined.

METHODS AND ANALYSIS: In this study, we aim to recruit 100 individuals with schizophrenia spectrum disorders who are recently discharged from the Institute of Mental Health (IMH), Singapore. Participants are followed up for 6 months, where digital, clinical, cognitive and functioning data are collected while health utilisation data are obtained at the 6-month and 1-year timepoint from study enrolment. Associations between digital, clinical and health outcomes data will be examined. A data-driven machine learning approach will be used to develop prediction algorithms to detect clinically significant outcomes. Study findings will inform the design, data collection procedures and protocol of future interventional randomised controlled trial, testing the effectiveness of digital phenotyping in clinical management of individuals with schizophrenia spectrum disorders.

ETHICS AND DISSEMINATION: Ethics approval has been granted by the National Healthcare Group (NHG) Domain Specific Review Board (DSRB Reference no.: 2019/00720). The results will be published in peer-reviewed journals and presented at conferences.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- The longitudinal design facilitates evaluating the utility of the digital biomarkers in predicting clinical health outcomes in individuals with schizophrenia
- The study will provide insight into the acceptability of passive sensing methods in obtaining digital data
- Loss to follow-up, compliance issues related to wearing wearable devices particularly during sleep and missing data points may limit accuracy of relapse prediction

INTRODUCTION

Schizophrenia is a disabling and chronic illness marked with periods of remission and relapse. Estimates indicate that about 80% of individuals with schizophrenia suffer at least one relapse within 5 years after initial remission, with the likelihood of a second relapse at 78% [1]. Despite adherence to treatment, some individuals may find themselves decompensating which may lead to subsequent relapse [2]. Relapses often worsen the course of illness with deterioration in functioning, quality of life, as well as increased residual symptoms, treatment resistance, neurobiological sequelae and economic burden [3–5]. Given the recurring nature of relapse and its detrimental effects, early identification and relapse prevention remains a primary treatment goal for long-term management of schizophrenia.

To date, primary means of illness management are heavily reliant on direct assessments by clinicians during routine clinical visits. This has significant drawbacks as such clinical evaluations are often brief and provide episodic snapshots of an individual's mental health status. In addition, utility of information gathered are limited by the accuracy and insightfulness of patient recall and observations reported by family members retrospectively, if available. Furthermore, clinical evaluations and treatment management are dependent on attendance of these individuals at the scheduled clinic visits. While evidence suggests that relapse is often preceded by unique changes in observable behaviour [6], which include changes in sleep patterns, psychomotor and physical activity, social withdrawal, exacerbation of psychotic symptoms and medication nonadherence [7,8], these behavioural precursors may go unknown to the clinician in between consults. This increases the likelihood of missing the optimal timing to provide intervention to those who are at an increased risk of relapse [9].

Effective illness management requires continuous monitoring and reliable identification of antecedents of relapse. Digital technologies have shown potential in bridging the gap and augment traditional clinical management of schizophrenia. With advances in technology and the exponential growth in ownership of personal digital devices over the years [10,11], this has created an unprecedented opportunity to quantify user behaviours in their natural environment [12,13] through continuous capture of objective digital data, known as digital phenotyping. Digital phenotyping is based on information from sensors (e.g. global positional system (GPS), ambient light, accelerometer), speech (e.g. sentiment and prosody) and human-computer interactions (e.g. keystrokes such as taps, scrolls and swipes on phone screen) [14]. These real-world data from passive sensing methods serve as proxies for human behaviours and when processed through algorithms of machine learning, may derive social and behavioural signals [15] to glean deeper understanding on the nature of diseases and their trajectories. In the following section, we explore some features of passive sensing technologies and evidences of its use in mental health, particularly in the schizophrenia population.

Behavioural and social signals

Location

Various indices can be derived from GPS which include time spent at home, distance travelled from home, location entropy, locations visited and more. Characteristic mobility patterns of the schizophrenia population have been reported, with a tendency to spend more time at home and engage in shorter distance travelled overall [16]. This is not uncommon as individuals with

schizophrenia may tend to isolate themselves during episodes of psychotic exacerbations [17,18]. Objective measures of mobility were also found to differentiate individuals with schizophrenia and healthy controls as seen from the large difference in magnitude of distance travelled in a week [16].

Associations between location-based features, symptoms and functioning have been demonstrated. Greater negative symptoms, particularly diminished expression was associated with less GPS mobility whereas higher community functioning weakly associated with greater GPS mobility [16]. Location and mobility features computed (e.g. location entropy, location routine index, total distance travelled and maximum displacement from home) were also found to be strongly associated with symptoms of schizophrenia [19]. Changes in typical, daily mobility were observed to precede clinical relapse by up to 2 weeks [20].

Sociability

Social dysfunction is one characteristic of schizophrenia and may be used to identify periods of psychotic exacerbations or relapse. Periods of social isolation is known to be associated with increased risk of such events. The level of social interaction and communication can be evaluated from one's call and text logs; how often calls and texts are made or sent, or how fast a missed call or text is returned. Reductions in the number and duration of outgoing calls, and number of text messages were reported to be associated with relapse events while the number and duration of incoming phone calls were not [21]. Sociability anomalies were detected 2 weeks prior to relapse [20].

Sleep

Anomalies in sleep patterns may indicate changes in one's mental health status [7]. Sleep disturbances are often one of the earliest signs of symptom exacerbation and relapse [22,23]. Preliminary results in a study by Meyer and colleagues showed that sleep disturbances often accompany relapse and was observed prior to deterioration in more than half of the relapse events [24].

Sleep information can be gathered from various sensors in digital devices. Ambient light as gathered from a phone's in-built sensor provide information on an individual's environmental context, i.e. dark versus illuminated environment. This together with various smartphone usage patterns can predict sleep duration. While there are some disadvantages to estimate sleep information through ambient light, for example lack or minimal detection when phones are placed in the pocket or face down on surfaces, or in cases where users sleep with the lights on, its accuracy has been demonstrated to be comparable with wearable sensors to estimate sleep duration [25]. Commercially available wearable devices, e.g. Fitbit (Fitbit Inc, San Francisco, CA, USA), use a combination of heart rate and movement data to estimate duration of sleep and its stages.

Physical activity

Exercise can help manage symptoms of schizophrenia. Symptoms have been found to be associated with lower activity or changes in activity level as measured by either smartphone or wearables [19,26,27]. Activity levels may also be disturbed during episodes of relapse. A study has observed a decline in physical activity prior to relapse, as measured via the smartphone accelerometer [28].

