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

Nur Amirah Abdul Rashid, Wijaya Martanto, Zixu Yang, Xuancong Wang, Creighton Heaukulani, Nikola Vouk, Thismu Buddhika, Yuan Wei, Swapna Verma, Charmaine Tang, Robert J T Morris, Jimmy Lee

To cite: Abdul Rashid NA, Martanto W, Yang Z, et al. BMJ Open 2021;11:e046552. doi:10.1136/bmjopen-2020-046552

ABSTRACT

Introduction The course of schizophrenia illness is characterised 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.

Trial registration number NCT04230590.

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%. Despite treatment adherence, some may find themselves decompenating, leading to subsequent relapses. 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. 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, such as sleep, psychomotor and physical activity, social withdrawal, exacerbation of psychotic symptoms and medication non-adherence; 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, this has created an unprecedented opportunity to quantify user behaviours in their natural environment through continuous capture of objective digital data, known as digital phenotyping. Digital phenotyping is based on information from sensors (eg, global positional system (GPS), accelerometer), speech (eg, sentiment and prosody) and human–computer interactions (eg, keystrokes such as taps and swipes on phone screen). 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 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. This is not uncommon as they may isolate themselves during episodes of psychotic exacerbations. Objective mobility measures differentiated individuals with schizophrenia from healthy controls, as seen from the large difference in distance travelled in a week. 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. Location and mobility features (eg, location entropy) were also strongly associated with symptoms of schizophrenia. Changes in typical daily mobility have been reported to precede clinical relapse by up to 2 weeks.

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, for example, 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. Sociability anomalies were detected 2 weeks before relapse.

Sleep

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

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 that is, 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 to wearable sensors in estimating sleep duration. Commercially available wearable devices, for example, Fitbit (Fitbit, San Francisco, CA, USA), uses 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. 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.

Finger taps

Typing and scrolling rhythms on a smartphone are predictive of one’s cognition and emotional state. Zulueta and colleagues 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. Digital biomarkers derived from tactile user activity on smartphones were found to correlate with standard neurocognitive tests in healthy individuals. No existing study has examined this in schizophrenia; however, finger taps may be helpful as a proxy measure of cognitive deficits, a known core feature in schizophrenia and an important determinant of functioning and functional recovery. Also, the potential of predicting emotional state from finger taps may aid in identifying occurrence.
of mood disturbances such as depression, which is known to have adverse effects on schizophrenia progression, morbidity and mortality.  

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 are highly sensitive, 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 the 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, such as 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 21–65 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 and are within 8 weeks post-discharge from hospitalisation at IMH. Individuals are excluded if they: (1) are female and currently pregnant or planning a pregnancy within 6 months; (2) 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 and (3) have visual or physical motor impairment that could interfere with study tasks.

Digital data

Digital data are collected from a wrist wearable device (Fitbit Charge 3 or Charge 4), a smartphone and their corresponding smartphone applications (apps): Fitbit app and our in-house developed HOPES app (Health Outcomes through Positive Engagement and Self-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 utilise 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. 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 beats per minute at a frequency of up to every 5 s.
2. **Physical activity.** Number of steps is computed from accelerometer data and recorded every minute.
3. **Sleep.** Sleep is computed based on body movements. If no body movement is detected for about an hour (while Fitbit is worn), the device records that as sleep. Analysed with heart rate, it estimates sleep levels (ie, light, deep, rapid eye movement, 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 (eg, 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 (eg, 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 are encrypted using industry standard encryption algorithms: 256-bit AES (Advanced Encryption Standard) on content encryption with 2048-bit RSA on AES key encryption and deidentified. All uploaded digital phenotyping data is stored deidentified and encrypted on the AWS cloud. These data are 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 are 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.

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.

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.

4. **Columbia Suicide Severity Rating Scale (CSSRS).** This scale assesses both suicidal ideation and behaviour.

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.

6. **Brief Negative Symptom Scale (BNSS).** A 13-item scale measuring five negative symptom domains (blunted affect, alogia, asociality, anhedonia and avolition) and lack of normal distress. A higher total score indicates greater negative symptoms.

