# CONNECT: using electronic devices (e.g. smartphones, smartwatches) to predict relapse of psychosis

# Research Protocol

**HRA Protocol Compliance Declaration**

This protocol has regard for the HRA guidance and order of content

**Protocol Version Number and Date**

Version 13.0, 28.02.26

**Research Reference Numbers**

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|---|---|
| **IRAS Number:** | 322875 |
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**This protocol has regard for the HRA guidance and order of content.**

**(Template Version 1.2, March 2016)**

**Full Title of the Study**

CONNECT: using electronic devices (e.g. smartphones, smartwatches) to predict relapse of psychosis.

**Short Trial Title / Acronym**

CONNECT

**Signature Page**

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

**For and on behalf of the Study Sponsor:**

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Position: Research Practice Governance Manager

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**Chief Investigator:**

Signature: SBucci Date: 13/Mar/2026

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Name: (please print): Sandra Bucci

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**ii. List of Abbreviations**

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

| | |
|---|---|
| AE | Adverse Event |
| API | Application Programming Interface |
| ASM | Active Symptom Monitoring |
| ASSIST | Alcohol, Smoking and Substance Involvement Screening Test |
| AWS | Amazon Web Services |
| CDS | Calgary Depression Scale |
| CGI | Clinical Global Impression |
| CI | Chief Investigator |
| CRF | Case Report Form |
| DPIA | Data Protection Impact Assessment |
| DRM | Digital Remote Monitoring |
| DWQ | Dunn Worry Questionnaire |
| EHR | Electronic Health Record |
| ERG | Expert Reference Group |
| EWS | Early Warning Signs |
| FoRSe | Fear of Recurrence Scale |
| GAD | Generalised Anxiety Disorder |
| GCP | Good Clinical Practice |
| GDPR | General Data Protection Regulation |
| GPS | Global Positioning System |
| HEI | Higher Education Institution |
| ICH | International Conference for Harmonisation |
| ICMJE | International Committee of Medical Journal Editor |
| IG | Information Governance |
| IN | Involvement Network |
| IRAS | Integrated Research Application System |
| LEAP | Lived Experience Advisory Panel |
| MARS | Medication Adherence Rating Scale |
| NHS | National Health Service |
| NHS R&D | National Health Service Research & Development |
| NICE | National Institute for Health and Care Excellence |

| | |
|---|---|
| PANSS | Positive and Negative Syndrome Scale |
| PCPW | Perceived Criticism & Perceived Warmth Scale |
| PI | Principal Investigator |
| PIS | Participant Information Sheet |
| PMG | Project Management Group |
| PPI | Patient and Public Involvement |
| PSM | Passive Symptom Monitoring |
| PSSUQ | Post-Study System Usability Questionnaire |
| PSYRATS | Psychotic Symptom Rating Scales |
| RDMS | Research Data Management System |
| REC | Research Ethics Committee |
| REDCap | Research Electronic Data Capture |
| RSG | Research Steering Group |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SMS | Short Message Service |
| SOP | Standard Operating Procedure |
| UoM | University of Manchester |
| WSAS | Work and Social Adjustment Scale |

### iii. Study Summary

Conventional methods of monitoring and assessing psychosis involve face-to-face assessments that rely on individuals recalling their symptoms and emotional states over the period since their last assessment. Understandably, recall can be inaccurate, resulting in imprecise assessment and treatment planning, and assessment is not frequent enough to detect early warning signs, thereby increasing the risk of relapse.

The study aims to recruit a cohort of relapse-prone individuals sufficient in size, collect passively and actively sensed data, with high sampling frequency, to develop a risk prediction model for estimating an individual's risk of relapse, which gets updated as more information becomes available about them over time. Moreover, the study aims to develop an adaptive sampling regime for maximising engagement and information obtained from digital remote monitoring (DRM); that is, asking the right questions, at the right frequency and time, for the right individuals. This will enable relapse to be predicted more accurately.

| | | |
|---|---|---|
| Study Title | Can we use information from electronic devices (e.g. phones) to predict if someone will have a relapse of psychosis? | |
| Short Title | CONNECT | |
| Objectives | 1. To develop a scalable digital platform that combines active and passive remote symptom monitoring, along with clinical assessments and a relapse prediction algorithm.<br>2. To predict psychosis relapse<br>3. To examine the utility of passive data<br>4. To develop an adaptive sampling framework | |
| Study Design | Prospective, observational (non-randomised) non-interventional study with an in-built process evaluation and assessment of feasibility and acceptability of wearable devices, using commercially available wearable technology and smartphone sensors, representing no change to the usual care or treatments of participants due to participation. | |
| Study Participants (planned sample size) | Relapse-prone individuals with experience of psychosis *(n* = 1100) | |
| Study Duration | 47 months | |
| Planned Study Period | August 2023 - December 2026 | |
| | Outcomes | Outcome Measures |
| Primary | To derive and validate a personalised risk prediction algorithm to estimate the short-term risk of psychosis relapse | Clinical relapse, occurring within the next 7 or 28 days, measured every 4 months |
| Secondary | To derive and validate an adaptive sampling regimen for maximising engagement and information obtained from digital remote monitoring (DRM) | Disengagement with DRM devices |

| | | |
|---|---|---|
| | Acceptability of a wearable device | Assessment of data collected; satisfaction questionnaire |
| | Acceptability of DRM and study procedures | Participants report procedures are acceptable via qualitative interviews and satisfaction questionnaire |
| Eligibility Criteria | Inclusion criteria:<br>(i) Adults (16 years and over);<br>(ii) within the past two years have had at least one acute episode of psychosis (including relapse and first episode) leading to an unscheduled episode of acute care, including inpatient admission or acute home treatment/crisis intervention;<br>(iii) received a clinical diagnosis of, or confirmed by the treating clinician to meet the criteria of, schizophrenia spectrum disorder (ICD10 F20-29);<br>(iv) current presentation does not include severe acute symptoms;<br>(v) in accordance with the Mental Capacity Act, mental capacity will be assumed. If there is any doubt, then a capacity assessment will be carried out by a clinician from the study team or the responsible clinician.<br><br>Exclusion criteria*:* Experienced a recent relapse within the previous 12 weeks as confirmed by the treating clinician; non-English speaking. | |
| Statistical Methodology and Analysis | Extraction of sensor features; estimate association between these features and clinical status using mixed-effects models and unsupervised machine learning.<br><br>Regression modelling and other supervised machine learning approaches to develop risk prediction algorithm.<br><br>Information and decision theoretic methods to build adaptive sampling algorithm.<br><br>Qualitative methods (e.g. Framework analysis) to measure acceptability. | |

### iv. Funding and Support in kind

| Funder(s) | Financial and Non Financial Support Given |
|---|---|
| The Wellcome Trust | This project is funded by a Wellcome Trust funded grant (222875/Z/21/Z) CONNECT: Digital markers to predict psychosis relapse. The views expressed are those of the author(s) and not necessarily those of the Wellcome Trust. |

### v. Role of Study Sponsor and Funder

Neither the study sponsor nor the study funder will control final decisions regarding study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results. The proposed project has been reviewed by an international panel of experts convened by The Wellcome Trust and was recommended for funding. The project sponsor is The University of Manchester (UoM) who will oversee study setup, delivery and close-out to ensure research governance compliance. The analysis, interpretation and preparation of outputs will be the responsibility of the Principal Investigator (Bucci) and the project team. The views expressed will be those of the authors and not necessarily those of the Wellcome Trust or UoM.

### vi. Roles and Responsibilities of Study Management Committees / Groups & Individuals

#### Project Management Group (PMG)

Operational management and governance of transitions between workstreams will be through monthly meetings of the PMG, chaired by the Principal Investigator (PI; Professor Bucci) or her nominated Deputy, and comprising study Co-Investigators (including the site PIs and a Patient & Public Engagement (PPI) co-applicant), the project manager, the recruitment site research co-ordinators and postdoctoral researchers. Meetings will be held primarily remotely. The PMG will monitor study progress, identify risks, and develop solutions to managing risks to ensure the project will be delivered in a timely manner and within budget.

#### Project Board

The Board shall comprise of Professor Sandra Bucci, Professor John Ainsworth, one nominated representative from each academic institution, being Manchester, KCL, Glasgow, Edinburgh, Cardiff, and Sussex and Annabel Walsh on behalf of McPin (the “Board Members”). All significant operational matters relating to the Project will be decided upon by the Board. The Board shall monitor and assess the progress of recruitment of participants to the study and shall conduct an annual review of each participating site from the date of commencement of recruitment. The Board will meet every 6 months at venues to be agreed and at any time when reasonably considered necessary at the request of any of the Parties.

#### Research Steering Group (RSG)

The RSG will operate as the key forum through which the funder will be kept up to date about project progress. The RSG will meet every 6 months for the life of the project, or from time to time as the RSG may reasonably request. The RSG will advise the funder when and whether each of the research phases, research outputs or targets of the project have been achieved. The RSG will provide oversight of the protection of any Wellcome-funded IP, the development of the commercialisation strategy for such IP, and the commercialisation and dissemination efforts relating to such IP (including the project results), which shall be a standing agenda item for each RSG meeting. Tasks for the RSG include:

1. To monitor the performance and technical content of the Project against the Project Plan;

2. To critically assess the results of the project regularly throughout the project (including milestone reviews);

3. To identify and address any weaknesses or delays in the Project;

4. To co-ordinate internal and outsourced components of the project, including agreeing the use of third party collaborators or sub contractors not specifically identified in the project plan;

5. To recommend modifications to the implementation of the Project (including the implementation of the Project objectives) as necessary from time to time;

6. To review reports from the Site Visit Group.

The RSG will also monitor ethical issues of consent, consider reports and recommendations, and will approve relevant protocols and procedures. Adverse events will be monitored by the RSG. The RSG will comprise: the Principal Investigator; the deputy Principal Investigator (being John Ainsworth or his successor); at least one independent expert adviser with experience which is relevant to the Project; one representative of the University of Manchester's technology transfer office (in an advisory and non-voting capacity); and two representatives or nominees of The Wellcome Trust.

**Advisory Group**

The project will be guided by ongoing consultations with experts by experience led by our PPI collaborator Annabel Walsh, with further support from the McPin Foundation. There are three advisory groups for the project. An Involvement network (IN), comprising members where possible across the recruitment sites, a smaller Lived Experience Advisory Panel (LEAP), drawn from the IN, and an Expert Reference Group (ERG), comprising members from a range of professional disciplines (e.g. clinicians, computer scientist, software engineer), as well as a person with lived experience and a carer. The IN will meet twice a year, while the LEAP and ERG will meet approx. quarterly or at key points throughout the life of the project.

The advisory groups will help steer the project, contribute to study procedures, project design, DRM development and dissemination, and ethical issues that might arise. McPin will develop and shape the PPI plans with public contributors, set and refine the overall PPI strategy, provide appropriate induction and training to advisory group members (in addition to the training we will offer) and ensure that involvement is aligned to UK Standards for Public Involvement and GRIPP2 guidance.

### vii. Protocol Contributors

The following individuals or groups have contributed to the study protocol:

- Professor Sandra Bucci, Dr Jane Lees, Professor John Ainsworth, Dr Pauline Whelan (a study co-applicant on a previous version of this protocol), Professor Shôn Lewis.
- Study investigators: Professor Kathryn Greenwood, Professor Dame Til Wykes, Dr Matteo Cella, Professor Andrew Gumley, Professor Matthias Schwannauer, Professor James Walters, Professor Richard Drake, Professor Gillian Haddock, Annabel Walsh
- PPI contributors: Alex Kenny, and people with lived experience from the study Involvement Network and Lived Experience Advisory Panel (LEAP).

Statistical guidance was provided by Professor Richard Emsley, Dr Matthew Sperrin, and Dr Glen Martin.

**viii. Key Words** schizophrenia, psychosis, serious mental illness, relapse, digital, m-health

## ix. Study Design Flowchart

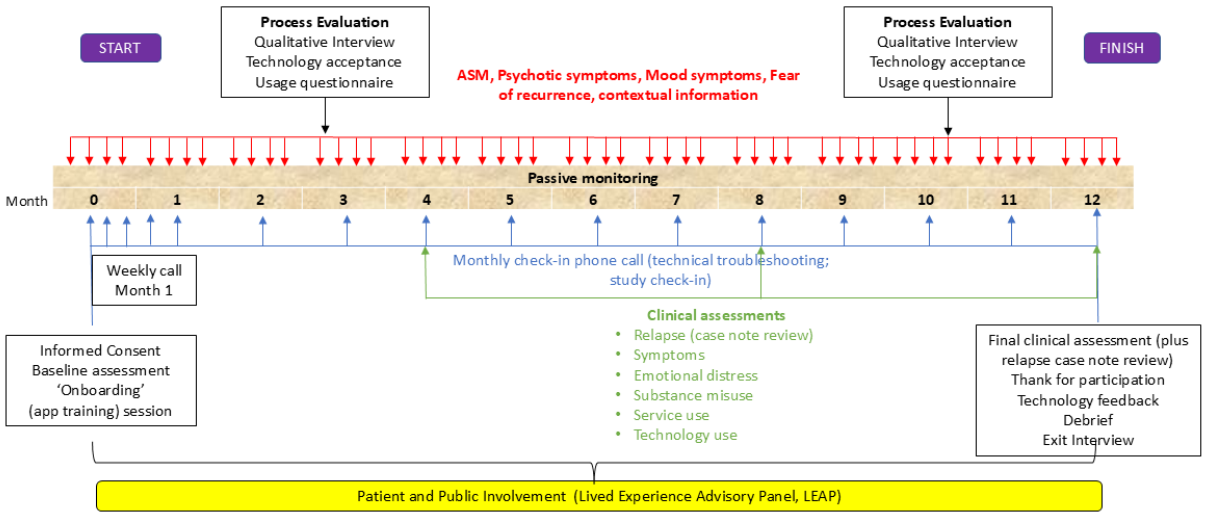


Figure 1. Summary of cohort study (4 month assessment schedule)

Note: Participants who provided consent before mid-January 2025 were scheduled to complete clinical assessments post-Baseline every three months (i.e., at 3, 6, 9, and 12 months). Participants consented thereafter followed a 4-monthly (i.e. at 4, 8 and 12 months) follow-up schedule.