Finger taps

Typing and scrolling rhythms on a smartphone are predictive of one's cognition and emotional state. Zulueta and colleagues [29] found that keyboard typing can be used as a proxy for cognition in individuals with bipolar disorder. In addition, increased rate of typing errors were associated with impaired concentration in more depressed states [29]. Digital biomarkers derived from tactile user activity on smartphones have been reported to correlate with standard neurocognitive tests in healthy individuals [30]. There is no existing study that has examined this in schizophrenia, however finger taps may be helpful as a proxy of cognition which is a known core feature in schizophrenia [31,32] and an important determinant of functioning and functional recovery [33]. Also, the potential of predicting emotional state from finger taps [29] may aid in identifying occurrence of mood disturbances such as depression which is known to have adverse effects on schizophrenia progression, morbidity and mortality [34].

The current study

Initial findings in the extant literature demonstrate the potential of leveraging on digital technologies to overcome barriers of traditional illness management in schizophrenia. However, most of these studies outlined above were based on relatively small sample sizes. In mental health research, where data collected is highly sensitive [35], an individual's perception on data handling and privacy concerns may undermine acceptance of use of such devices and digital phenotyping. Also, as digital phenotyping research is relatively new in schizophrenia, further investigation is required to understand and draw meaning from various digital biomarker signals before translation for use in the clinical setting. Therefore, the Health Outcomes via Positive Engagement in Schizophrenia (HOPE-S) study is initiated to examine use of devices such as smartphone and commercially available wrist-wearable device to gather digital data via passive sensing methods and explore its initial utility in predicting health outcomes in individuals with schizophrenia spectrum disorders.

In this paper, we outline the protocol of the study which aims to:

1) Understand whether the digital markers (i) can predict clinical and health utilisation outcomes in individuals with schizophrenia, and (ii) are correlated with clinical status, i.e. symptoms and functioning
2) Examine the feasibility and acceptability of collecting digital markers passively via wrist-wearable device and smartphone from individuals with schizophrenia

METHODS AND ANALYSIS

Study design

This is an observational study with an active participant follow-up period of 6 months and an administrative follow-up at 1 year. The study is conducted at the Institute of Mental Health (IMH), Singapore in collaboration with the Ministry of Health Office for Healthcare Transformation (MOHT), Singapore.

Patient and public involvement

Patients and the public were not involved in the design of the study. Direct patient involvement includes completing clinical interviews, cognitive tasks, and questionnaires at scheduled visits, and continuous collection of digital data during the 6 months period.

Recruitment and participant selection

Participants are recruited via clinician referrals, posters or brochures placed in IMH outpatient clinics and inpatient wards, or by word of mouth. Individuals are recruited if they are aged 21 to 65 years old, English speaking, able to provide informed consent, having a diagnosis of schizophrenia spectrum disorders based on the Structured Clinical Interview for DSM-5-RV [36] and are within 8 weeks post-discharge from hospitalization at IMH. Individuals who meet any of the following exclusion criteria are ineligible for participation: (i) female who is currently pregnant or planning a pregnancy within 6 months; (ii) has any other clinically significant medical condition or circumstance that, in the opinion of the Investigator, could affect participant safety, preclude evaluation of response, interfere with the ability to comply with study procedures, or prohibit completion of the study; (iii) has visual or physical motor impairment that could interfere with study tasks.

Digital data

We have developed the HOPES (**H**ealth **O**utcomes through **P**ositive **E**ngagement and **S**elf-Empowerment) platform and its smartphone application (app) based on the open-source Beiwe platform (https://www.beiwe.org/). The HOPES platform serves to integrate a wide range of digital data from smartphone sensors and wearable devices such as sleep, heart rate, physical activity, locational information (obfuscated), sociability indices, finger taps, and ambient light. Currently, the HOPES app is supported only on Android phones. We utilize Amazon Web Services (AWS) cloud service for secured hosting of the HOPES digital phenotyping app and its agile modification, debugging, and testing and also to allow training, tuning, and testing of machine learning prediction models for digital phenotyping [37].

Internal testing of wrist-wearable devices and the HOPES app was done to select the best wearable device based on user experience and accuracy of digital data collected as well as checking and fine-tuning the HOPES app. Dry run of the onboarding process on various Android smartphone brands was conducted internally to identify potential problems during apps installation and estimate the duration required for the process. Clinicians provided input on the selection of relevant digital data to be investigated. During the 6-months study period, the following digital data are collected via the HOPES and Fitbit apps:

From Fitbit:

1. *Sleep and heart rate.* The Fitbit device measures heart rate constantly. It then computes the sleep time and sleep level from accelerometer and heart rate if available.
2. *Physical activity.* Number of steps is recorded daily and is computed from the Fitbit's accelerometer data.

From smartphone (HOPES app):

3. *Ambient light.* This is measured through the smartphone's built-in light sensor to detect ambient brightness which might be associated with participants' daily activities.
4. *Location parameters.* Locations of the smartphone, departure from typical travel patterns, and variance of the locations travelled derived from GPS are recorded.
5. *Sociability indices.* A summary of different types of social interactions via smartphone will be obtained such as the frequency and duration (or length) of phone calls (or messages) on various platforms (e.g. SMS, WhatsApp, etc.) as well as the amount of time spent on designated apps such as social media.
6. *Finger taps.* Characteristics of finger taps such as timing and types of selection made on the smartphone are recorded. Timestamps of taps into apps of the enter key, backspace, alphabets, numbers, and punctuations are recorded. All alphanumeric and other keyboard keys are captured and converted into a classification symbol.

Considering the sensitive nature of information collected, details of digital data collected, measures taken to preserve participants' privacy and potential risks such as data breach are explained to participants during consent taking procedures. In the case of location data, GPS coordinates are obfuscated via a random origin displacement (different for each participant), thus the actual or absolute GPS locations will not be transmitted from participant's smartphone. For sociability indices, no content information of the calls and messages are recorded while for finger taps, only the classification symbol are downloaded and stored by the HOPES app, thus no tracking of specific keys typed. This is done to preserve the privacy of participants. Data transmitted from the mobile HOPES app to the AWS cloud is encrypted (using industry standard encryption: 256-bit AES/Advanced Encryption Standard) and de-identified. Data may be decrypted to run analytics within the AWS cloud in main memory but will not be stored decrypted (only fully encrypted). This data will only be downloaded to local MOHT server where it can be decrypted. Participant-identifiable data will not be uploaded on the AWS cloud.