7. **Calgary Depression Scale for Schizophrenia (CDSS).** This scale assesses levels of depression in schizophrenia, distinguishing depressive symptoms from negative and positive symptoms. A higher total score reflects greater severity.

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.

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.

10. **5-level-EQ-5D (EQ-5D-5L).** A standardised 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.

11. **Subjective Well-being under Neuroleptics Scale-short form (SWNS).** A self-rated instrument that assess well-being based on the patient’s experiences during antipsychotic treatment. A higher total score indicates greater well-being.

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 (eg, clinic appointments) and unscheduled service use (eg, 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 inter-rater reliability. Deidentified data are entered into a database and hardcopy documents are kept onsite 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 readmission due to mental deterioration or an overall increase by two 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...
### Table 1  Study schedule

| Events                                                                 | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Post study Follow-up |
|------------------------------------------------------------------------|---------|---------|---------|---------|---------|----------------------|
| Written informed consent                                              | Week 0  | Week 3  | Week 6  | Week 9  | Week 12 | Week 24/termination  |
| Demographics and socioeconomics status                                |         |         |         |         |         | Week 52              |
| Medical history                                                        |         |         |         |         |         |                      |
| Medication current and history/concomitant medication                 |         |         |         |         |         | X                    |
| Structured clinical interview for DSM-5 (SCID-5-RV)                   |         |         |         |         |         | X                    |
| Clinical global impression scale-improvement (CGI-I)                  |         |         |         | X       | X       | X                    |
| Clinical global impression scale-severity (CGI-S)                      | X       |         | X       |         | X       |                      |
| Brief Adherence Rating Scale (BARS)                                   | X       |        | X       |         |         | X                    |
| Positive and Negative Syndrome Scale (PANSS)                          |         |         |         |         |         | X                    |
| Brief Negative Symptom Scale (BNSS)                                   |         |         |         |         |         | X                    |
| Calgary Depression Scale for Schizophrenia (CDSS)                     | X       |         | X       |         |         | X                    |
| Columbia Suicide Severity Rating Scale (CSSRS)                        | X       |         | X       |         |         | X                    |
| Social and Occupational Functioning Assessment Scale (SOFAS)          |         |         | X       |         |         | X                    |
| Brief Assessment of Cognition in Schizophrenia (BACS)                 |         |         |         |         |         | X                    |
| 5-Level EQ-5D (EQ-5D-5L)                                              | X       |         |         |         |         | X                    |
| Subjective well-being under neuroleptics scale-short form (SWNS)      | X       |         |         |         |         | X                    |
| Acceptability questionnaire                                           |         |         |         |         |         | X                    |
| Healthcare utilisation                                                |         |         |         |         |         | X                    |
| Continuous collection of the data from the apps and wrist-wearable device |         |         |         |         |         | X                    |
| Audio recording                                                       |         |         |         |         |         | X                    |
| Collection of the wrist-wearable device and apps installation         |         |         |         |         |         | X                    |
| Uninstallation of apps                                                |         |         |         |         |         | X                    |
scales will be examined. Acceptability of passive digital data collection via smartphone and wrist-wearable device will be evaluated.

**Study procedures**

**Baseline**

After 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 24 hours daily, 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 are used; however, in cases where the phone is too old or unsuitable, a study phone is loaned, and user data is migrated so that the study 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 participants’ mobile phones and the Fitbit is gifted to them. Loaned study phones are collected back once migration of content back to participants’ personal phones is complete. 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 are 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 suggested that a sample size of at least 30 participants generally allow adequate hypothesis testing while providing reasonable effect size.26-32 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 paper37 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 participants who relapse during the study. 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 signals/behaviours 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

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 generalised across individuals, and longitudinal perspectives, in which we explore which signals precipitate individual changes in clinical state.