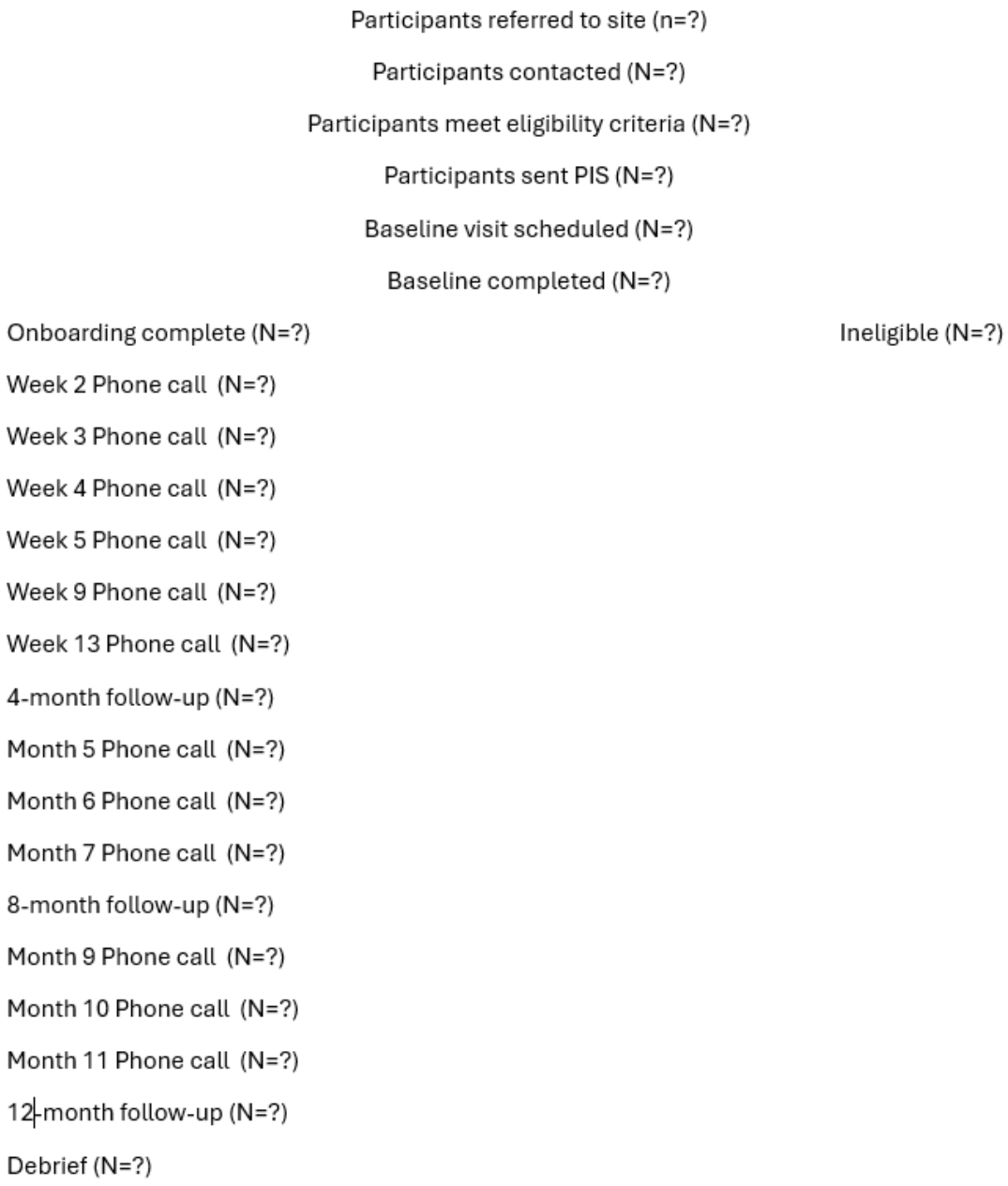


Figure 2. Study flowchart (4-month assessment schedule)
**Note:** Participants who provided consent before mid-January 2025 were scheduled to complete clinical assessments post-Baseline every three months (i.e., at 3, 6, 9, and 12 months).

**STUDY PROTOCOL**

Can we use information from electronic devices (e.g. phones) to predict if someone will have a relapse of psychosis?

# 1 Background

## 1.1. Overview

Psychosis is a severe mental health problem and a huge public health challenge. Psychosis has a high burden of disease, with 80% of people experiencing at least one relapse within five years of a first episode (Alvarez-Jimenez, et al., 2012). Local service structures are under immense pressure to keep up with demand. Long waiting times, stigma of accessing mental health services, gender and socio-economic factors, and reactive care result in delayed and inefficient treatment. Delays in receiving the right treatment at the right time increases risk of relapse. This is significant: each relapse is costly to health services (Ascher-Svanum, et al., 2010) and increases the individual's risk of developing persistent psychotic symptoms and disconnection from education, employment, and social development, adversely affecting long-term outcomes (Penn, et al., 2005).

Conventional methods of monitoring and treating psychosis rely on asking people to recall symptoms over the preceding week(s) or month(s) at a scheduled appointment time. Appointments are typically clinic based and often infrequent in over-stretched mental health services, understandably resulting in imprecise retrospective recall of symptoms. This is problematic in a condition that requires precise, time-sensitive treatment, particularly in response to signs of emerging relapse. The challenge is to improve outcomes by delivering personalised intervention strategies when/where someone needs them most (and is most receptive to them) without adding to the workload of over-stretched mental health services or over-burdening people with lived experience themselves. Advancements in technology can help address this challenge and widespread development of digital mental health systems is underway.

## 1.2. Definitions of key terms

**Active symptom monitoring** (ASM) allows people with lived experience of psychosis to provide real-time symptom reports using a smartphone app. The app sends regular prompts asking the user to complete a digital questionnaire. Responses are immediately uploaded to a server where they can be securely accessed by a health professional (and/or researcher).

**Passive symptom monitoring** (PSM) uses data obtained continually from a smartphone or wearable device's sensors to provide a measure of social and/or behavioural functioning. For example, sensors in the mobile device that detect movement and surrounding context may give an estimate of sleep disturbance, inactivity, social avoidance or sedentary behaviour. Changes in passive data linked to deterioration in emotional and psychosis symptoms could also be used to identify people for whom an intervention addressing these passive physiological markers may be helpful.

**Machine learning** in healthcare uses algorithms that can sift through a large number of variables to detect complex high dimensional non-linear interactions to predict individual outcomes reliably. Machine learning methods automate model building by learning from data with minimal human intervention; the best model is typically selected by assessing the prediction accuracy of unseen data using for example cross-validation methods (Hastie, et al., 2009).

## 1.3 Relapse in psychosis

Psychosis is the most common reason for contact with secondary care mental health services in the UK and a leading cause of disability worldwide. Relapses are common. A systematic review of help seeking samples (Alvarez-Jimenez, et al., 2012) found pooled prevalence rates of relapse in positive symptoms following first episode of 28% (range = 12 - 47%) at one year follow up, 43% (35 - 54%) at 18 months, 54% (40 - 63%) at three years, and 80% within 5 - 10 years, with similar relapse rates identified in more recent longitudinal studies.

Direct treatment costs for people who experience a relapse are three times higher than they are for people who do not, with the majority of additional costs associated with unplanned episodes of acute care such as inpatient admissions (Ascher-Svanum, et al., 2010). As relapse in psychosis is associated with a lifetime risk of functional and clinical deterioration, there is an urgent need to be able to efficiently predict an individual's risk of relapse (and how this changes through time) to enable timely intervention and personalised treatment response.

Research suggests that it is possible with intensive monitoring to intervene to reduce the likelihood of psychosis relapses with risk reductions of between 13.6% and 37.0% (Vigod, et al., 2015). At the same time, it is currently not possible to make specific recommendations of the predictors which should be included in a prognostic model due to a lack of high-quality data and evidence (Sullivan, et al., 2017). Therefore, we need high quality data to develop valid and reliable risk predictive models to meet this unmet clinical need and improve quality of care. A well-justified, but challenging, approach for relapse prevention is monitoring for 'Early Warning Signs' (EWS: (Birchwood, et al., 2000)). EWS, commonly reported to emerge in the days and weeks before a relapse, include anxiety, dysphoria, insomnia, and incipient psychotic experiences. The profile of prodromal symptoms tends to be consistent within an individual – the 'relapse signature'. Detecting EWS will allow preventative action to be taken, minimising the chance of full relapse occurring. However, it has been difficult to implement EWS in practice, because:

(i) there is no agreed National Institute for Health and Care Excellence (NICE) recommendation;
(ii) community services involve infrequent clinical contact so EWS are missed;
(iii) people have different relapse signatures and individual thresholds for EWS;
(iv) disengagement from clinical services and management is frequent.

Review evidence suggests considerable variation in the proportion of relapses correctly predicted by EWS. More frequent clinical monitoring and the inclusion of both affective and psychosis symptoms was found to improve prediction.

Consensus groups (San, et al., 2015) agree that relapse comprises a re-appearance of at least one week of psychotic symptoms from a stable baseline, with impaired social functioning, plus a resulting change in management. Feelings of fear, helplessness and depression are commonly experienced prior to full relapse and are important treatable targets for intervention (Gumley, et al., 2015). Fear of relapse represents an individual's cognitive and emotional response to subtle changes in wellbeing that are suggestive of relapse. It is as predictive of relapse as traditional EWS, is linked to previously traumatic episodes of psychosis, and results in delayed help-seeking, thus reducing the opportunity for relapse detection and prevention. Digital remote monitoring (DRM), which incorporates both Active Symptom Monitoring (ASM) and PSM, is perfectly poised to address the practicality issues of EWS monitoring and to gather the high-quality evidence needed to justify its wider recommendation as an evidence-based practice.

### 1.4 Digital technology for early signs monitoring and relapse prediction

According to the NHS long-term plan, 'digitally-enabled primary and outpatient care will go mainstream'. DRM technologies offer promise in early detection and prevention of relapse. Real-time and context-specific lived experience-generated data has the potential to provide early warning of the need for intervention, improve treatment decisions, and support scheduling of healthcare contacts based on need, thereby using scarce healthcare resources efficiently. DRM also reduces recall bias and forgetting, often associated with retrospectively gathered data (Shiffman, et al., 2008), enabling a more valid, reliable, and accurate picture of changes in emotional and/or behavioural states.

*Active symptom monitoring (ASM) in psychosis:* To achieve real-time sampling of an individual's current difficulties, a smartphone sends regular prompts requesting that the user complete a digital item-set (questionnaire) adapted to individual need. To date, ASM has predominantly been used in small ($n$ < 100) studies in selected populations. A systematic review (Chivilgina, et al., 2020) of psychosis studies identified 17 active monitoring apps; several by members of our research team. App use duration ranged from 1 week to 14 months, with self-assessment prompts ranging from multiple times per day to weekly. People typically adapted their response strategy to less frequent ASM over time. App assessments were well tolerated, ranging from 69%-88% compliance with app assessments completed. All studies showed that people found ASM acceptable and useful, despite some negative effects reported (e.g. increased awareness of symptoms).

*Passive monitoring in psychosis:* Smartphone and wearable device passive sensors have emerged as tools to assess behavioural patterns in a range of populations. Compared to conventional rating scales, social behaviour captured by measures from a smartphone/wearable device can provide a valid, real-world measure of social and behavioural functioning. Sensors in the mobile device that detect movement and surrounding context may indicate sleep disturbance, inactivity, social avoidance or sedentary behaviour. Changes in passive data linked to deterioration in emotional and psychosis symptoms can also be used to identify people for whom an intervention addressing these passive physiological markers may be helpful. As such, PSM tools have been utilised to both reduce burden associated with ASM and gather additional objective, behavioural data.