Assessment tools

A series of scales and tasks are done based on the study schedule (refer to Table 1):

1. *Structured Clinical Interview for DSM-5 Research Version (SCID-5-RV).* This instrument is used to ascertain participant's diagnosis of having met the inclusion criteria of a schizophrenia spectrum disorder [36].
2. *Clinical Global Impression scale (CGI).* This scale measures severity of illness and improvement on a 7-point scale. Assessment of severity of illness is evaluated based on the clinician's experience with patients of the same diagnosis, where a higher rating indicates greater severity. The Improvement item measures how much the patient's illness has improved or worsened relative to a baseline state, where a higher rating indicates greater worsening of illness [38].

3. *Brief Adherence Rating Scale (BARS).* A clinician-administered instrument which assess antipsychotic medication adherence of outpatients with schizophrenia. Greater proportion of doses taken in the past month indicate greater adherence [39].
4. *Columbia Suicide Severity Rating Scale (CSSRS).* This scale assesses both suicidal ideation and behaviour [40].
5. *Positive and Negative Syndrome Scale (PANSS).* A 30-item scale measuring positive symptoms, negative symptoms, and general psychopathology. A higher total score indicates greater symptom severity [41].
6. *Brief Negative Symptom Scale (BNSS).* A 13-item scale that measures five negative symptom domains (blunted affect, alogia, asociality, anhedonia and avolition) and a subscale on lack of normal distress. Higher total score indicates greater negative symptoms [42].
7. *Calgary Depression Scale for Schizophrenia (CDSS).* This scale is designed for the assessment of depression in schizophrenia, which differentiates between depression and the negative and positive symptoms of schizophrenia. A higher total score reflects greater severity [43].
8. *Social and Occupational Functioning Assessment Scale (SOFAS).* This scale evaluates an individual's level of social and occupational functioning. Its rating is not directly influenced by the overall severity of the individual's psychological symptoms. A greater rating reflects superior functioning in various areas of life [44].
9. *Brief Assessment of Cognition in Schizophrenia (BACS).* A cognitive battery which assesses attention, verbal and working memory, motor and processing speed, verbal fluency, reasoning and problem solving. Higher composite score indicates better cognitive function [45].
10. *5-level-EQ-5D (EQ-5D-5L).* A standardized instrument developed as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments. A higher score indicates best health imagined [46].
11. *Subjective Well-being under Neuroleptics scale – short form (SWNS).* A self-rated instrument to assess well-being from a patient's perspective based on their subjective experiences during antipsychotic treatment. Higher total score indicates greater well-being [47].
12. *Acceptability questionnaire.* This self-constructed questionnaire consists of an item measuring participants' satisfaction based on their experience using digital devices on a 7-point scale. Two other qualitative items in this questionnaire gather feedback on the strengths and suggested improvement for the system and user satisfaction.
13. *Healthcare utilisation.* This information is obtained from patient's medical records. Healthcare utilisation information of interest include hospitalisations, outpatient non-attendances, scheduled (e.g. clinic appointments, psychotherapy sessions, etc.) and unscheduled service use including visits to psychiatric emergency department and community crisis team activations.

These scales are administered by clinicians (scales 1-4) and research assistants (scales 5-12) who have been trained in the use of the scales and achieved good interrater reliability. Medical records will be accessed to gather healthcare utilisation over a 1-year duration in the study. De-identified data are entered into a database and the hardcopy documents are kept on site under lock and key.

Outcomes

Primary outcome

Changes in digital phenotype that are associated with relapse during the 6 months will be examined. Relapse is defined as a re-admission due to mental deterioration or an overall increase by 2 points or more on the CGI severity item.

Secondary outcome

We will examine changes in psychiatric rating scales (refer to 'Assessment tools' scales 3-11) measuring symptom severity, cognition and functioning. Changes in digital phenotype that coincide with observed changes in rating scales will be examined. Acceptability of passive digital data use via smartphone and wrist-wearable device will be evaluated.

Study procedures

Baseline

Upon consent taking and enrolment, participants will complete a baseline assessment visit which consists of a series of clinical, cognitive, functioning scales and collection of demographic information (refer to Table 1 for scales and tasks done). A wrist-wearable device (Fitbit) that is to be worn daily except when charging, is provided to participants. The HOPES and Fitbit apps are installed in participant's smartphone for continuous, passive digital data collection during the 6 months. In the event where the participant's phone is incompatible with the study apps (i.e. Android user with an operating system of less than 7 or iPhone user), a study phone will be loaned to them. Participants are provided a participant booklet and briefed on its contents which include how to charge Fitbit and its maintenance, troubleshooting problems with the Fitbit device or the study apps, and participant's responsibilities during the study period.

Follow-up

Participants will complete four follow-up visits at 6-weekly intervals (Weeks 6, 12, 18, 24). Follow-up assessment scales are completed according to the study schedule outlined in Table 1. Four audio recorded telephone calls are made to participants who consented to this task, between assessment visits. On the final (Week 24) or termination visit, the study apps are uninstalled from participant's mobile phone and the Fitbit is gifted to them. Loaned study phones are collected back from participants after migration of content back to their personal phones is completed. An administrative follow-up is done at the 6-month/termination visit and 1-year timepoint since enrolment to gather healthcare utilisation information.

Monitoring of the digital data dashboard is done daily to ensure that data is continuously uploaded to our server and to also inform the team of any technical issues or non-compliance behaviours in participants. In the event of no data upload from the HOPES and/or Fitbit app for 4 days or more, the case is highlighted to the study team members, who will contact the participant to resolve the problem. Participants are reimbursed for their digital data, mobile data usage and completion of assessment at every follow up visit. Additionally, participants are incentivised if data from the Fitbit are available for more than 75% of the time between the two adjacent study visits.

Sample size calculation

As this is an observational study, sample size was determined based on feasibility. Several studies suggest that a sample size of at least 30 participants generally allow adequate hypothesis testing while providing reasonable effect size [48–50]. Assuming a 10% drop-out rate, a sample size of 100 will provide 80% probability to observe at least 30 participants who relapse within 6 months, if true relapse rate is 37%. This relapse rate is an assumption derived based on binomial distribution as information on relapse rates are unavailable. If the true relapse rate is lower than 37%, the probability to observe at least 30 participants who relapse within 6 months will be less than 80%. If the true relapse rate is higher than 37%, then the probability will be more than 80%.