How missing data will be handled and problems with multiple comparisons will need to be considered carefully. We emphasise 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 are kept confidential and only deidentified data are 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 an 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. In addition, the large amount of complex, high-dimensional and heterogeneous longitudinal data, pose significant challenges in data analysis and interpretation. Other issues such as inevitable data gaps due to non-compliance, faulty devices or technical issues, and variability in data quantity between participants, present further obstacles in digital phenotyping. Nevertheless, this study hopes to contribute to the growing field of digital phenotyping research in schizophrenia as well as behaviour and mental health in general. 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 personalised treatment and to optimise care.

STUDY STATUS

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

Author affiliations

Research Division, Institute of Mental Health, Singapore
Office for Healthcare Transformation, Ministry of Health, Singapore
Singapore Clinical Research Institute, Singapore
East Region & Department of Psychosis, Institute of Mental Health, Singapore
Duke-NUS Medical School, Singapore
North Region & Department of Psychiatry, Institute of Mental Health, Singapore
Yong Loo Lin School of Medicine, National University of Singapore, Singapore
Neuroscience and Mental Health, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

Acknowledgements

The authors would like to thank Dr Shi Luming and Dr Charles Zheng Gishi for their help with the study design, and financial and potential cost impact analysis, Dr Teoh Yee Leong, Dr Gerard Wong, Dr Ang Seng Bin, Professor Michael Chee, Dr Ong Ju Lynn, Dr Soon Chun Siong for their advisory role and expert guidance, and Ms Melody Lai, Ms Ang Su Ann and Ms Amilia Sng for their assistance with study initiation and monitoring. We also thank the IMH doctors and case managers for their referrals and assistance with recruitment.

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.

Funding

The study is supported by the Ministry of Health Office for Healthcare Transformation (grant no.: N/A) and the Ministry of Health National Medical Research Council Centre Grant (NMRC/CG/M002/2017.IMH). JL is supported by the Ministry of Health National Medical Research Council Clinician Scientist Award (NMRC/CSANV1/Nov005).

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.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

Open access

This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs

Nur Amirah Abdul Rashid http://orcid.org/0000-0002-1047-3106
Jimmy Lee http://orcid.org/0000-0002-7724-7445