A systematic review of studies (Chivilgina, et al., 2020) identified four PSM studies (we identified a further five), with usage ranging from 5 to 365 days in sample sizes ranging from 5 to 62 participants. Acceptability is reported in two studies, which showed PSM was largely acceptable; although, 20% participants reported privacy concerns and 20% felt upset by it. More specifically, Barnett and colleagues (Barnett, et al., 2018) followed 17 people with lived experience of psychosis using the Beiwe PSM app installed on their smartphone for up to 3 months and identified anomalies in mobility patterns and social behaviour in the 2-weeks prior to relapse. This was also observed in a slightly larger (n = 60) study by members of the same group using a neural network approach (Adler, et al., 2020). In another study, Ben-Zeev and colleagues (Ben-Zeev, et al., 2017) noted sensor data changes including physical activity, geolocation, phone unlock duration, and speech frequency and duration in psychosis participants prior to relapse. Wisniewski and colleagues (Wisniewski, et al., 2019), in a case series, also noted high variability in behavioural patterns observed through PSM between individuals, suggesting a stratified approach (using individualised digital phenotype mechanisms) to identify individuals entering a clinically high-risk state. Cella and colleagues (Cella, et al., 2018) found that wearable technologies were acceptable and reliable for measuring autonomic activity (heart rate variability) in 30 people with lived experience of schizophrenia. Members of our team also conducted initial experiments to identify daily activities relevant for assessing social functioning from Global Positioning System (GPS) data, using a publicly available annotated digital map (OpenStreetMap). In 21 people with psychosis (Fraccaro, et al., 2019), we were able to predict daily activities reflective of

social functioning with a precision of 0.75 and a recall of 0.60. PSM studies have shown that most people with lived experience of psychosis are comfortable, able and willing to use wearable devices to monitor outcomes in their daily life (Cella, et al., 2019), with emerging evidence supporting identification of an impending relapse through changes in passively collected behavioural data. However, robust safety data is needed to understand the utility of this approach more clearly.

*Machine learning in psychosis:* Machine learning in healthcare uses algorithms that can sift through a large number of variables to detect complex high dimensional non-linear interactions to reliably predict individual's outcomes. Machine learning methods automate model building by learning from data with minimal human intervention; the best model is typically selected by assessing the prediction accuracy of unseen data using, for example, cross-validation methods (Hastie, et al., 2009). A recent review identified 16 studies that have used digital phenotyping and machine learning in psychosis (Benoit, et al., 2020). Studies focused on random forest, support vector machines, and neural nets to largely examine:

i) the power of brain imaging data to classify people with lived experience of schizophrenia or a first episode of psychosis compared to healthy controls;

ii) to identify biomarkers for psychosis; and

iii) to identify longer-term outcomes. As this activity is in its infancy, the authors of the review concluded that larger studies, with improved data quality, utilising the application of machine learning to passive data, are needed in psychosis.

***How to minimise the burden of Active Symptom Monitoring (ASM)***

Before Digital Remote Monitoring (active and passive monitoring) can be implemented into practice, a key outstanding issue is long-term user engagement. How do we balance the frequency and timing of ASM to ensure that symptom changes and relapses are detected quickly (and accurately), while not over-burdening people in order that they remain engaged? There is a utility tolerability trade-off between collecting information at sufficient frequencies and quantities to be useful, and over-burdening the user or the underlying technology (e.g. battery life). Tolerability may be reduced with high sampling frequency. Conversely, utility may be reduced if the sampling frequency is too low, individuals may also become disengaged with daily requests to provide data if their condition is stable.

Research has shown good participant engagement over initial months (e.g. up to 6 months), followed by 'alert fatigue' (reduced engagement) (Eisner, et al., 2019). For example, people with lived experience of psychosis tracking symptoms every day have said 'putting all the readings at zeros became tiring because some of them [questions] are there every day, it's very repetitive'. Selecting the next sampling time adaptively can manage this trade-off. One potential solution is to use adaptive sampling and dynamically alter the timing and frequency of requests for information based on an individual's health state at any given time. Adaptive sampling reduces unnecessary sampling during low-risk periods (e.g. when a person with lived experience is well) whilst maintaining or increasing the sampling frequency during high risk periods (e.g. when symptomatic).

We have experimented with the ClinTouch dataset (described below) to model how the burden of continuous ASM could be reduced to improve engagement in the flow of everyday life. We used clustered continuous-time hidden Markov models to identify response clusters in a psychosis group (Hulme, et al., 2021). The models allowed us to predict, at any given sampling time, the probability of an individual moving to a high-risk state, such that the next sample time is scheduled only when this probability has exceeded a given threshold. We examined how the adaptive sampling scheme behaves under different model parameters and risk thresholds, and how the average sampling can be

substantially reduced whilst maintaining a high sampling frequency during high-risk periods. We will use this experimental work as the methodological foundation for examining adaptive sampling in the current study (the second goal of this project). Specifically, we will use a data-driven approach for variable selection combined with machine learning to dynamically update a risk prediction model that balances utility and tolerability and is thus individually and personally tailored. Dynamic optimisation of the timing and frequency of requests for completing ASM at the individual level is needed to realise the vision for integrating DRM into routine clinical practice. How best to go about this remains a methodological and design challenge, largely because a sufficiently large dataset on which to examine these questions does not exist. This is the second objective of the current project.

### *The ClinTouch, CareLoop, & EMPOWER trials*

Our group has developed, evaluated and deployed DRM for psychosis built on the same digital platform: ClinTouch - EMPOWER (NIHR HTA 2017-2020) built on CareLoop (MRC 2013 - 2016), which in turn built on ClinTouch (MRC 2010 - 2012). We summarise these trial findings below.

**ClinTouch** (Lewis/Ainsworth/Machin/Wykes; (Palmier-Claus, et al., 2012)): is a smartphone-based platform invented by Co-Investigator's Lewis/Ainsworth for real-time ASM in psychosis. Using 'experience-driven design', it was developed with people with lived experience, clinicians and software engineers. It set out to achieve a step change in the quality and efficiency of care by enabling self-management of symptoms and facilitating early intervention to prevent relapse. It works as a personalised smartphone app which triggers, collects and wirelessly uploads symptom data to a central server several times daily. It has been shown to be acceptable and feasible for people with prodromal, early and chronic psychosis. When validated against the Positive and Negative Syndrome Scale (PANSS) gold standard clinical rating scale, key items of mood and psychosis showed high correlations of $r > 0.7$.

**CareLoop** (Lewis/Ainsworth/Wykes/Machin; (Lewis, et al., 2020)): We next built ClinTouch into an end-to-end system (CareLoop). ASM alert data were made visible in the Electronic Health Record (EHR) to a community mental health team (CMHT) using an application programming interface (API). The two-centre randomised controlled trial (RCT) showed that:

(i) the ClinTouch app was taken up by 45% of relapse prone users with psychosis, 90% of whom used the app consistently over 3 months;
(ii) alert data visible on the clinician dashboard was acceptable to health professionals, all of whom accessed the dashboard regularly;
(iii) the end-to-end CareLoop system led to significantly faster improvement in psychotic symptoms than standard care in an early psychosis group ($p < 0.02$) because clinicians were able to intervene earlier;
(iv) a simple alert algorithm generated by the ClinTouch app detected EWS of relapse, but specificity was low (high false positive rate).

**EMPOWER** (Gumley/Bradstreet/Ainsworth/Lewis/Bucci/Schwannauer; (Gumley, et al., 2020)): Extending the ClinTouch platform technology further, the EMPOWER app collected similar ASM data to the ClinTouch survey items now linked to a more sophisticated (but still static) baseline algorithm that supported the delivery of tailored messaging and clinical triage of possible EWS of psychosis relapse. Seventy-three relapse-prone people with lived experience of psychosis were randomised to receive either the EMPOWER system or to treatment as usual (TAU) in a multi-centre cluster randomised control trial (RCT). Primary outcome data were collected for 84% of participants at 12-months. Actual app usage was high, with 91% of users who completed the baseline ASM period meeting app compliance. There were 8/33 (24%) relapses in the EMPOWER group and 13/28 (46%)

in TAU (RR = 0.50, 95% CI = 0.26 - 0.98). Time to first relapse was longer in the EMPOWER group compared to TAU (HR = 0.32, 95% CI = 0.14-0.74). At 12-months, EMPOWER participants were less fearful of having a relapse compared to TAU. There were few app related negative impacts or adverse events (*n* = 14), with only one of those classified as 'serious'. These findings demonstrated that this approach was feasible, acceptable and potentially efficacious, but further testing in a larger sample is needed.

Our primary aim is to reliably detect the signs of relapse of psychosis in those who have already experienced a first episode of psychosis or beyond, and improve outcomes, thereby lessening the impact of relapse on people's lives, improving education and employment prospects, and overall quality of life, leading to longer life expectancy. Schizophrenia costs England £6.7bn a year, £2bn of which is direct health costs, and each relapse costs £10 - 25k in excess treatment. Our relapse prediction algorithm can be used to establish new treatment thresholds in clinical practice, delivered in real-time, monitored and dynamically updated over the course of an individual's involvement with a service, thereby benefiting clinical practice. If the algorithm enables prevention of 50% of relapses, this will save the NHS >£250m per year nationally.

## 2 Rationale

Complex digital data capture systems (those incorporating active symptom monitoring, passive sensing and/or machine learning algorithms) may provide a key to improving outcomes by allowing remote, low-burden mental health monitoring, with personalised intervention strategies delivered when needed. Over the past decade, we have developed, evaluated and deployed DRM for psychosis built on the same digital platform: ClinTouch - EMPOWER (NIHR HTA 2017-2020) built on CareLoop (MRC 2013 - 2016), which in turn built on ClinTouch (MRC 2010 - 2012). ClinTouch comprises a clinically validated smartphone app that tracks symptoms daily. In CareLoop, we showed that this technology could be used for real-time monitoring and can be integrated into health-service systems. In EMPOWER, we expanded the functionality with a relapse risk prediction algorithm and a digitally-enhanced model of care and demonstrated that this is a valid model for reducing relapse in psychosis. Our platform technology, built off a systematic development of trial and development, is safe, feasible, has high concurrent validity with researcher and clinician assessment of symptoms, and is acceptable to both patients and health professionals. Research internationally has confirmed that psychosis patients are generally comfortable with the application of DRM to support self-management.

However, our ability to predict relapse accurately is currently constrained by the limited availability of data in terms of breadth, depth and resolution. Our goal is to recruit a cohort of relapse-prone individuals sufficient in size (breadth: size and variability), collect passively and actively sensed data (depth), with high sampling frequency (resolution). We will use a prospective observational cohort study design to derive and test a personalised risk prediction algorithm to estimate the short-term risk of psychosis relapse. A second goal is to develop an adaptive sampling regimen for maximising engagement and information obtained from digital remote monitoring. This study represents a crucial step for understanding the potential for DRM to detect parameters predictive of relapse. At this stage, the main purpose of the study is to collect data. The study is not intended to prevent or treat psychosis.

## 3 Objectives and Outcome Measures/Endpoints

### 3.1 Aims

The aims of this study are to collect sufficient data that will enable us to derive and validate:

i) a risk prediction model that can use actively and passively collected data from DRM to accurately (and dynamically through time) predict an individual's risk of clinical relapse occurring within the next 7 or 28 days;

ii) an adaptive sampling regimen for maximising engagement and information obtained from DRM.

### 3.2 Objectives

There are four objectives:

*Objective 1:* To develop a scalable digital platform that incorporates active symptom monitoring (of psychotic and mood/emotion symptoms), and uses sensor-based behavioural, contextual and environmental data gathered from a smartphone and wearable device.

*Objective 2:* To predict psychosis relapse. We will recruit a cohort of relapse-prone individuals with psychosis and collect information described in Objective 1 to determine whether we can develop a risk prediction algorithm of relapse (we will not test the algorithm in this study; rather, we will collect the data to develop the algorithm, ready for testing in a later clinical trial).

*Objective 3:* To examine the utility of passive data. Passively collected data via smartphones and wearable devices could be used both as predictors of relapse and as a way of reducing the burden imposed by ASM. We will evaluate the data quality and acceptability of different wearable devices (smartwatch vs Fitbit comparison) that integrate with the digital data capture platform in order to assess which is the most feasible and acceptable wearable device to use longer term.

*Objective 4:* To develop an adaptive sampling framework. In the future, we aim to develop an integrated digital platform that not only predicts relapse, but also requests information from an individual at the right time and frequency, thereby minimising the burden on the user, while striking the right balance between ASM vs PSM.

### 3.3 Research questions

The research questions are focused around our two key goals: relapse prediction algorithm and adaptive sampling algorithm:

1. Are there a set of variables that are most predictive of relapse? Are passive and/or active predictors of greatest relevance and for which types of symptoms/outcomes?
2. Can the data collected be used to develop a new prediction algorithm that uses ASM, physiological and behavioural data collected via continuous passive sensing technology, to predict relapse at different time-points (e.g. 7 or 28 days) using a range of advanced analytical methods, with high (and clinically acceptable) specificity and sensitivity?
3. What level of usability, acceptability and adherence to ASM and PSM is required to provide real-time multidimensional indications of clinical state in individuals with psychosis?
4. How does our risk prediction algorithm compare against static risk prediction models (i.e. existing risk prediction models that don't use DRM information)?
5. Is the use of prediction algorithms to support care acceptable to people with lived experience and clinicians?

6. Which statistical methods for adaptive sampling regimens show most promise in maximising engagement with, and information obtained from, digital data collection?
7. Are there 'at risk' periods where engagement might be lost (e.g. a prediction algorithm where stable, low symptom severity leads to sustained disengagement)?

### 3.4 Primary outcomes

Our primary outcome is clinical relapse, occurring within the next 7 or 28 days.