Data analysis plan

Here we broadly outline the statistical methods to be used in our analysis. As a high-volume of digital and clinical data will be collected, our analysis plan will start with processing raw digital data to extract relevant features and deriving composite scores of clinical scales. Some preliminary analysis plans include examining the relationship between various digital biomarkers and clinical variables cross-sectionally via correlational and regression analyses.

We expect to utilize various other approaches when more data becomes available across various timepoints. These analyses will identify patterns in digital data that may be associated with changes in clinical data and relapse when it occurs. Suitable approaches, which include anomaly detection methodology in machine learning, will be adopted to predict shifts in psychiatric rating scales or relapse. Mean and median rating of the acceptability questionnaire will be presented, and open-ended responses will be examined.

Ethics and dissemination

Participants will undergo consent taking procedures with a study team member and a witness before starting any research related activity. All collected data will be kept confidential and only de-identified data is analysed. Findings of this study will be disseminated through publications in scientific journals and applicable conferences.

SUMMARY

Digital phenotyping holds promise to address the unmet needs and challenges in treatment of schizophrenia spectrum disorders. The ubiquity of sensing technologies provides easier access to previously untapped information such as passive data and their derived digital biomarkers. In this study, linking digital and assessment data with health utilisation records creates opportunity for machine learning approaches to explore whether specific types of digital data are associated with changes in clinical, cognitive or functioning measures as well as its ability to forecast future relapse event.

While digital phenotyping approach has its merits (objective, continuous flow of information, low cost, low user burden, scalable), it is very much a work in progress as issues such as information security and privacy are complex, unclear and needs to be addressed [35,51,52]. In addition, with the influx of high-dimensional longitudinal data, such complex data may pose challenges to distil meaning from it

[53] due to the large volume, high noise and heterogeneity in the data [54]. Other issues like data incompleteness (due to non-compliance, faulty devices, or technical issues) and variability in data quantity between participants may present itself as obstacles in digital phenotyping. Nevertheless, this study hopes to contribute to the growing field of digital phenotyping research in schizophrenia and provide initial insight to acceptance of such technology and methods in local setting. Current clinical management methods, if combined with digital biomarkers, have the potential to better elucidate the nature and trajectory of schizophrenia illness and identify early warning signals for better personalized treatment and optimized care.

STUDY STATUS

Recruitment commenced end October 2019. Data collection started in November 2019 and is currently ongoing.

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Contributors: JL, SV, CT and ZY were involved in the design of the clinical aspects of the study. RJTM, WM, XW, NV and TB's contributions to the protocol were on the digital technology, its operations and system architecture. YW contributed to the biostatistical design and planning. NAAR drafted the paper with input from all authors. All authors reviewed and approved the final manuscript.

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Competing interests: JL, ZY and NAAR received funding from the Ministry of Health Office of Healthcare Transformation during the course of the study. JL is further supported by the Ministry of Health National Medical Research Council. RJTM, WM, XW and NV have a patent on systems, devices, and methods for self-contained personal monitoring of behaviour to improve mental health and other behaviourally-related health conditions pending. Nothing in this patent will affect freedom of use in the application of the techniques described in the submitted paper. All other authors declare that they have no competing interests.

Ethics approval: The study protocol has been reviewed and approved by the National Healthcare Group (NHG) Domain Specific Review Board in September 2019 (DSRB Reference no.: 2019/00720).

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Table 1. Study schedule.

Events	Visit 1 Week 0	Telephone Contact Week 3	Visit 2 Week 6	Telephone Contact Week 9	Visit 3 Week 12	Telephone Contact Week 15	Visit 4 Week 18	Telephone Contact Week 21	Visit 5 Week 24 / Termination	Post-Study Follow up Week 52
Written Informed Consent	X									
Demographics and Socio-Economics Status	X								X	
Medical History	X									
Medication Current and History / Concomitant medication	X		X		X		X		X	
Structured Clinical Interview for DSM-5 (SCID-5-RV)	X									
Clinical Global Impression scale – Improvement (CGI-I)			X		X		X		X	
Clinical Global Impression scale – Severity (CGI-S)	X		X		X		X		X	
Brief Adherence Rating Scale (BARS)	X		X		X		X		X	
Positive and Negative Syndrome Scale (PANSS)	X		X		X		X		X	
Brief Negative Symptom Scale (BNSS)	X								X	
Calgary Depression Scale for Schizophrenia (CDSS)	X		X		X		X		X	
Columbia Suicide Severity Rating Scale (CSSRS)	X		X		X		X		X	
Social and Occupational Functioning Assessment Scale (SOFAS)	X		X		X		X		X	
Brief Assessment of Cognition in Schizophrenia (BACS)	X								X	
5-Level EQ-5D (EQ-5D-5L)	X				X				X	
Subjective Well-being under Neuroleptics scale – short form (SWNS)	X								X	
Acceptability Questionnaire									X	
Healthcare Utilisation									X	X
Continuous Collection of the Data from the Apps and Wrist-wearable Device	X		X		X		X		X	
Audio Recording		X		X		X		X		
Collection of the Wrist-wearable Device and Apps Installation	X									
Uninstallation of Apps									X	

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Evaluating the utility of digital phenotyping to predict health outcomes in schizophrenia: Protocol for the HOPE-S observational study

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Evaluating the utility of digital phenotyping to predict health outcomes in schizophrenia: Protocol for the HOPE-S observational study

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ABSTRACT

INTRODUCTION: The course of schizophrenic illness is characterized by recurrent relapses which are associated with adverse clinical outcomes such as treatment-resistance, functional and cognitive decline. Early identification is essential and relapse prevention remains a primary treatment goal for long-term management of schizophrenia. With the ubiquity of devices such as smartphones, objective digital biomarkers can be harnessed and may offer alternative means for symptom monitoring and relapse prediction. The acceptability of digital sensors (smartphone and wrist-wearable device) and the association between the captured digital data with clinical and health outcomes in individuals with schizophrenia will be examined.