REFERENCES

1. Robinson D, Woerner MG, Alvir JM, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. Arch Gen Psychiatry 1999;56:241–7.
2. Alphs L, Nasrallah HA, Bossie CA, et al. Factors associated with relapse in schizophrenia despite adherence to long-acting injectable antipsychotic therapy. Int Clin Psychopharmacol 2016;31:202–9.
3. Wyatt RJ. Neuroleptics and the natural course of schizophrenia. Schizophr Bull 1991;17:325–51.
4. Takeuchi H, Sui C, Remington G, et al. Does relapse contribute to treatment resistance? Antipsychotic response in first- vs.
second-episode schizophrenia. Neuropsychopharmacology 2019;44:1036–42.
5 Lin L, Zhao YJ, Zhou HJ, et al. Comparative cost-effectiveness of 11 oral antipsychotics for relapse prevention in schizophrenia within Singapore using a Markov model. Health Econ 2019;28:43–55.
6 Sutton DL. Relapse signatures and insight: implications for CPNs. J Psychiatr Ment Health Nurs 2004;11:569–74.
7 Birchwood M, Spencer E, McGovern D. Schizophrenia: early warning signs. Adv Psych Treat 2000;6:93–101.
8 Spaniel F, Bakstein E, Anzy J, et al. Relapse in schizophrenia: definitely not a bolt from the blue. Neurosci Lett 2018;669:68–74.
9 Wang R, Wang W, Angus MSH. Predicting symptom trajectories of schizophrenia using mobile sensing. Proc ACM Interact Mob Wearable Ubiquitous Technol 2017.
10 Firth J, Cotter J, Torous J, et al. Mobile Phone Ownership and Endorsement of “mHealth” Among People With Psychiatry: A Meta-analysis of Cross-sectional Studies. Schizophr Bull 2016;42:448–56.
11 Smart Nation. Transforming Singapore. Available: https://www.smartnation.gov.sg/why-Smart-Nation/transforsing-singapore [Accessed 6 May 2020].
12 Onnela J-P, Rauch SL. Harnessing smartphone-based digital phenotyping throughout daily phenotyping: a pilot study. Neuropsychopharmacology 2016;41:1691–6.
13 Torous J, Kiang MV, Lorme J, et al. New tools for new research in psychiatry: a scalable and customizable platform to empower data driven smartphone research. JMIR Ment Health 2016;3:e16.
14 Insel TR. Digital phenotyping: technology for a new science of behavior. JAMA 2017;318:1215–6.
15 Guimond S, Keshavan MS, Torous JB. Towards remote digital phenotyping of cognition in schizophrenia. Schizophr Res 2019;208:36–8.
16 Depp CA, Baskin J, Moore RC, et al. GPS mobility as a digital biomarker of negative symptoms in schizophrenia: a case control study. npj Digit Med 2019;2:1–7.
17 Freeman D. Suspicious minds: the psychology of persecutory delusions. Clin Psychol Rev 2007;27:425–57.
18 Buck B, Hallgren KA, Scherer E, et al. Capturing behavioral indicators of persecutory ideation using mobile technology. J Psychiatr Res 2019;116:112–7.
19 Wang R, Angus MSH, Abdullah S. CrossCheck: toward passive sensing of mental health changes in people with schizophrenia, in: proceedings of the 2016 ACM international joint conference on pervasive and ubiquitous computing. Heidelberg, Germany: Association for Computing Machinery, 2016: 886–97.
20 Barnett I, Torous J, Staples P, et al. Relapse prediction in schizophrenia through daily phenotyping: a pilot study. Neuropsychopharmacology 2018;43:1660–6.
21 Buck B, Scherer E, Brian R, et al. Relationships between smartphone social behavior and relapse in schizophrenia: a preliminary report. Schizophr Res 2019;208:167–72.
22 Benson KL. Sleep in schizophrenia. in: proceedings of the 2016 ACM international joint conference on pervasive and ubiquitous computing. Heidelberg, Germany: Association for Computing Machinery, 2016: 886–97.
23 Reeve S, Sheaves B, Freeman D. The role of sleep dysfunction in the occurrence of delusions and hallucinations: a systematic review. Clin Psychol Rev 2015;42:96–115.
24 Meyer N, Joyce DW, Karr C. P029 sleep and circadian rhythm disturbances and relapse in schizophrenia: a digital phenotyping study. BMJ Open Res 2019;6:A17.
25 Chen Z, Liu M, Chen F. Unobtrusive sleep monitoring using smartphones. In: 2013 7th International Conference on Pervasive Computing Technologies for Healthcare and Workshops. 2013:145–52.
26 Shin S, Yeom C-W, Shin C, et al. Activity monitoring using a mHealth device and correlations with psychopathology in patients with chronic schizophrenia. Psychiatry Res 2016;246:712–8.
27 Tren T, Reshef YS, Bazhmin M. Real-time schizophrenia monitoring using wearable motion sensitive devices. In: Perego P, Rahmani AM, eds. Wearable motion sensitive devices. In: Perego P, Rahmani AM, eds. CrossCheck: integrating self-report, behavioral sensing, and smartphone use to identify digital indicators of psychotic relapse. Psychiatric Rehabil J 2017;40:266–75.