### 3.5 Secondary outcomes

Our secondary outcomes are:

ii) Disengagement with DRM devices
iii) Acceptability of a wearable device
iiii) Acceptability of DRM and study procedures

### 3.6 Work leading to current study

We have obtained ethical approval to conduct qualitative interviews in Phase 1 of the research programme (West of Scotland REC 4, IRAS ID 305509). The aim of this study is to inform the DRM platform and our study procedures. Briefly, the Phase 1 qualitative work involves interviewing approx. 60 people with lived experience of psychosis and approx. 40 staff members (or until data saturation is reached) about their views on complex DRM systems and their potential for use in managing severe mental health problems. Specifically, we seek to understand:

- barriers, enablers (and unintended consequences) relevant to the uptake of a DRM system for psychosis and its future integration into existing NHS and/or digital mental healthcare provision infrastructure;
- barriers to people with lived experience of psychosis and staff engaging with digital tools in the context of mental healthcare;
- concerns people with lived experience of psychosis and staff have around remote monitoring, machine learning systems and passive sensing technologies;
- views about the potential for using active symptom monitoring, passive sensing technology and machine learning methods for relapse prediction specifically;
- concerns around data sharing and trust online;
- ethical/governance issues associated with data storage/tracking in a digital health context;
- operability and design features;
- how should data collected via DRM systems be optimally managed, processed and stored;
- what levels of sensitivity and specificity are acceptable to service users and staff? i.e. acceptable levels of efficacy.

To prepare the DRM platform for deployment in the cohort study, we build on our existing ASM platform (i.e., ClinTouch, EMPOWER) to deliver CONNECT. The Background intellectual property (IP) has already been well established by researchers and software engineers based at the University of Manchester. For example, ClinTouch was developed through an MRC funded project (PI: Lewis) as smartphone monitoring system to record real-time data on current symptoms, establish the

acceptability of mobile monitoring in psychosis and compare against conventional and gold standard measures of psychiatric symptoms. CareLoop, was also funded by the MRC (PI: Lewis) and builds on ClinTouch. EMPOWER (funded by the NIHR HTA; PI Gumley) extended the ClinTouch item set to include fear of relapse and contextual items to inform a relapse prevention pathway.

This platform consists of an ASM app operable on both iOS and Android smartphones, a data repository for real-time data collection, and a portal for participant management and reviewing data. The platform is being enhanced to provide tools and computing power for algorithm development and passive data integration (using the open-source Radar-base framework) and a dashboard for participants to view their data. The platform will be stress-tested prior to deployment in the cohort study to ensure it is scalable to the data volumes, responsive and robust to failure. We will undertake usability testing on the near-final (Beta) version of the digital platform through consultation with members of our advisory group and research team to ensure defects are fixed and the platform is accessible, clear, usable and functional prior to deployment in the cohort study. Emphasis in user and usability testing will be on assessing the ease with which test users can navigate the platform and perform simple tasks. Feedback will be reviewed by the research team to optimise the navigation, look and feel and usability of the DRM platform.

# 4 Study Design

## 4.1 Design

Prospective, observational (non-randomised, non-interventional) study with an in-built process evaluation and assessment of feasibility and acceptability of wearable devices, using commercially available wearable technology and smartphone sensors, representing no change to the usual care or treatments of participants due to participation. There is no control comparison group, or randomised group allocation.

We aim to recruit 1100 relapse-prone individuals with a schizophrenia spectrum diagnosis. To achieve our objectives, we will recruit one cohort (data will be split into two groups):

i) Group 1 (*n* = 800): in which we will derive and internally test a personalised relapse risk prediction algorithm using ASM items, passively collected behavioural, environmental and contextual data, integrated using machine learning (see statistical analysis section for details of the methods). We will also develop the adaptive sampling algorithm.

ii) Group 2 (*n* = 300): in which we will apply and temporally test the risk prediction algorithm and the adaptive sampling algorithm from Group 1. Note the adaptive sampling algorithm will not change the data collection in any way, nor will it be used to monitor, prevent or treat psychosis; we will simply use the data collected to test the algorithm.

This design of derivation/internal validation and subsequent temporal validation is appropriate to assess the algorithm's validity. Group 2 acts as a temporal validation set to test the prediction model and the adaptive sampling model on previously unseen individuals (recruited latest in time).

A future study will examine whether our predictive and adaptive sampling algorithms can improve clinical decision-making on early intervention for psychosis relapse (but this will not be tested in the proposed study).

## 4.2 Study setting

This is a multi-site study, with participant recruitment and data collection occurring across six geographical locations (Manchester, Glasgow, Edinburgh, London, Sussex, and Cardiff). Across these locations, the study involves:

- Nine NHS mental health Trusts/Boards: Greater Manchester Mental Health NHS Foundation Trust; Pennine Care NHS Foundation Trust; South London and Maudsley NHS Foundation Trust; Cardiff and Vale University Health Board; Aneurin Bevan University Health Board; Cwm Taf Morgannwg University Health Board; Sussex Partnership NHS Foundation Trust; Greater Glasgow and Clyde NHS Scotland; NHS Lothian.

- Six Higher Education Institutions (HEIs): University of Manchester; King's College London; Cardiff University; University of Sussex; University of Glasgow; University of Edinburgh.

## 4. 3 Eligibility criteria

Participants will be people with lived experience of psychosis on existing caseloads of secondary care mental health teams in NHS Trusts/Health Boards who are:

I. Adults (16 years and over);
II. within the past two years have had at least one acute episode of psychosis (including relapse and first episode) leading to an unscheduled episode of acute care, including inpatient admission or acute home treatment / crisis intervention;
III. received a clinical diagnosis of, or confirmed by the treating clinician to meet the criteria of, schizophrenia spectrum disorder (ICD10 F20 - 29);
IV. current presentation does not include severe acute symptoms;
V. in accordance with the Mental Capacity Act, mental capacity will be assumed. If there is any doubt, then a capacity assessment will be carried out by a clinician from the study team or the responsible clinician. Capacity will be recorded on the Referral Form (Appendix N).

Exclusion criteria*:* Experienced a recent relapse within the previous 12 weeks as confirmed by the treating clinician; non - English speaking.

## 5 Study Procedures

Participants will be asked to wear a wrist-worn device (either a Fitbit or smartwatch) for the study period, during which longitudinal heart rate, accelerometery data, for example, will be prospectively collected. During the same period, standard in-built smartphone sensors will collect for example data on call activity (not the content of calls), (obfuscated rather than exact) location, physical activity, sleep, battery life, light levels. Participants will be prompted via the CONNECT app throughout the week to provide subjective information (rated on a Likert scale using a simple slider in the app) about symptoms, mood and other contextual items. The subjective report provides reliable insight into the variability of participants experiences over time, and has been used in previous studies ( (Bucci, et al., 2018) (Eisner, et al., 2019) (Lewis, et al., 2020) (Palmier-Claus, et al., 2012)).

All participants will receive usual multi-disciplinary care. No treatment will be withheld as it would be unethical to restrict the therapeutic options of the clinical teams participating. All routine and additional treatments will be monitored and recorded (from the medical record and in clinical assessments) over the study period.

Participants will be asked to complete, either face-to-face or remote (online or via telephone), multiple visits with a member of the research team (See Section 12.1 for Schedule of Assessments). No research activities will take place prior to informed consent being obtained.

### 5.1 Consent and baseline assessment (approx. 90 minutes)

Members of the research team will confirm eligibility, obtain informed consent (if not already given) and undertake a Baseline assessment. Key socio-demographic (age, ethnicity, gender, education, relationship status, work status, living situation) and clinical characteristics will be recorded at Baseline.

We will seek consent from participants for access to their medical record throughout the study period to capture key information on relapse and factors including (not limited to) self-harm/suicidal ideation and service contacts (missed appointments, service use, admissions) to examine other important moderators and predictors of relapse. Additional optional consent will be sought to access information held by NHS England/NHS Scotland/NHS Wales and/or their local Integrated Care Board/Health Board, and link this to the information already collected. Access to this information will only be carried out for the study and there will no further access once the study ends.

### 5.2 Onboarding (approx. 60 minutes)

All participants will receive an initial 'Onboarding' session (after the Baseline visit) where they will meet with a researcher who will introduce the rationale for using the CONNECT app and wearable device, collaboratively set up, customise and familiarise the participant with the devices (the smartphone and wearable device of their choice), and conduct simple awareness training around digital data capture (including pros / cons / anticipated benefits). Practical information will be provided, including how to switch devices on and off, how to charge devices, and how to respond to alert notifications in the CONNECT app. We will also remind people what data we will not be accessing (e.g. no access to photos, precise location, etc).

The participant will be provided with:

i. the choice of a smartwatch (Apple watch) or fitness tracker (Fitbit) wearable device (depending on their preference and type of smartphone used);
ii. an Android smartphone if they do not already own a smartphone, if their smartphone is not compatible with the DRM software platform, or if they would like one. If a participant already owns and uses a DRM compatible smartphone, they will be able to use it.

The researcher will assist the participant in installing the CONNECT app. Each participant's digital literacy skills will be assessed to identify where there are gaps and spend longer training, where needed. At the end of the training session, participants will be asked to start using the wearable and smartphone, and active and passive recording of data will begin (see description of CONNECT app items and passive data we will collect in Section 5.8). Participants will be encouraged to live their life as normal, responding to alerts and notifications when requested.

### 5.3 Technical support calls (approx. 15 minutes)

Previous work by our group has shown that technical issues are more likely to occur early in the use of a DRM system. Therefore, participants will receive follow-up contact (e.g. phone call, text message) weekly for the first four weeks and monthly thereafter to facilitate engagement throughout the study,

provide reminders on how to use the app, remind participants of upcoming outcome assessments, troubleshoot technical difficulties, and discuss any anomalies identified by the study team (e.g. a possible relapse, a serious adverse event). Participants will be provided with an App and Wearable Guide, which includes commonly asked questions and guidance on using the app, wearable and phone. They will be encouraged to contact their local research team with any technical problems that they cannot resolve using the guide. The researcher will work through the problem with the participant, requesting the help of the software team if needed.

Semi-automatic emails / texts will be sent to participants to support engagement and allow people to report issues.

### 5.4 Follow-up assessments (approx. 90 minutes)

In a previous version of the protocol, participants consented into the study up to mid-January 2025 followed a 3, 6, 9, 12 month assessment schedule. Following an ethical amendment, clinical measures and review of medical records will take place at baseline and every 4 months thereafter (i.e. repeated at 4, 8, and 12 months)*. See section 5.8 for a description of clinical measures. Regular assessments are undertaken to label and validate behavioural data collected from the passive and contextual data collected via the smartphone and wearable device.

Research workers will be trained in the use of all the instruments and scales, to achieve a satisfactory level of inter-rater reliability. Regular training sessions including the use of video and role play will be conducted to maintain reliability and prevent rater drift. Participants will be offered choices regarding length of assessments, including the option of breaks and multiple occasions.

At the final follow-up meeting (12 months), participants will be given the opportunity to debrief about the study. We will also remind people that they can keep their wearable device and phone (if received a study phone) and that we will no longer pay for mobile phone data. We will also give participants the opportunity to view and discuss their data. We expect this final 12-month visit to take approx. 90 - 120 minutes to complete (for those who wish to discuss their data).

Assessments will be done in person if possible, or remotely if more convenient (or restrictions dictate so). Self-report assessments can be completed online via a link.

In the event a participant withdraws from the study before 12 months, permission will be sought to conduct a qualitative interview to understand their reasons (Appendix E). Participants will also be able to view their data and debrief about the study, but only if they wish.

** Those participants who have previously consented into the study will be able to continue with quarterly assessments (i.e. repeated at 3, 6, 9 and 12 months), or they will be offered the option to re-consent and follow the updated assessment schedule.*

### 5.5 Qualitative exit interview *(approx. 60 minutes)*

An in-depth qualitative exit interview will be carried out with a purposively selected group of participants at the point of drop-out (number not specified) or at the end of the study with approx. 10 participants per recruitment site (or until data saturation is reached). Participants will be informed about and asked to consent to the qualitative interview when information is provided and consent taken for the cohort study. Participants will be selected according to a sampling framework to capture

varied demographics and levels of engagement with the DRM platform. Participants who consent to take part will be asked to complete this qualitative interview as part of an in-person or remote meeting with a research worker.

Participants will be asked questions that seek to find out, for example:

i. how they found the DRM platform;
ii. what level of support might be needed to facilitate engagement with the platform;
iii. overall impressions of the platform (e.g. what participants liked and/or did not like about the platform in terms of content and usability);
iv. how the platform helped and/or did not help;
v. what changes we should make;
vi. barriers and facilitators to use, engagement, and longer-term use (see Appendix G, Topic Guide).

Data obtained throughout the course of qualitative work will be used, if necessary, to make iterative developments to the platform software, to optimise usability of the system.

The interviews will be audio-recorded for transcription and analytic purposes using devices enabling password protection at the point of recording. Meetings will take approximately 60 minutes, depending on the extent to which the participant requires breaks or further support / guidance and to include a full debrief.

In-person meetings will only take place after satisfactory risk assessments (COVID-19 and other risks) and appropriate mitigation procedures have been put in place (e.g. ensuring meetings take place in sufficiently ventilated rooms / locations). In-person meetings will take place at locations that are mutually convenient for research workers and participants (these can include the participant's home, NHS premises, University premises).