METHODS AND ANALYSIS: In this study, we aim to recruit 100 individuals with schizophrenia spectrum disorders who are recently discharged from the Institute of Mental Health (IMH), Singapore. Participants are followed up for 6 months, where digital, clinical, cognitive and functioning data are collected while health utilisation data are obtained at the 6-month and 1-year timepoint from study enrolment. Associations between digital, clinical and health outcomes data will be examined. A data-driven machine learning approach will be used to develop prediction algorithms to detect clinically significant outcomes. Study findings will inform the design, data collection procedures and protocol of future interventional randomised controlled trial, testing the effectiveness of digital phenotyping in clinical management of individuals with schizophrenia spectrum disorders.

ETHICS AND DISSEMINATION: Ethics approval has been granted by the National Healthcare Group (NHG) Domain Specific Review Board (DSRB Reference no.: 2019/00720). The results will be published in peer-reviewed journals and presented at conferences.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- The longitudinal design allows collection of extensive digital and clinical data to identify patterns in digital behaviour and symptoms.
- Results from this study provide insights into the digital signals or anomalies that precede relapse.
- Privacy concerns and the nature of study procedures may hinder participant recruitment.
- Loss to follow-up, compliance issues related to wearing wearable devices daily and missing data points may pose challenges to developing a relapse prediction model.

INTRODUCTION

Schizophrenia is a disabling and chronic illness marked with periods of remission and relapse. Estimates indicate that about 80% of individuals with schizophrenia suffer at least one relapse within 5 years after initial remission, with the likelihood of a second relapse at 78% [1]. Despite treatment adherence, some may find themselves decompensating, leading to subsequent relapse [2]. Relapses often worsen the course of illness with deterioration in functioning, quality of life, and increased residual symptoms, treatment resistance, neurobiological sequelae and economic burden [3–5]. Given the recurring nature of relapse and its detrimental effects, early identification and relapse prevention remain a primary treatment goal for long-term management of schizophrenia.

To date, primary means of illness management are heavily reliant on direct assessments by clinicians during routine clinical visits. This has significant drawbacks as such clinical evaluations are often brief and provide episodic snapshots of an individual's mental health status. Additionally, utility of information gathered is limited by the accuracy of patient recall, and observations reported by family members retrospectively, if available. Furthermore, clinical evaluations and treatment management are dependent on attendance of these individuals at the scheduled clinic visits. While evidence suggests that relapse is often preceded by unique changes in observable behaviour [6], such as sleep, psychomotor and physical activity, social withdrawal, exacerbation of psychotic symptoms and medication nonadherence [7,8], these behavioural precursors may go unknown to the clinician in between consults. This increases the likelihood of missing the optimal timing to provide intervention to those at an increased risk of relapse [9].

Effective illness management requires continuous monitoring and reliable identification of antecedents of relapse. Digital technologies have shown potential in bridging the gap and augment traditional clinical management of schizophrenia. With advances in technology and the exponential growth in ownership of personal digital devices over the years [10,11], this has created an unprecedented opportunity to quantify user behaviours in their natural environment [12,13] through continuous capture of objective digital data known as digital phenotyping. Digital phenotyping is based on information from sensors (e.g., global positional system (GPS), accelerometer), speech (e.g., sentiment and prosody) and human-computer interactions (e.g., keystrokes such as taps and swipes on phone screen) [14]. These real-world data from passive sensing methods serve as proxies for human behaviours and when processed through algorithms of machine learning, may derive social and behavioural signals [15] to glean deeper understanding of the nature of diseases and their trajectories. In the following section, we explore some features of passive sensing technologies and evidence of its use in mental health, particularly in the schizophrenia population.

Behavioural and social signals

Location

Various indices can be derived from GPS, which include time spent at home, location entropy, and more. Characteristic mobility patterns of the schizophrenia population have been reported, with a tendency to spend more time at home and engage in shorter distance travelled overall [16]. This is not uncommon as they may isolate themselves during episodes of psychotic exacerbations [17,18]. Objective mobility measures differentiated individuals with schizophrenia from healthy controls, as seen from the large difference in distance travelled in a week [16].

Associations between location-based features, symptoms and functioning have been demonstrated. Greater negative symptoms particularly diminished expression was associated with less GPS mobility, whereas higher community functioning weakly associated with greater GPS mobility [16]. Location and mobility features (e.g., location entropy) were also strongly associated with symptoms of schizophrenia [19]. Changes in typical, daily mobility have been reported to precede clinical relapse by up to 2 weeks [20].

Sociability

Social dysfunction is one characteristic of schizophrenia and may be used to identify psychotic exacerbations or relapse. Periods of social isolation are known to be associated with increased risk of such events. The level of social interaction can be partially evaluated from one's call and text logs, how often calls and texts are made or sent, or how fast a missed call or text is returned. Reductions in the number and duration of outgoing calls, and text messages were reported to be associated with relapse events, while the number and duration of incoming phone calls were not [21]. Sociability anomalies were detected two weeks before relapse [20].

Sleep

Sleep disturbances are often one of the earliest signs of symptom exacerbation and relapse [22,23]. Preliminary results showed that sleep disturbances often accompanied relapse and were observed prior to deterioration in more than half of the relapse events [24].

Sleep information can be gathered from various sensors in digital devices. Ambient light detected from a phone's in-built sensor provides information on an individual's environmental context i.e., dark versus illuminated environment. This, together with various smartphone usage patterns, can predict sleep duration. While there are some disadvantages in estimating sleep information through ambient light, for example, minimal detection when phones are placed in the pocket or face down on surfaces, or in cases where users sleep with the lights on, its accuracy has been demonstrated to be comparable with wearable sensors to estimate sleep duration [25]. Commercially available wearable devices, e.g., Fitbit (Fitbit Inc, San Francisco, CA, USA), use a combination of heart rate and movement data to estimate sleep duration and its stages.

Physical activity

Symptoms were found to be associated with lower activity or changes in activity level, as measured by either smartphone or wearables [19,26,27]. Activity levels may also be disturbed during episodes of relapse. A study had observed a decline in physical activity prior to relapse, as measured via the smartphone accelerometer [28].

Finger taps

Typing and scrolling rhythms on a smartphone are predictive of one's cognition and emotional state. Zulueta and colleagues [29] found that keyboard typing can be used as a proxy for cognition in individuals with bipolar disorder. Additionally, increased rate of typing errors was associated with impaired concentration in more depressed states [29]. Digital biomarkers derived from tactile user activity on smartphones were found to correlate with standard neurocognitive tests in healthy individuals [30]. No existing study has examined this in schizophrenia; however finger taps may be helpful as a proxy of cognition, a known core feature in schizophrenia [31,32] and an important

determinant of functioning and functional recovery [33]. Also, the potential of predicting emotional state from finger taps [29] may aid in identifying occurrence of mood disturbances such as depression which is known to have adverse effects on schizophrenia progression, morbidity and mortality [34].