28 Zulueta J, Piscitello A, Rasic M, et al. Predicting mood disturbance severity with mobile phone keystroke metadata: a BIAffect digital phenotyping study. J Med Internet Res 2018;20:e241.
29 Daqum P. Digital biomarkers of cognitive function. NPJ Digit Med 2018;1:1–3.
30 Elvevåg B, Goldberg TE. Cognitive impairment in schizophrenia is the core of the disorder. Crit Rev Neurobiol 2000;14:1–21.
31 Green MF, Harvey PD. Cognition in schizophrenia: past, present, and future. Schizophr Res Cogn 2014;1:e1–9.
32 Green MF, Meier CM. Cognitive improvement and functional outcome in schizophrenia and bipolar disorder. J Clin Psychiatry 2006;67:e12.
33 Miller A, Schmidt U, Angermeyer MC, et al. Humanistic burden in schizophrenia: a literature review. J Psychiatr Res 2014;54:85–93.
34 Delting T, Gao F, Schneider S, et al. Exploring the far side of mobile health: information security and privacy of mobile health apps on iOS and android. JMIR Mhealth Uhealth 2015;3:e8.
35 First MB, Williams JBW, Karg RS. Structured clinical interview for DSM-5 research version (SCID-5 for DSM-5, research version; SCID-5-RV). Arlington, VA: American Psychiatric Association, 2015.
36 Wang X, Vouk N, Haukulan C, et al. HOPES: an integrative digital phenotyping platform for data collection, monitoring, and machine learning. J Med Internet Res 2021;23:e23984.
37 Fitbit. How does my Fitbit device automatically detect sleep? Available: https://help.fitbit.com/articles/en_US/Help_article/1314. [Accessed 5 May 2021].
38 Fitbit. How does my Fitbit device automatically detect my sleep stages? Available: https://help.fitbit.com/articles/en_US/Help_article/2163. [Accessed 5 May 2021].
39 Guy W. ECDU assessment manual for psychopharmacology. Rev edn, Rockville, MD: U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs, 1976.
40 Byerly MJ, Nakonezny PA, Rush AJ. The brief adherence rating scale (BARS) validated against electronic monitoring in assessing the antipsychotic medication adherence of outpatients with schizophrenia and schizoaffective disorder. Schizophr Res 2008;100:60–9.
41 Poskern K, Brown GK, Stanley B, et al. The Columbia-suicide severity rating scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2010;167:1266–77.
42 Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–76.
43 Kirkpatrick B, Strauss GP, Nguyen L, et al. The brief negative symptom scale: psychometric properties. Schizophr Bull 2011;37:300–5.
44 Addington D, Addington J, Schissel B. A depression rating scale for schizophrenia. Schizophr Res 1990;3:247–51.
45 Goldman HH, Skodol AE, Lave TR. Revising axis V for DSM-IV: a review of measures of social functioning. Am J Psychiatry 1993;150:1148–56.
46 Keefe RSE, Goldberg TE, Harvey PD, et al. The brief assessment of cognition in schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr Res 2004;68:283–97.
47 Herdmann M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1277–36.
48 Naber D. A self-rating to measure subjective effects of neuroleptic drugs, relationships to objective psychopathology, quality of life, compliance and other clinical variables. Int Clin Psychopharmacol 1995;10:133–8.
49 Mooney CZ, Duval RD. Bootstrapping: a nonparametric approach to statistical inference. Sage, 1993.
50 Isaac S, Michael WB. Handbook in research and evaluation: a collection of principles, methods, and strategies useful in the planning, design, and evaluation of studies in education and the behavioral sciences. 3rd edn. San Diego, CA: Edits Publisher, 1995.
51 Hill R. What sample size is “enough” in internet survey research. IJPCF-J 1998:6:10.
52 Bernardos AM, Pires M, Cillé D. Digital phenotyping as a tool for personalized mental healthcare, in: proceedings of the 13th EAI International Conference on pervasive computing technologies for healthcare. Trento, Italy: Association for Computing Machinery, 2019: 403–8.
53 Avelar DC, Zhang M, Schueller SM. Personal sensing: understanding mental health using ubiquitous sensors and machine learning. Annu Rev Clin Psychol 2017;13:23–47.
54 Lydon-Staley DM, Barnett I, Satterthwaite TD, et al. Digital phenotyping for psychiatry: accommodating data and theory with science phenotyping methodologies. Curr Opin Biomed Eng 2019;9:8–13.
55 Liang Y, Zheng X, Zeng DD. A survey on big data-driven digital phenotyping of mental health. Information Fusion 2019;52:290–307.