## 5.6 Recruitment

### *5.6.1 Participant identification*

Participants will be identified from NHS mental health Trusts / Health Boards at the recruitment sites using several methods:

1. Clinical staff from acute inpatient units and community-based mental health teams (e.g. Community Mental Health Teams, Early Intervention Teams, Assertive Outreach Teams, Crisis Teams) will be given a verbal presentation and leaflets about the study. They will be asked to provide potentially eligible people with initial information about the study, either verbally or using a leaflet (Appendix F). If the person with lived experience of psychosis is interested in the study, the clinician will ask for consent to pass on the individual's contact details to a researcher to receive more information about the study. This consent-to-contact can be written or verbal (preferred procedure to be agreed with each study site). Written consent-to-contact must be recorded in the form provided in Appendix I. Verbal consent-to-contact must be documented by the clinician in the individual's clinical notes. The clinician will then pass on the potential participant's contact details to the research team and provide the additional information needed to complete a risk assessment and to confirm eligibility (by completing the Referral Form, Appendix N).

2. Clinical Studies Officers (CSOs) will help recruit participants to the study. Usually, CSOs will recruit participants via clinical staff (as per point 1). However, some sites (e.g. GMMH) have a local

‘delegated first contact’ system in place whereby CSOs may approach potential participants of certain clinical teams directly. In this case, a signed agreement is in place between the CSO team and the clinical team indicating that CSOs may approach potential participants directly with information about the study. If the potential participants is interested, the CSO would then ask for their consent to pass on their contact details to the researcher (as per consent-to-contact procedure described in point 1).

3. Participants may also be identified from an anonymous search of electronic records in certain Trusts/Boards. For example, GMMH employs a recruitment facilitator who can perform an automated, anonymous search of records to identify potentially eligible individuals. In this case, the researcher will receive a table of care co-ordinator names with a count of potentially eligible participants that each care co-ordinator is responsible for. No potential participant details will be passed to the researcher at this stage. The researcher will then contact the relevant care co-ordinators to ask them to pass on initial study information to eligible people, either verbally or using leaflets. If the potential participant is interested in the study, the clinician will ask for consent to pass on the contact details to a researcher to receive more information about the study. This consent-to-contact can be written or verbal (preferred procedure to be agreed with each study site). Written consent-to-contact must be recorded in the form provided in Appendix I. Verbal consent-to-contact must be documented by the clinician in the clinical notes. The clinician will then pass on the potential participant’s contact details to the research team and provide the additional information needed to complete a risk assessment and to confirm eligibility (by completing the Referral Form, Appendix N). A further example is the system in Cardiff and Vale Health Board, where eligible participants can be approached under an opt out system.

4. Participants (with consent) may be referred by other ethically approved studies. In this case, the referring study will provide the potential participant with a study leaflet for the current study. If the potential participant is interested in the current study, they will either contact the current study researchers directly or will give permission to the referring study to pass on their contact details to the study researcher. The potential participant's care co-ordinator will be contacted prior to any face-to-face meeting to obtain the information needed to complete a risk assessment and to confirm eligibility (by completing the Referral Form, Appendix N).

5. Some of the study sites have access to existing cohorts who have given permission to be approached for research purposes.

6. We will advertise the study using, for example, displaying a poster in secondary care mental health services (Appendix F), or on social media to allow participants to self-refer to the study. This will give brief details of the study. In all such instances we will contact the relevant clinical team and discuss suitability for participation.

7. The Mental Health Research Network (MHRN) in Scotland facilitates the recruitment of NHS patients into clinical research studies. The Network does this by working closely with NHS clinical teams to publicise studies to patients and clinicians through targeted advertising in clinical areas, and directly to the public. Where possible, the Network works with clinicians to identify potential participants, or pre-screens patient databases and reviews clinical records to create shortlists of potential participants for clinical review.

8. SHARE is a register for people in Scotland who are interested in taking part in health research projects. When people register, they give permission to be contacted by SHARE about research studies. Staff at SHARE will run a database search to identify potential participants for the study. They will then contact the potential participants with information about the study. If the person is interested,

they will be asked for verbal consent for their contact details to be passed to the research team. Details will be shared via a secure web-based tracker, which the researchers would be able to access to contact the potential participant.

9. Avon and Wiltshire Mental Health Partnership NHS Trust (AWP) will use an opt-out postal approach called ‘Everyone Included’ for the purpose of participant identification and recruitment. ‘Everyone Included’ was developed by AWP between 2012 and 2014, based on service user preference to be contacted directly via post about potential opportunities to take part in research, unless they choose otherwise.

‘Everyone Included’ is an AWP-approved approach used by AWP Research and Development. Clinical teams are informed about the use of the ‘Everyone Included’ approach for specific studies that could involve their service user populations being sent letters. Service users are informed about the ‘Everyone Included’ approach as part of ‘Consent to Share: Overview and Information Booklet’ received under the ‘Your Team, Your Conversation, Your Plan’ approach to care planning. Information about ‘Everyone Included’ is readily available on the AWP website, including details of the studies currently using the approach, as well as contact information to raise questions about the approach.

‘Everyone Included’ relies on using information analysis searches of the RiO Electronic Patient Record (EPR) system to identify those that could be eligible to take part in a specific study, based on some study eligibility criteria, which can be searched. This process is used to identify those that could meet the broad eligibility criteria for a specific study; however, ‘Everyone Included’ is not designed to confirm study eligibility or capacity to take part in research, it is purely intended to raise awareness of research studies.

Research and Development staff facilitating the ‘Everyone Included’ approach will manually screen the Electronic Patient Record (EPR) of all service users, including, but not limited to, their recent clinical progress notes, within 24-hours of ‘Everyone Included’ letters being sent. This mitigates some risk of approaching service users during phases of acute mental health concerns, defined as mental health crisis.

‘Everyone Included’ letters sent to service users about specific studies contain the following documents:

- An ‘Everyone Included’ cover letter, which provides the recipient with information about the ‘Everyone Included’ approach; why they are being contacted; clear communication that the specific study referenced in the enclosed patient-facing resources might not be suitable for them; their response options; and options to raise questions or concerns about the ‘Everyone Included’ approach.
- Patient-facing resources about the specific study, that are ethically approved by the Health Research Authority (HRA) and NHS Research Ethics Committee (REC).
- A reply slip, that the recipient can post back to the AWP Research and Development team to express interest in finding out more about the specific study referenced in the enclosed patient-facing materials, or choose to opt-out of hearing about research via the ‘Everyone Included’ approach.
- A freepost addressed envelope to post an ‘Everyone Included’ reply slip to the AWP Research and Development team.

It is always the service user's choice whether to express interest in finding out more about a research study promoted to them via 'Everyone Included'. The service user is clearly informed in the 'Everyone Included' cover letter that their decision to ignore the letter or opt-out of receiving future 'Everyone Included' letters will have no impact on care provision.

'Everyone Included' responses are documented on the service user's progress notes on the RiO EPR. Responses to 'Everyone included' letters that include expression of interest from a service user in finding out more information about a specific research study are securely forwarded to a member of AWP Research Delivery staff working on the study. AWP Research Delivery staff subsequently follow the study protocol and local standard operating procedures with regards to contacting service users about the specific research study. Further eligibility screening by AWP Research Delivery staff, post-'Everyone Included' approach, might reveal that the service user is ineligible for a specific study; however, this is not part of the 'Everyone Included' approach by this stage. AWP Research Delivery staff are trained to discuss research eligibility with service users.

All service user populations within secondary mental health services could be characterised as "vulnerable"; however, 'Everyone Included' is designed to bolster the inclusivity of research through increasing the number and diversity of AWP service users that hear about, and have the autonomy to exercise their right, to find out about research that could be beneficial to them.

'Everyone Included' has been and/or is being used as an approach to support the delivery of NIHR Portfolio observational studies and clinical trials involving populations with psychosis in AWP.

*For points two to eight, where the potential participant is unclear about, for example, the name of their clinical team or clinician or aspects of eligibility (e.g. diagnosis), the researcher will ask for verbal permission to check their clinical notes to confirm such details, as well as information needed to determine/manage any risk that may arise when arranging to visit the participant. This will reduce burden on clinical teams, research workers, and potential participants, and also reduce the amount of time between first contacting the participant and being able to consent them into the study. We will record the potential participant's verbal consent to check these details.*

Participant recruitment will take place over a 29-month period, with all participants being followed up for 12 months from the time of their recruitment.

### *5.6.2 Payment*

Participants will receive £20 per clinical assessment, and for taking part in a qualitative interview (should they choose) (using vouchers, in cash or via a bank payment) and reimbursement for reasonable travel expenses, if applicable. The amount was decided upon based on NIHR INVOLVE guidelines.

Participants will be provided with a smartphone (if they do not own one or choose to use a study handset) and a wearable device. Data network charges for the study period (up to 12 months) will be paid for, irrespective of whether the participant is given a handset/not (£10/month). The CONNECT platform will be developed to have optimal data usage, relying on WIFI to upload information securely. It is anticipated that participation will not exceed monthly data allowances, however this will be assessed and iterative changes will be made where required.

## 5.7 Consent

Consent will be taken by trained members of the research team. In no cases will participants be recruited if their capacity to consent is in doubt. Fully informed consent will be sought from participants and obtained prior to data collection and participants accessing and using study equipment. Prospective participants will be provided with HRA/REC approved copies of the Participant Information Sheet. All prospective participants will be provided with a verbal explanation of the study and given opportunities to discuss the study, ask questions about the study and have their questions answered during in-person or remote meetings with a member of the research team. The researcher(s) will explain in concise and clearly understandable terms to all persons invited to take part:

1. who is conducting the research;
2. why it is being conducted (including the purpose of the research);
3. why they have been asked to take part;
4. what it requires of them (including the amount of time they will be required to commit and what they will have to do);
5. what will happen to the data they provide;
6. whether and how their anonymity and confidentiality will be maintained;
7. that their participation is voluntary and they are free to withdraw at any time without detriment.

People will be reminded that once their de-identified data has been fed into the machine learning algorithm it will not be possible for them to withdraw completely from the study.

Generally (but not always), the first approach to potential participants will be made by the potential participant's care coordinator or another clinician involved in their care. As detailed above, clinicians or CSOs will provide potential participants with initial information about the study. The exception to this procedure is if the potential participant is identified by searching existing databases of individuals who have given prior consent to be contacted directly about research studies. Where prior consent-to-contact has been given, potential participants will be contacted directly.

Potential participants will be given at least 24 hours to consider all the information provided before formal consent is obtained to give them sufficient time to decide whether or not to take part (although, if a participant expresses a strong preference to participate sooner this will be allowed). The researcher will explain to all potential participants that participation is voluntary and that they can withdraw their consent at any point during the study without giving a reason. It will be made clear to participants that, as taking part in the study does not replace standard care (it is in addition to standard care), withdrawal from the study will not impact on the participant's ability to continue to access standard care within the referring service, or other sources of support they might access contemporaneously. Participants will continue to be actively supported by the service during their participation in the study and study participation will not affect any form of therapeutic support participants receive.

If the potential participant wishes to take part, they will be asked to provide consent via one of the following methods:

- online consent via a weblink
- signed paper consent form
- signed consent form emailed / posted back to the researcher
- audio-recorded consent

If this conversation takes place in person at a participant's home, the researcher will need to obtain an up-to-date risk assessment from the potential participant's care co-ordinator beforehand. To do so, the researcher will first ask the potential participant to provide verbal consent (e.g. over the phone), or confirmation via email, that they are happy for their care co-ordinator to supply a risk assessment. The researcher will record the outcome of this conversation in the contacts database (kept separate from any research database). If the potential participant does not agree for a risk assessment to be sought, the researcher would not conduct an in-person home visit and instead would go through the Participant Information Sheet (PIS) and any questions remotely or at a clinic (if the potential participant agreed to this procedure).

Three copies of the consent form will be produced: 1 original for the research team, 1 copy for the participant, and 1 electronic copy to be uploaded to medical notes.

A date for the Baseline assessment will be scheduled once participants confirm that they are satisfied with the information described in the PIS and consent form and would like to take part in the study. At the time the Baseline assessment is scheduled, participants will be asked if they have a preference in relation to whether they would like the assessment to take place over the telephone, via online conferencing (e.g. Zoom / Microsoft Teams / NearMe) or face-to-face (taking into account Covid restrictions at the time).

Research workers will check before commencing the visit itself (if this is on another day) that participants still understand what the study is about and remain willing to take part. This will be recorded in the participant's file. If a participant loses capacity to consent during the study, the participant will be withdrawn from the study. Identifiable data already collected with consent will be retained and used in the study. No further data will be collected, or any other research procedures carried out in relation to the participant.

Those participants who have already consented into the study can continue with quarterly assessments (i.e. repeated at 3, 6, 9 and 12 months), or they will be offered the option to re-consent and follow the updated 4-monthly follow-up assessment schedule.

## 5.8 Study assessments

### *5.8.1 Active Symptom Monitoring (ASM)*

Our existing ASM app has been developed through consultation and testing with people using services, and mental health professionals. We will continue to include lived experience involvement to develop the CONNECT app and the ASM item set.