The current study

Initial findings in the extant literature demonstrate the potential of leveraging digital technologies to overcome barriers of traditional illness management in schizophrenia. However, most of the studies outlined above were based on relatively small sample sizes. In mental health research, where data collected is highly sensitive [35], an individual's perception regarding data handling and privacy concerns may undermine acceptance of such devices and digital phenotyping. As digital phenotyping research is relatively new in schizophrenia, further investigation is required to understand and draw meaning from various digital biomarker signals before translation to the clinical setting. Therefore, the Health Outcomes via Positive Engagement in Schizophrenia (HOPE-S) study was initiated to examine use of devices such as smartphones and commercially available wrist-wearables to gather digital data via passive sensing methods and explore their utility in predicting health outcomes in individuals with schizophrenia spectrum disorders.

In this paper, we outline the protocol of the study which aims to:

1) Understand whether the digital markers (i) are correlated with clinical status, i.e., symptoms and functioning, and (ii) can predict clinical and health utilisation outcomes in individuals with schizophrenia

2) Examine the feasibility and acceptability of collecting digital markers passively via wrist-wearable devices and smartphones from individuals with schizophrenia

METHODS AND ANALYSIS

Study design

This is an observational study with a 6-month active participant follow-up and an administrative follow-up at 1 year. The study is conducted at the Institute of Mental Health (IMH), Singapore in collaboration with the Ministry of Health Office for Healthcare Transformation (MOHT), Singapore.

Patient and public involvement

Patients and the public were not involved in the design of the study. Direct patient involvement includes completing clinical interviews, cognitive tasks, questionnaires at scheduled visits, and continuous digital data collection for 6 months.

Recruitment and participant selection

Participants are recruited via clinician referrals, posters or brochures placed in IMH outpatient clinics and inpatient wards, or word of mouth. Individuals are recruited if they are 21 to 65 years old, English speaking, able to provide informed consent, have a diagnosis of schizophrenia spectrum disorders based on the Structured Clinical Interview for DSM-5-RV [36] and are within 8 weeks post-discharge from hospitalization at IMH. Individuals were excluded if they: (i) are female and currently pregnant or planning a pregnancy within 6 months; (ii) have any other clinically significant medical condition or circumstance that, in the opinion of the Investigator, could affect participant safety, preclude evaluation of response, interfere with the ability to comply with study procedures, or prohibit completion of the study; (iii) have visual or physical motor impairment that could interfere with study tasks.

Digital data

Digital data is collected from a wrist wearable device (Fitbit Charge 3™ or Charge 4™), a smartphone and their corresponding smartphone application (app: Fitbit app and our in-house developed HOPES app [**H**ealth **O**utcomes through **P**ositive **E**ngagement and **S**elf-Empowerment]). These data are uploaded to the HOPES platform which serves to integrate a wide range of digital data from the smartphone sensors and Fitbits. We have developed the HOPES platform and its smartphone app based on the open-source Beiwe platform (https://www.beiwe.org/). We utilize Amazon Web Services (AWS) cloud service for secure hosting of the HOPES digital phenotyping platform backend and its agile modification, debugging, and testing, and also to allow training, tuning, and testing of machine learning prediction models for digital phenotyping [37]. Currently, our HOPES app is supported only on Android phones.

During the 6-months, these digital data are collected:
From Fitbit:

1. *Heart rate.* This is measured as long as the device is worn. It records heart rate in bpm (beats per minute) at a frequency of up to every 5 seconds.
2. *Physical activity.* Number of steps is computed from accelerometer data and records it every minute.
3. *Sleep*. Sleep is computed based on body movements, where no body movement detected for about an hour (while it is worn), is recorded as sleep [38]. Analysed with heart rate, it estimates sleep levels [39] (i.e., light, deep, REM, awake), and the start and stop times of every

sleep segment. It also determines the main sleep based on the time and total duration of the sleep.

From smartphone (HOPES app):

4. *Ambient light.* This is measured through the built-in light sensor to detect ambient brightness, which may be associated with participants' daily activities.
5. *Location parameters.* Locations of the smartphone, departure from typical travel patterns, and variance of the locations travelled derived from GPS are recorded.
6. *Sociability indices.* A summary of different types of social interactions is obtained such as the frequency and duration of phone calls (or messages) on various platforms (e.g., SMS, WhatsApp, etc.) and the amount of time spent on designated apps such as social media.
7. *Finger taps.* Characteristics of finger taps such as timestamp, timezone, screen orientation and the app name in which the tap is made on the smartphone are recorded. The identity of the key is captured, converted into a classification symbol (such as <enter>, <backspace>, <alphabet>, <numeric>, <symbol>) and then recorded.

Considering the sensitive nature of information collected, measures taken to preserve participants' privacy and potential risks (e.g., data breach) are explained to participants during consent-taking. For location data, GPS coordinates are obfuscated via a random origin displacement (different for each participant). Actual or absolute GPS locations are not transmitted from participant's smartphone. For sociability indices, no content information of the calls and messages are recorded while for finger taps, only the classification symbols are downloaded and stored by the HOPES app, thus there is no tracking of specific keys typed. These are done to preserve the privacy of participants. Data transmitted from the HOPES app to the AWS cloud is encrypted (using industry standard encryption algorithms: 256-bit AES (Advanced Encryption Standard) on content encryption with 2048-bit RSA on AES key encryption) and de-identified. All uploaded digital phenotyping data is stored de-identified and encrypted on the AWS cloud. This data is later downloaded to a controlled on-premise server, which is the only place where it can be decrypted. Participant identification is managed using a non-personally-identifying study ID. Participant-identifiable data is not uploaded onto the AWS cloud.