Participants will be asked to complete a series of short assessments throughout the course of the study, administered via the CONNECT app, which contains a set of configurable items reflecting domains including psychotic symptoms, mood, anxiety, self-esteem, connectedness to others, fear of relapse. Items include both positive (e.g. 'I've been feeling close to others') and negative (e.g. 'I've been worrying about relapse') content. This will provide real-time self-reported information about these clinical domains. Each item is completed using a simple screen swipe, which enables quick and efficient completion by users. Each item is automatically scored on a Likert scale. Where particular items score over a certain threshold, users are invited to complete supplementary questions to enable more fine-grained assessment of that domain. Variability of psychotic symptoms will be measured via the validated *ClinTouch* psychotic symptom item set within the app. We will also include items about a

person's whereabouts (e.g. work, home) and who they are with (e.g. alone, with a significant other, with others more generally) to contextualise data.

The CONNECT app will deliver an auditory and visual notification on the participant's home screen between 4pm and 9pm. Participants will have until midnight to respond to notifications. They will also be able to self-initiate use at any time, but will only be able to complete the questions once per day. Data are wirelessly uploaded in real-time to the secure cloud-hosting with AWS supported by a UoM-approved IT supplier. We will include the ability to configure the app in the event a participant is comfortable with using some aspects of the software system (e.g. ASM), but not others (e.g. passive sensor monitoring; wearable device).

App development will be supported by a series of PPI consultations. This enables the end users to influence the design and functionality of the app, leading to the development of an app that is more likely to be acceptable and have better uptake. As with our other app builds, by working together, developers and users can learn together and optimise platform functionality, with designers being responsible for pointing out technical options, and users providing information about their needs, practices and how they will use the system. When building the app, working software examples will be delivered and reviewed by the clinical team and advisory groups who will provide interim feedback on the user interface developed, the software performance and its usability. Any changes required are then incorporated into the next iteration of platform development and continue until the fully functioning system is available.

The research team will review the data collected on the CONNECT dashboard at regular intervals and may contact participants if there is a loss of data stream from a device to determine if there are issues relating to functionality or user-experience (and will be a metric of feasibility and acceptability). In the event a symptom question is no longer relevant (e.g. the individual stops hearing voices), or a new symptom emerges (e.g. an individual starts hearing voices), the personalised question set at baseline will be altered.

### *5.8.2 Passive data collection*

*Smartphone sensors*

All modern smartphones have measurement sensors. Data collected passively via the smartphone sensors and a wearable device will be collected via the CONNECT app. These data will be passively collected, requiring minimal or no input from participants. Data collected passively correspond to a range of categories considered putatively relevant to the study, including:

i. movement sensors: acceleration, gyration, and steps, and obfuscated relative GPS location (relative location to a unknown fixed point only);
ii. social characteristics: call metadata, SMS metadata, and nearby Bluetooth handsets;
iii. environmental sensors: ambient light, battery level, magnetic field, and weather conditions;
iv. user interaction with other applications and their phone (see Figure 3 below).

GPS location data will be anonymised; that is, providing relative location data, not absolute coordinates (preventing identification of an individual's home address or precise geographical location). Relative location collects the relative degrees of latitude and longitude data from GPS and/or using cell tower and WI-FI signals. To ensure participants privacy, the absolute location is converted to a relative location by adding a random number to both the longitude and latitude. The random number added is different for longitude and latitude; it is also different for every participant. This pair of random numbers is created by the app and stored for later use. The pair of random numbers is not

available or known by the researchers – it never leaves the participant's phone. No absolute location data is streamed to, or stored on, the server.

Secure software (Matomo and Bugfender) will be used to record user activity within the CONNECT app, as well as collect information to help reproduce and resolve technical issues more effectively and produce technical support. Matomo and Bugfender only monitor use of the CONNECT app; they do not monitor other apps or anything else on the participant's device.

Data transfer from the phone to the data repository is dynamically scheduled according to data volumes, phone in low power mode and availability of Wi-Fi connection.

Data collected from the wearable devices are processed on the device by vendor algorithms to provide information such as heart rate, movement, daytime and sedentary activity, physical exercise, step count, and sleep efficiency. The app and data collection platform are configured in such a way that participants do not need to consent to all aspects of data collection (i.e. participants will be able to opt-in/opt-out dynamically of any of the passive data collection).

Data availability and access is dependent on the APIs and permissions provided by the manufacturer. On Apple devices we will be using Location Services, HealthKit API and the SensorKit API. Each of these requires the user to give the app permission to access data. Both SensorKit and HealthKit collates data from iPhone and watch to provide a single interface for the app to access data. We will require approval from Apple to use SensorKit.

Figure 3. Data collected passively from smartphone sensors and wearable devices

On Android devices we will use the Sensor API (provides access to raw data), Google Fit, Activity Recognition API, Sleep API, Location API. Google Fit provides access to health data from linked smartwatch.

For accessing data from the Fitbit wearable, we will use the Fitbit Web-API. This provides access to data from users if they have authorised it. By default, only daily summarises are available from Fitbit. We will require special approval from Fitbit to access intraday data.

For participants who were using a Samsung Galaxy watch in a previous version of this protocol, the HealthConnect app is used to pull health data collected via the Samsung watch off android phones via the Samsung app. The user is required to register for a Samsung user account to allow this.

*Wrist-worn wearable devices*

Participants will be asked to wear a wrist-worn device for the duration of follow-up (12 months), which will provide ongoing data collection (summarised in Figure 3 above).

#### *5.8.2.1 Nested wearable comparison study*

A pre-planned pilot phase was conducted to evaluate the feasibility and acceptability of different wearable devices (comparing smartwatches and Fitbits) within the main cohort study. Participants could choose between a Fitbit, an Android smartwatch, or an Apple Watch, depending on their smartphone compatibility. iPhone users could select either an Apple Watch or a Fitbit, while Android users could choose an Android smartwatch or a Fitbit. Those who already owned a compatible device could continue using it. The study monitored device acceptability and data quality, assessing:

1. The most frequently chosen wearable;
2. Participant acceptability after use;
3. The device providing the highest quality data over at least two months.

After six months, we assessed the quality of data collected from pilot study participants, ensuring that each had at least two months of follow-up. We also evaluated the acceptability of the devices used. To account for potential selection bias, we compared participants' baseline data across different wearables. A predefined set of parameters, outlined in our statistical analysis plan, guided our decision-making for the next steps following the six-month data collection period (see Figure 4). These decision parameters included factors such as

- If one wearable is clearly superior, we will recommend this wearable for the remainder of the cohort.
- If there are no differences between the wearables, we will check for non-inferiority of the Fitbit compared to smartwatch against pre-defined non-inferiority bounds.
- If non-inferiority is established, we will switch to Fitbit as it is the most affordable option.
- If the data is inconclusive (i.e. not superior but also not non-inferior), we will continue to collect data for a further 6 months and repeat analysis based on the *a priori* parameters on all recruited participants with at least 2 months of follow-up time.

Following analysis of the pilot data in January 2025, the Samsung Galaxy Watch was discontinued for the study. This decision was based on several factors: the low quantity and quality of data recorded, the significant resources required to resolve issues with data flow, and the limited metrics provided by the device. In contrast, the Fitbit was retained due to its ability to record a high volume of data, the quality and reliability of the data, and the additional metrics it offers to address the study's primary research objectives. However, the Fitbit did not demonstrate non-inferiority compared to the Apple watch. Therefore, the Apple watch was retained due to its high acceptability and uptake among participants, and the additional metrics available over and above the Fitbit in meeting the study's

research objectives. As this is a nested study, the dataset gathered from pilot participants will form part of the main cohort dataset.

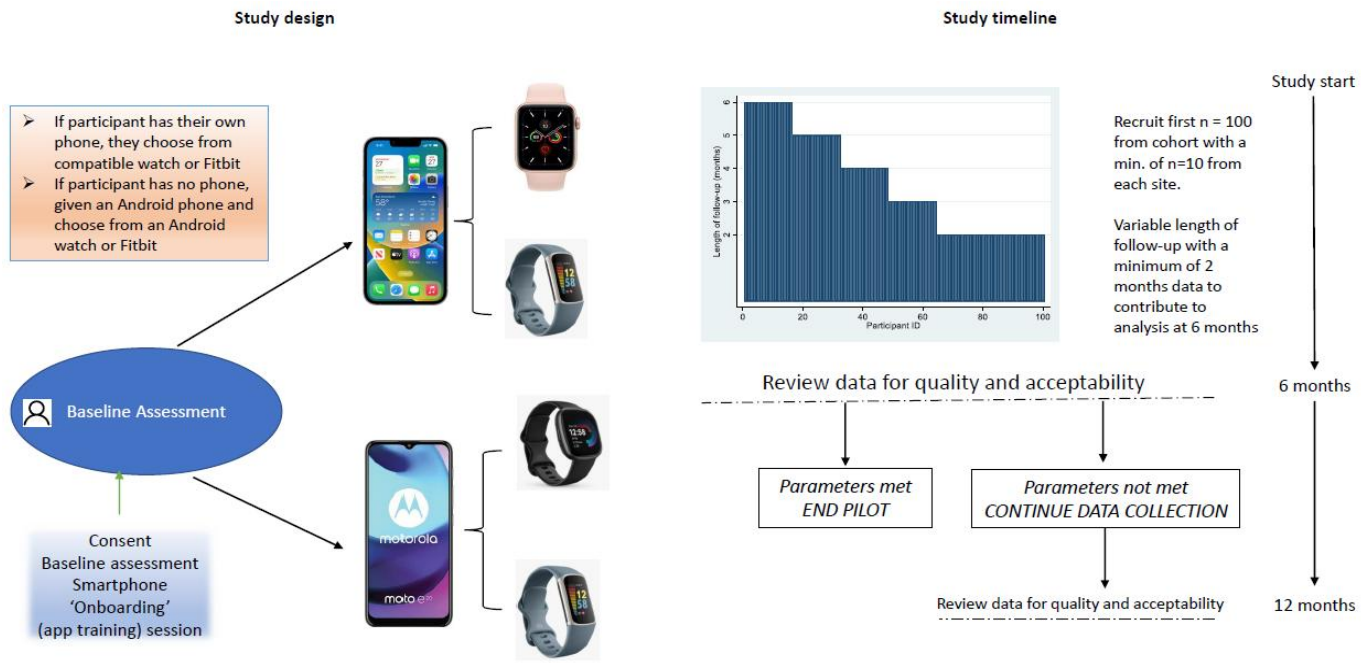


Figure 4. Nested study examining utility of different types of wearable device

***5.8.2.2***

Following the results of the nested wearable comparison, the Samsung Galaxy watch will no longer be offered to participants.

*Wearable Device Options for Participants*

*Participants with iPhones:*

- May choose between an Apple Watch or a Fitbit, as both devices are compatible with iOS.
- Participants who already own either an Apple Watch or a Fitbit may continue using their existing device.

*Participants with Android Phones:*

- Will be offered a Fitbit, as it is the only compatible wearable device for Android users.
- Participants who already own a Fitbit may continue using their existing device.

This approach minimises the need for participants to carry two phones and ensures seamless integration of wearable data with their respective smartphones.

Participants who enrolled during the pilot phase or the interim period while awaiting ethical approval for revised study procedures, and are using a Samsung smartwatch, may continue using the Samsung smartwatch for the study duration and keep it, but they will be encouraged to switch to a Fitbit, the only remaining compatible device for Android phones, for the remainder of the study.

### *5.8.3 Clinical measures*

*Participants enrolled before mid-January, 2025:*

Participants consented into the study before this time were invited to complete clinical measures at Baseline and every 3 months thereafter (i.e., at 3, 6, 9, and 12 months).

*Participants enrolled from mid-January, 2025 onwards:*

Following an approved ethical amendment, participants consented after this date are invited to complete clinical measures at 4 month intervals post-Baseline (i.e., at 4, 8, and 12 months).

*Transition Option for Early Participants*:

Participants who consented before the approval of this schedule change will have two options:

1. Continue with the original 3-month assessment schedule, or
2. Re-consent and switch to the updated 4-month assessment schedule for the remainder of their participation in the study.

The schedule of study events outlines when outcomes will be assessed for all participants based on their selected follow-up schedule.

Clinical measures

| | |
|---|---|
| Mental Health Status: | Clinical Global Impression-Schizophrenia scale (Haro, et al., 2003) |
| | Psychotic Symptom Rating Scales (PSYRATS) distress and frequency scale (Haddock, et al., 1999). |
| Emotional Distress: | Calgary Depression Scale (Addington, et al., 1990) |
| | Fear of Recurrence Scale (FoRSE; (Association, 1994)) |
| | Work and Social Adjustment Scale (Mundt JC, 2002) |
| | Criticism and Warmth Scale (PCPW) (Hooley, et al., 1989) |
| | Dunn Worry Questionnaire (DWQ) (Freeman, et al., 2020)) |
| | General Anxiety Disorder Questionnaire (Spitzer RL, 2006) |
| | EQ-5D-5L (Herdman, et al., 2011) |
| Substance misuse: | Alcohol, Smoking and Substance Involvement Screening Test - LITE ( (Ali, et al., 2013); (Ali, et al., 2013)) |
| Service use: | Captured from the medical record; Medication Adherence Rating scale (Thompson K, 2000) |

| | |
|---|---|
| Technology use: | Self-reported acceptability and usability; Post-Study System Usability Questionnaire (PSSUQ; (Lewis, 2002) |

*Relapse:*

We will use the relapse criteria definition detailed in Appendix R (and is the criteria we used in our NIHR HTA-funded *EMPOWER* trial). We will measure relapse over the 12-months following introduction of the CONNECT app. The criteria for relapse includes:

i. a return or exacerbation in psychotic symptoms of at least moderate degree, a return or exacerbation of affective symptoms of at least a moderate degree, a return or exacerbation of cognitive disorganisation of at least a moderate degree, a return or exacerbation of excitement of at least a moderate degree, and
ii. where symptoms were at least one-week in duration, and
iii. where there is evidence of a decline in functioning or an increase in risk to self or others, and
iv. there is evidence of an escalating clinical response from services.

Independent and blind observer ratings are applied to detailed extracts taken from clinical notes from a participant's medical record using our detailed Relapse Assessment Protocol (Appendix R) by a research worker at every clinical assessment follow-up time point (this will be date/time-based on case notes of when a relapse occurred in the preceding extraction period and explored during the monthly participant phone call and at the follow-up assessment in the event a relapse is not recorded in the case notes) to identify potential episodes of relapse and exacerbation. These episodes will provide the basis for individual anonymised case vignettes that will be submitted to our independent adjudication panel (comprising members of the research team with the necessary knowledge, experience and skills to make independent blinded judgements regarding relapse/exacerbation) for final confirmation of relapse/not. All vignettes will be fully anonymised.

We will seek consent from participants for access to their medical record throughout the study period to capture key information on relapse and factors including (not limited to) self-harm or suicidal ideation and service contacts (missed appointments, service use, admissions) to examine other important moderators and predictors of relapse.

### 5.9 Engagement

Asking people to actively symptom monitor for a 12-month period might be challenging. Following a systematic review of what improves retention in clinical studies (Edwards, et al., 2009), and following consultation with our advisory groups, a variety of strategies to mitigate user disengagement will be implemented, which may include:

- providing participants with a mobile phone and a wearable device plus the cost of data plan at £10 per month for up to 12 months;
- regular phone calls to troubleshoot technical difficulties and check-in; workshops, newsletters, engagement events to update participants on project progress and to create a sense of inclusion/identity with CONNECT;
- thank you cards following assessments;
- a regular non-personalised email (shown to lead to improved engagement);

- a semi-automatic email/text to allow people to directly report issues; resource/toolkit section from the Actissist app (Bucci, et al., 2018), comprising self-help resources, recovery stories, mindfulness/relaxation guides, links to helpful website/blogs/forums;
- rewards/badges earned when a significant percentage of data points are completed each week; motivation reminders sent by push notifications to prompt participants to complete questions.

Participants will be able to view their data in a relevant and accessible format (with support from a researcher) on the participant-facing dashboard at study end.

We will give participant's the option to pause the prompt schedule if they would like a break from receiving regular notifications.

No constraints are placed on referring services on their practice. Similarly, participants in receipt of services will be encouraged to continue to access their clinical service according to their local care co-ordinator, psychiatrist and other care planning arrangements. There are no requirements from the CONNECT study for participating teams to change or modify their existing practice in response to study procedures.

### 5.10 Withdrawal criteria

Participants wishing to withdraw from the study will be free to do so at any time. There may be several reasons for withdrawal from the study:

i. participant choosing to no longer participate: participants will be informed both in writing and verbally that participation is voluntary, that non-participation will not influence their medical care, and that they are free to withdraw from the study at any point without providing reasons;
ii. the research team may withdraw the participant in the event of serious adverse event (SAE), protocol violation, administrative or other reasons;
iii. the participant loses capacity for continued participation.

In the case of participant self-withdrawal, all attempts will be made to follow-up with the participant to establish cause of withdrawal, and to collect qualitative data regarding experience of participation.

Psychosis relapse itself is not cause for automatic withdrawal; unless they choose to stop, participants who are identified as experiencing a relapse will continue to participate until study end-point. All data, including those from withdrawn participants, will be retained and included in the final analysis. No further data will be collected or any other research procedures carried out in relation to a withdrawn participant.

Withdrawing participants will be able to request deletion of data from the dataset if they wish. However, participants will be unable to withdraw their data after the destruction of the pseudo key. After this time, data will be anonymous and it will be impossible to identify.

There can be a time lag on accessing clinical notes. In the event a participant withdraws from the study and does not request deletion of data from the dataset, clinical notes may be accessed after the point of withdrawal, but only for records up to the date of withdrawal. In the event the participant requests the deletion of all study data, no further data will be extracted.

### 5.11 End of study

The end of the study is defined as the last participant completing their debrief interview, or at the completion of the last qualitative interview, whichever comes last.

At the end of the research study, we will notify the review bodies that the study has ended and provide final reports, confirm arrangements for future use of research data, and publish the results of the research.

## 6 Statistics and Data Analysis

Statistical aspects of the study have been developed by the statisticians within the research team. A pre-specified analysis pan will be developed.

### 6.1 Sample size calculation

With a relapse rate of between 25% (commonly reported in literature) and 40% (found in our NIHR-funded EMPOWER study) in a 12-month period, 1100 participants (800 for training, 300 for validation) are required. This is based on sample size criteria for prediction models of binary outcomes (Riley, et al., 2018), allowing for the (correlated) repeated measures at the individual level. Specifically, pilot analyses on the ClinTouch and EMPOWER datasets for this proposal, found that the within-person correlation of the most asked questions in these datasets were 0.52 and 0.51, respectively. If we assume our risk prediction algorithm will explain 15% of the maximum variation, then our sample size will be sufficient to develop an algorithm with between 5-7 predictor variables (depending on the exact relapse rate). We therefore aim to recruit a total of 1100 relapse-prone individuals across six UK sites.

### 6.2 Planned recruitment rate

Participants from our proposed NHS Trusts / Health Boards will be recruited over an estimated 29-month window across six sites with high levels of diversity and social adversity. Our target is to recruit approximately 6.5 participants consented per month, per site.

#### *6.2.1 Risk of selection bias*

We will ensure that the cohort is sufficiently representative of our target group (people across the UK with experience of psychosis) so that the risk prediction algorithm is broadly applicable. The multi-site nature of the cohort will ensure heterogeneity of clinical response and varied socio-demographic characteristics, increasing the opportunity to develop a robust model in the context of care as usual. We will regularly review the socio-demographics of the cohort and adopt a more purposive sampling recruitment strategy if we observe a socio-demographic bias in our sample. Additionally, if we identify over- or under-represented groups within our dataset (relative to the target population), then we can apply weighting methods to all models.

#### *6.2.2 Attrition*

We acknowledge that there might be some level of loss-to-follow-up. We will monitor attrition closely. In our previous digital psychosis trials, dropout rates have been low (e.g. retention rate in EMPOWER at 12-months of 85%; and 84% in Actissist 2.0 at 6-month follow-up). We will use evidence-based strategies to maximise retention and minimise loss to follow-up (see section 5.9, Engagement). In the case of large attrition, we can still build a risk prediction algorithm; however, we may need to build an

algorithm based on fewer predictors (e.g. 4 - 6 instead of 5 - 7). Nonetheless, attrition is of direct interest for the adaptive sampling algorithm part of the study as we would like to know what predicts attrition and then incorporate this knowledge in an adaptive sampling algorithm to mitigate attrition in future DRM studies. Our primary outcome (relapse) should be available for almost all participants as we will be able to access medical records, which will document this outcome.

### 6.3 Procedure(s) to account for missing or spurious data

For partially missing data (i.e. a subject has completed a questionnaire but has not completed all elements of that questionnaire), we will be using validated instruments and will follow the established procedures for calculating overall scores in the presence of partially missing data.

When data are completely missing for a whole questionnaire, we will record the occurrences of this, and use multiple imputation assuming these data are missing at random. The same approach will be used for all other occurrences of missing data, e.g., in the passively sampled data. We will also investigate appropriate sensitivity type analyses if we think these data may be informatively missing i.e., missing not at random, to see whether our findings are robust to these missing data.

Maximising follow-up and preventing missing data is of direct interest in the adaptive sampling methods. Therefore, this study will not take specific measures to prevent missing data, but we will learn from the missing data patterns to inform design of future studies in this regard.

### 6.4 Statistical analysis plan

Statistical analyses are required for the study research questions. We provide a summary of our statistical analysis plans (SAP) below, which will be expanded into a detailed SAP upon project start (published on open-access repositories: the open science framework).

#### *6.4.1 Identification of prognostic variables (Research question 1)*

We will use descriptive statistics and unsupervised machine learning techniques to identify individual variables, and sets of variables, that are most predictive of relapse. Simple or low fidelity/dimension variables will be analysed in simple regression models to calculate their association with relapse outcomes. High fidelity variables (such as passively collected data from phones) will first be passed through machine learning algorithms such as autoencoders to reduce their dimensionality, then tested for association with relapse. Promising variables will be identified, summarised and passed forward to predictive algorithm development. To be clear, as per best-practice, all identification of prognostic variables will be based on multivariable analyses: we will not use results from univariable analysis to inform predictor selection for the risk model development (which would be a sub-optimal approach).

#### *6.4.2 Developing a prediction algorithm (Research question 2)*

We will follow best-practice guidelines in the development of risk prediction algorithms (Collins, et al., 2015) and will report findings according to the TRIPOD statement (Spitzer RL, 2006) and the guidelines for developing and reporting machine learning predictive models in biomedical research (Luo, et al., 2016). We will adopt an agile approach to algorithm development that will be responsive to data as it accrues and to evolving algorithm performance. As we do not know in advance which combination of predictors and analytical method will be most effective, we will employ the following strategy that enables us to systematically explore the combinations. When we have enough data to begin algorithm development, the data scientists, clinical experts, in consultation with advisory group

members, will identify a list of candidate predictors (ready for variable selection using the data) and corresponding methods to develop the initial algorithms; research question 3 will inform discussions of candidate predictors. These will be deployed into the model development sandbox.

We will develop the risk prediction algorithm using Group 1 (n = 800), which will then be validated and refined as needed in Group 2 (n = 300). Under the assumption that data will be missing at random, multiple imputation will be applied for covariates, any covariates with over 60% missingness will be excluded in the interests of clinical utility (see Section 6.3). The primary outcome will be the binary indication of relapse in either, for example, 7 days (model 1) or 28 days (model 2) from time-of-prediction. For an individual participant, such outcomes will be defined in a 'rolling manner', where we define outcomes at the end of each week (model 1) or each month (model 2). To achieve the best performing model, we will consider a range of analytical models, including (but not limited to): logistic regression, artificial neural networks, support vector machines, random forests, hidden Markov models, and Bayesian approaches. For example, the hidden Markov models will use certain features of an individual's inputs (ASM and PSM) and use the data to calculate for each individual a risk of being in one of a small number of mutually exclusive 'states' which correspond to, for example, remission, deteriorating, relapse. The data will also allow a day-to-day calculation of instability ('entropy') – the likelihood of remaining in that state (Figure 5). Individuals can 'switch' between states. We will include interactions between predictors to allow certain subgroups of individuals to have slightly different 'versions' of the algorithm; that is, tailor the model to subgroups across the heterogeneous target population.

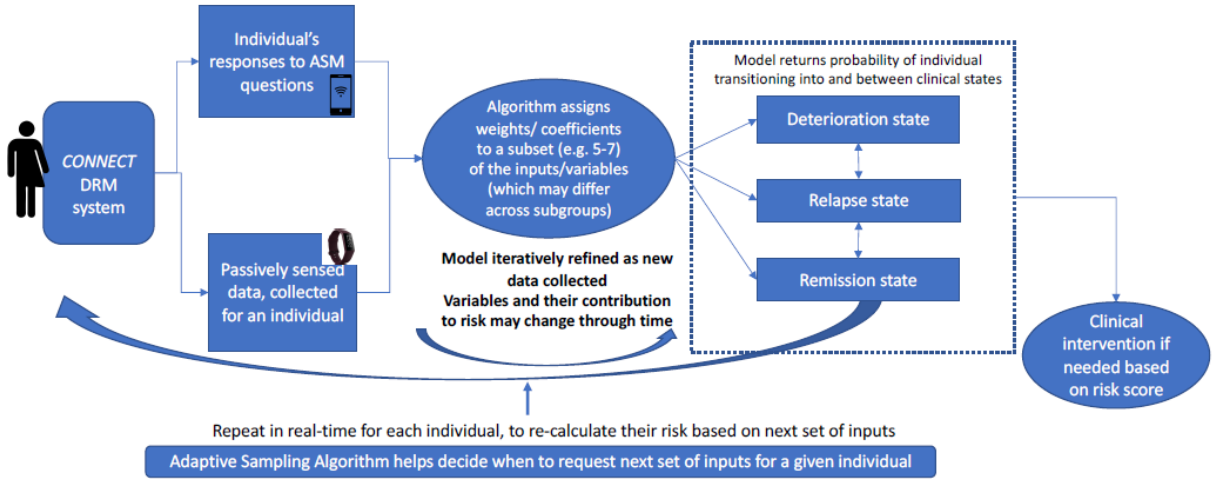


Figure 5. Graphical representation of algorithm functionality

Repeated measures for an individual will be appropriately accounted for in any models (e.g. random effects at the participant-level, or use of landmarking techniques). We will use a data-driven approach to select predictors for inclusion in the final risk prediction algorithm. This variable selection procedure will choose from a pre-defined list of candidate predictors (as defined above). For example, candidate predictors will likely be an aggregate of various actively and passively collected observations over a historical time-window as well as demographic variables. For regression-based models (e.g. logistic regression), we will perform variable selection using penalised maximum likelihood (e.g. LASSO L1-regularization), while variable selection is inherent to the machine-learning methods. The use of penalised regression will also help mitigate against overfitting (Riley, et al., 2019).