Assessment tools

These scales and tasks are done based on the study schedule (refer to Table 1):

1. *Structured Clinical Interview for DSM-5 Research Version (SCID-5-RV).* This is used to ascertain the participant's diagnosis [36].
2. *Clinical Global Impression scale (CGI).* This measures severity of illness and improvement on a 7-point scale. Severity of illness is evaluated based on the clinician's experience with patients of the same diagnosis, where a higher rating indicates greater severity. The Improvement item measures how much the patient's illness has improved or worsened relative to a baseline state, where a higher rating indicates greater worsening of illness [40].
3. *Brief Adherence Rating Scale (BARS).* It assesses antipsychotic medication adherence of outpatients with schizophrenia. A greater proportion of doses taken in the past month indicates greater adherence [41].
4. *Columbia Suicide Severity Rating Scale (CSSRS).* This scale assesses both suicidal ideation and behaviour [42].

5. *Positive and Negative Syndrome Scale (PANSS).* A 30-item scale measuring positive symptoms, negative symptoms, and general psychopathology. A higher total score indicates greater symptom severity [43].
6. *Brief Negative Symptom Scale (BNSS).* A 13-item scale measuring five negative symptom domains (blunted affect, alogia, asociality, anhedonia and avolition) and a subscale on lack of normal distress. A higher total score indicates greater negative symptoms [44].
7. *Calgary Depression Scale for Schizophrenia (CDSS).* This scale assesses level of depression in schizophrenia, distinguishing depressive symptoms from negative and positive symptoms. A higher total score reflects greater severity [45].
8. *Social and Occupational Functioning Assessment Scale (SOFAS).* It evaluates an individual's level of social and occupational functioning. Its rating is not directly influenced by the overall severity of the individual's psychological symptoms. A greater rating reflects superior functioning in various areas of life [46].
9. *Brief Assessment of Cognition in Schizophrenia (BACS).* A cognitive battery that assesses attention, verbal and working memory, motor and processing speed, verbal fluency, reasoning and problem-solving. A higher composite score indicates better cognitive function [47].
10. *5-level-EQ-5D (EQ-5D-5L).* A standardized instrument developed as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments. A higher score indicates best health imagined [48].
11. *Subjective Well-being under Neuroleptics scale – short form (SWNS).* A self-rated instrument to assess well-being from a patient's perspective based on their subjective experiences during antipsychotic treatment. A higher total score indicates greater well-being [49].
12. *Acceptability questionnaire.* This self-constructed questionnaire consists of an item measuring participants' satisfaction based on their experience using digital devices on a 7-point scale. Two other qualitative items gather feedback on the strengths and suggested improvement for the system and user satisfaction.
13. *Healthcare utilisation*. Information of interest such as hospitalisations, outpatient non-attendance, scheduled (e.g., clinic appointments) and unscheduled service use (e.g., psychiatric emergency room attendance) is obtained from medical records.

These scales are administered by clinicians (scales 1-4) and research assistants (scales 5-12) who have been trained and achieved good interrater reliability. De-identified data are entered into a database and hardcopy documents are kept on-site under lock and key.

Outcomes

Primary outcome

Changes to each unique digital biomarker that are associated with relapse during the 6 months will be examined. Relapse is defined as a re-admission due to mental deterioration or an overall increase by 2 points or more on the CGI severity item.

Secondary outcome

We will examine changes in psychiatric rating scales (refer to 'Assessment tools', scales 3-11) measuring symptom severity, cognition and functioning. Changes in digital phenotype that coincide with observed changes in rating scales will be examined. Acceptability of passive digital data use via smartphone and wrist-wearable device will be evaluated.

Study procedures

Baseline

Upon consent taking and enrolment, participants complete a baseline assessment which consists of clinical, cognitive, functioning scales and collection of demographic information (refer to Table 1). Participants are provided a Fitbit device which is worn daily and at night, except when charging. The HOPES and Fitbit apps are installed in the participant's smartphone for continuous, passive digital data collection during the 6 months. If possible, participants' personal phones were used, however in cases where the phone was too old or unsuitable, a study phone was loaned, and user data migrated so that the phone would become the participant's primary phone. Participants are provided a participant booklet and briefed on its contents including how to charge Fitbit, its maintenance, troubleshooting Fitbit device or app problems and participant's responsibilities during the study period.

Follow-up

Participants complete four follow-up visits at 6-weekly intervals (Weeks 6, 12, 18, 24). Follow-up assessment scales are completed according to the study schedule outlined in Table 1. Four audio-recorded telephone calls are made to participants who consented to this task between assessment visits. On the final (Week 24) or termination visit, the study apps are uninstalled from participant's mobile phone and the Fitbit is gifted to them. Loaned study phones are collected back once migration of content back to participants' personal phones is completed. An administrative follow-up is done at the 6-month/termination visit and 1-year timepoint since enrolment to gather healthcare utilisation information.

Monitoring of the digital data dashboard is done daily to ensure data is continuously uploaded to our server and to inform the team of any technical issues or non-compliance behaviours. If no data is uploaded from the HOPES and/or Fitbit app for 4 days or more, the case is highlighted to the study team members, who will contact the participant to resolve the problem. Participants are reimbursed for their digital data, mobile data usage and provided with an inconvenience fee for completion of the assessment at every follow-up visit. Participants are paid an additional fee if data from the Fitbit are available for more than 75% of the time between two adjacent study visits.

Sample size calculation

As this is an observational study, sample size was determined based on feasibility. Several studies suggest that a sample size of at least 30 participants generally allow adequate hypothesis testing while providing reasonable effect size [50–52]. Assuming a 10% drop-out rate, a sample size of 100 will provide 80% probability to observe at least 30 participants who relapse within 6 months, if true relapse rate is 37%. This relapse rate is an assumption derived based on binomial distribution as information on relapse rates is unavailable. If the true relapse rate is lower than 37%, the probability to observe at least 30 participants who relapse within 6 months will be less than 80%. If the true relapse rate is higher than 37%, then the probability will be more than 80%.

Data analysis plan

We will perform various exploratory analyses on the high volumes of digital and clinical data collected. Here we broadly outline the statistical methods to be used. We will start with processing and cleaning the raw digital data to extract features into usable forms (as outlined in our technical paper [37]) and derive composite scores of the clinical scales. Disambiguation between missing and invalid digital data

is done at this stage. Some digital features of interest include but are not limited to the following: heart rate, sleep efficiency, number of steps, radius of gyration, number of texts or calls and number of taps by apps. Mean and median ratings of the acceptability questionnaires, as well as open-ended responses will be examined.

We employ correlation and regression analyses to understand the relationship between digital features and clinical variables, as determined by the scales described above. This could enable us to detect symptom severity and their changes from the digital data alone. The most important digital features for determining symptom severity will also be identified.

We also employ survival analyses to understand the relationship between digital features and time to relapse for patients who relapse during the trial. This could enable us to predict the likelihood of imminent relapses from the digital data, as well as those features that are most important for that prediction.

We have also designed an anomaly detection dashboard using anomaly detection methods for time-series data to try to determine when a participant's clinical state changes (from their usual baseline state) in real-time. With the wide range of digital and clinical data recorded for up to 6 months, a baseline state of the participants' digital signal/behaviour may be established using statistical methods. Any deviations from this usual state may indicate behavioural changes preceding adverse events, such as relapse. Further details on the anomaly detection approach are outlined in our technical paper [37, pg. 8].

All information from the exploratory analyses above will aid in the development of prediction algorithms to forecast future relapse events. Note that these will be undertaken from both cross-sectional perspectives, in which we explore which digital signals of symptom severity and relapse can be generalized across individuals, and longitudinal perspectives, in which we explore which signals precipitate personalized changes in clinical state.

How missing data will be handled and problems with multiple comparisons will need to be considered carefully. We emphasize that our analyses are exploratory, where we seek to understand general trends regarding the relationships between the digital signals and clinical variables/relapse events, rather than to validate the predictability of a particular signal. As such, we will typically not know which machine learning models (for the clinical scale regression, survival analysis, or anomaly detection) or statistical methods (for missing data imputation or type I error mediation) would be most appropriate until seeing the data. As a general plan, however, we will explore complete case analyses, simple imputation strategies, and more complex methods like multiple and multivariate imputation as well as variable shrinkage/selection methods.

Ethics and dissemination

Participants will undergo consent-taking procedures with a study team member and a witness before starting any research-related activity. All collected data is kept confidential and only de-identified data is analysed. Findings of this study will be disseminated through publications in scientific journals and applicable conferences.

SUMMARY

Digital phenotyping holds promise to address the unmet needs and challenges in treatment of schizophrenia spectrum disorders. The ubiquity of sensing technologies provides easier access to previously untapped information such as passive data and their derived digital biomarkers. In this study, linking digital and assessment data with health utilisation records create opportunity for machine learning approaches to explore whether specific types of digital data are associated with changes in clinical, cognitive or functioning measures and its ability to forecast future relapse events.

While digital phenotyping approach has its merits (objective, continuous information, low cost, low user burden, scalable), it is still a work-in-progress. Issues such as information security and privacy are complex, and degrees of acceptability are unclear and need to be further addressed [35,53,54]. In addition, the large amount of complex, high-dimensional, and heterogeneous longitudinal data, poses significant challenges in data analysis and interpretation [55, 56]. Other issues such as inevitable data gaps (due to non-compliance, faulty devices, or technical issues), and variability in data quantity between participants, presents further obstacles in digital phenotyping. Nevertheless, this study hopes to contribute to the growing field of digital phenotyping research in behaviour and mental health in general, as well as schizophrenia in our particular trial. We hope that insights into acceptance of such technology will prompt further research in more usable devices and important issues such as privacy and security. Current clinical management methods, if combined with digital biomarkers, have the potential to better elucidate the nature and trajectory of behavioural science and mental health and identify important signals to aid in personalized treatment and to optimize care.

STUDY STATUS

Recruitment commenced end October 2019. Data collection started in November 2019 and is currently ongoing.

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Contributors: JL, SV, CT and ZY were involved in the design of the clinical aspects of the study. RJTM, WM, XW, NV and TB's contributions to the protocol were on the digital technology, its operations and system architecture. YW contributed to the biostatistical design and planning. CH contributed to the data analysis plan. NAAR drafted the paper with input from all authors. All authors reviewed and approved the final manuscript.

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Competing interests: JL, ZY and NAAR received funding from the Ministry of Health Office of Healthcare Transformation during the course of the study. JL is further supported by the Ministry of Health National Medical Research Council. RJTM, WM, XW and NV have a patent on systems, devices, and methods for self-contained personal monitoring of behaviour to improve mental health and other behaviourally-related health conditions pending. Nothing in this patent will affect freedom of use in the application of the techniques described in the submitted paper. All other authors declare that they have no competing interests.

Ethics approval: The study protocol has been reviewed and approved by the National Healthcare Group (NHG) Domain Specific Review Board in September 2019 (DSRB Reference no.: 2019/00720).

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Patient consent for publication: Not required

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Table 1. Study schedule.

Events	Visit 1 Week 0	Telephone Contact Week 3	Visit 2 Week 6	Telephone Contact Week 9	Visit 3 Week 12	Telephone Contact Week 15	Visit 4 Week 18	Telephone Contact Week 21	Visit 5 Week 24 / Termination	Post-Study Follow up Week 52
Written Informed Consent	X									
Demographics and Socio-Economics Status	X								X	
Medical History	X									
Medication Current and History / Concomitant medication	X		X		X		X		X	
Structured Clinical Interview for DSM-5 (SCID-5-RV)	X									
Clinical Global Impression scale – Improvement (CGI-I)			X		X		X		X	
Clinical Global Impression scale – Severity (CGI-S)	X		X		X		X		X	
Brief Adherence Rating Scale (BARS)	X		X		X		X		X	
Positive and Negative Syndrome Scale (PANSS)	X		X		X		X		X	
Brief Negative Symptom Scale (BNSS)	X								X	
Calgary Depression Scale for Schizophrenia (CDSS)	X		X		X		X		X	
Columbia Suicide Severity Rating Scale (CSSRS)	X		X		X		X		X	
Social and Occupational Functioning Assessment Scale (SOFAS)	X		X		X		X		X	
Brief Assessment of Cognition in Schizophrenia (BACS)	X								X	
5-Level EQ-5D (EQ-5D-5L)	X				X				X	
Subjective Well-being under Neuroleptics scale – short form (SWNS)	X								X	
Acceptability Questionnaire									X	
Healthcare Utilisation									X	X
Continuous Collection of the Data from the Apps and Wrist-wearable Device	X		X		X		X		X	
Audio Recording		X		X		X		X		
Collection of the Wrist-wearable Device and Apps Installation	X									
Uninstallation of Apps									X	

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-10; Periods of recruitment: 12
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7 & 10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Not applicable
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-11
		(*b*) Describe any methods used to examine subgroups and interactions	Not applicable
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Not applicable for study protocol
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	

		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	Not applicable for study protocol
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Not applicable for study protocol
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.