Internal k-fold cross validation within Group 1 will be used to validate the models, doing this at key landmark times to account for the dynamic (time-updated) nature of an individual's risk estimate. Here, we will quantify predictive performance using calibration (agreement between the observed and expected event proportion, across the full risk range) and discrimination (ability of the algorithm to separate those who have the event from those that do not). For discrimination, we will calculate sensitivity, specificity, positive and negative predictive values at clinically relevant cut-off points, and area under the receiver operating characteristic curve (AUC/C-statistic). For calibration, we will produce estimates of calibration-in-the-large, calibration slope and flexible calibration plots (Van Calster, et al., 2016). The internal validation results will be used to select between the analytical methods (i.e., logistic regression, artificial neural networks, support vector machines, random forests, hidden Markov models, and Bayesian approaches) for each model (i.e. for both models 1 and 2). The primary criteria for algorithm performance will be high specificity (valued by services), with sensitivity a secondary criterion (i.e. we want to maximise specificity whilst ensuring clinically useful sensitivity). This approach to algorithm development on real-time data also offers the potential to be able to stop data collection should an algorithm be developed that meets the requirements for sensitivity and specificity and meets the minimum sample size criteria. The specific requirements for an acceptable level of sensitivity and specificity is a central topic of investigation in this project; we will target performance that is not only statistically significant, but is also acceptable to end-users, clinicians and other stakeholders to maximise clinical utility of the model (i.e. we will establish this iteratively through our PPI and qualitative work).

#### *6.4.3 Adaptive sampling algorithm development* *(Research questions 6 and 7)*

We will use the data collected in Group 1 to develop an adaptive sampling algorithm to allow the time and frequency of input requests from users to be optimised. Existing approaches for adaptive sampling are primarily in the health screening literature, where the problem is to optimise the timing of the next screening test (e.g. cancer screening). We will use such approaches to underpin our methods development by extending them to suit ASM for psychosis. We will begin by summarising overall patterns of engagement in Group 1 and use this to learn 'what drives engagement'. Specifically, we will use both simple descriptive statistics of associations between participant characteristics and engagement with the app and apply latent class analyses to identify subgroups with different engagement patterns (building on our existing work (Bucci, et al., 2018) (Hulme, et al., 2021)) for hypothesis generation purposes. We will also model which factors (including demographics, histories of symptom response and patterns of response) predict engagement; outcomes for such models will include time-to-drop-out and intermittent non-response. This would imply a prediction model where stable, low symptom severity leads to sustained disengagement (Research question 7). Based on the learning from the generative models, we will build adaptive sampling models by considering a decision theoretic framework. This works by trading off, at any given time, what the value of requesting an observation would be (in terms of better predicting relapse, and ultimately improving clinical decisions), versus the cost of requesting the observation (e.g. possible disengagement of the user through alert fatigue). We will consider a number of approaches (Research question 6) including Hidden Markov models (in which observation frequency depends upon latent state, as we have explored previously (Hulme, et al., 2021) (Bucci, et al., 2018)), and joint models for longitudinal and time to event data (Rizopoulos, et al., 2016). We will simulate the action of the adaptive sampling model by subsampling from the Group 1 dataset. We will then explore how the risk prediction algorithm (discussed above) performs based on the now reduced data; i.e., to explore if the model on the subsampled data of Group 1 achieves comparable performance to the prediction model on the full

Group 1 data. Based on our learning here, we will select the adaptive sampling algorithm that best trades off the most accurate and timely relapse predictions, with minimal input demands on the user.

#### *6.4.4 **Algorithm validation** (Research questions 4, 1 (cont), 6 (cont))*

We will use Group 2 (*n* = 300) to temporally validate both the risk prediction model and the adaptive sampling algorithm developed in Group 1, providing unbiased estimates of predictive performance of each. Here, we will apply the risk prediction model (as developed and selected from Group 1; see above) to each participant in Group 2. We will examine the performance of this final model (in Group 2) in terms of calibration and discrimination using all of the aforementioned metrics. We will additionally aim to determine the clinical utility of the model (within Group 2) using decision-curve analysis, comparing 'net benefit' against extremes of a 'treat-all' vs. 'treat-none' approach across all combinations of risk threshold. The most basic interpretation of a decision curve is that the model with the highest net benefit at a particular threshold has the highest clinical value.

We will compare the performance of the developed algorithm (from Group 1) against existing (previously published) 'static' prediction algorithms (that are based only on baseline information and do not make use of the longitudinal or high fidelity data) in Group 2, on all of the metrics above *(Research question 4).*

For the adaptive sampling algorithm validation, we will subsample the data collected in Group 2 according to the adaptive sampling algorithm and evaluate the reduction in burden on participants and ensure that model performance of the risk prediction model is minimally affected by the reduction in available data. We will then use the validated adaptive sampling algorithm to further tailor the risk prediction model.

Note the adaptive sampling algorithm will not change the data collection in any way, nor will it be used to monitor, prevent, or treat psychosis; we will simply use the data collected to test the algorithm. There will be no change to the usual care or treatments of participants in this study due to testing of the adaptive sampling algorithm.

### 6.5 Qualitative data analysis plan

Qualitative research data such as field notes, reflective diaries and study team meeting minutes will be used to inform the in-built process evaluation. Audio-recorded qualitative interview data will be analysed using framework analysis (Gale, et al., 2013). We will use a qualitative analysis software package to manage the analysis process. Analysis of qualitative interviews will occur alongside transcription and data collection so that we can iterate our topic guide– these tasks will not be sequential but will occur in parallel. Researchers will keep notes on analytical insights during the analysis process using a reflective diary. We will initially use the Framework method to take an inductive approach to theme generation. Subsequent theme refinement will be deductive and guided by implementation science frameworks.

*Framework analysis*

Framework analysis allows the dataset to be examined in a thorough and methodical way. The framework method is not specifically aligned with either an inductive or deductive approach to coding data; the coding approach can be chosen depending on the research question. Hence, deductive coding can be used in cases where there is pre-existing theory and/or *a priori* questions to be examined and, conversely, inductive coding can be used in cases where there is little or no pre-

existing theory on the topic in question. A combined approach, using both deductive and inductive coding, is also acceptable (Gale, et al., 2013) and will be used in the current study. Inductive coding will allow space to explore unanticipated aspects of participants' views that do fall outside of pre-existing theory. The following steps will be followed during data analysis:

1. Transcription. Audio-recorded interviews will be transcribed verbatim.
2. Familiarisation. As soon as the first few interviews have been transcribed, members of the research team will read the transcripts and accompanying reflective logs and/or listen to audio recordings of interviews to familiarise themselves with the data. They will revisit each interview several times to immerse themselves in the content. They will make notes on potential themes and other key ideas at this stage.
3. Coding. Researchers will read the first five transcripts line by line and apply a code describing why each section is important. As described above, a combined deductive and inductive coding strategy will be used.
4. Developing a working analytical framework. Researchers will compare codes and agree a set of deductive and inductive codes to use for coding subsequent transcripts. This framework will be reviewed by PPI contributors.
5. Applying the analytical framework. Researchers will systematically apply the working analytical framework to subsequent transcripts. They will also revisit previous transcripts to ensure that coding is consistent with the agreed analytical framework. The analytical framework will be updated where necessary (e.g. new code needed), with changes discussed periodically within the team.
6. Charting data into the framework matrix. The research team will summarise the data in a framework matrix. The framework matrix contains one row per participant and one column per code, with codes grouped into provisional themes and sub-themes with input from the LEAP and Involvement Network.
7. Interpreting the data. Researchers will discuss analytical insights periodically during the analysis process. Once all transcripts have been coded and charted, the research team will meet to work towards an overall interpretation of the data. Guided by the original research questions, they will review the framework matrix and analysis diary to examine the data at a more abstract level. They will compare and contrast the views of participants with different demographic or clinical characteristics, search for patterns within participants' experiences and examine the relationships between themes to give a thorough synthesis of the data.

For external validation, a selection of transcripts will be read by and discussed with at least one other member of the research team to aid the reflexive process and facilitate discussion around potential themes. We will engage the wider research team, our lived experience advisory groups and stakeholders in the analysis process. Following this coding process, codes will then be mapped onto an implementation science framework to understand barriers and facilitators to use, engagement, and longer-term use of the DRM system.

## 7 Data Management

### 7.1 Data collection tools and source document identification

Robust data security measures will be implemented throughout the study, in full compliance with national policies and relevant data management and information governance (IG) policies and procedures of the participating Universities. Each individual site is responsible for data management,

including Case Report Form (CRF) checking, correcting of data queries, and ensuring the data uploaded to REDCap is accurate.

The processing of names, personal addresses, telephone numbers and other contact details are necessary to inform participants about the study, obtain consent, arrange research assessments and meetings to give them access to use the app, to arrange interviews, and after their participation, to keep them informed about the study findings and other research opportunities they might want to be approached about (only for participants who consent to this). All personally identifiable data will be stored separately from research data at each recruitment site. All research data will be pseudo-anonymised and unique study IDs will be assigned to participants and used instead of participant names / personally identifiable data. The pseudo-anonymised key linking unique study ID numbers to participants names will be stored electronically at each relevant site in an encrypted and password protected file only accessible to members of the research team with necessary privileges. Contact information will be kept securely from the research data using unique study ID numbers and will not contain names.

Assessment data will be entered into a secure web-based database system hosted on University of Manchester servers (REDCap). Access to the database will be restricted to members of the project team involved in data entry and analysis, using an in-built secure system to grant access and data management privileges that can be authorised only by the project Chief Investigator (CI).

Data gathered by the researchers from clinical assessments and case note reviews will be entered into a REDCap database accessible to authorised users at the sites. We will use pseudonyms for users in the central data repository. ASM and PSM data will be stored on a secure cloud-hosting with Amazon Web Services (AWS) supported by a University of Manchester-approved IT supplier; this is a secure data service with certification to international standards for cyber security, known as ISO27001 certification. ISO27001 certification is awarded to organisations that can demonstrate they employ best practice in maintaining the integrity and confidentiality of data. Data collected from participants via the smartphone will be wirelessly uploaded to the server. Data from wearables will be collected different depending on the device used:

- Fitbit: these data are processed on the device by vendor algorithms to provide information on heart rate, movement, daytime and sedentary activity, physical exercise, step count, and sleep efficiency. Data from the Fitbit will be collected into the data capture platform from the Fitbit Web API, using the 3rd Party Data Integration service.
- Samsung smartwatch: the HealthConnect app will pull data from the android phone off the watch via the Samsung app.
- Apple watch: data will be streamed directly via smartphone into the study data capture platform.

Fitbit are already integrated with the RADAR-base stack; the Apple Watch is not and will require integration.

Any hard copies of data including personal and research data will be kept in lockable storage and research and personal data will be stored separately. Hard copies of signed consent forms will be stored in a similar way, and will be kept separate from research data collected as part of the study.

Extracts from clinical notes (e.g. diagnosis, treatment regime in referring service and other sources of support) will be entered directly into the REDCap database. Data from GP, Mental Health Trust, and/or where available, regional coordinated NHS records will be linked and analysed with structured

health data in a secure environment. Interview transcripts will be stored on secure and automatically backed-up services available at the University/NHS servers. Audio recordings of interviews will be stored securely on University/NHS servers according to local IG procedures.

Interviews will be conducted using recording devices enabling encryption at the point of data collection, to provide additional data security. All interviews will be anonymised at the point of transcription, and all identifying details removed. Audio-recorded consent (including participants' names) will be recorded on a separate audio file so that this information cannot be directly linked with the interview transcripts or audio-recordings. Digitally encrypted audio recordings of the interviews (but not identifying consent data, see above) will be transferred to an external company (approved by the Universities and Sponsor) or a University member of staff (who is an approved transcriber) for transcription. Anyone outside the research team will sign a confidentiality agreement before accessing the data and will not have access to other personal data (e.g. name, address). Where an external transcription service is used, this must be on the list of services approved by the University of Manchester, and audio files will be transferred using a secure file transfer system (also approved by the University of Manchester). We will then use the secure file transfer system to transfer these transcripts to The University of Manchester for storage. Archiving of de-identified study data will be arranged by researchers at the University of Manchester once the study is completed.

Electronic transfer of data is necessary as data collection will be undertaken across several, geographically dispersed sites, and pseudo-anonymised research data will require transfer to the University of Manchester for analysis. The transfer of research data amongst participating sites will be managed via a secure web-based database system hosted on University of Manchester servers (REDCAP), or an alternative safe data transfer system approved by the Sponsor. Access to the database will be restricted to members of the project team, including the digital software team, involved in data entry and analysis, using an in-built secure system to grant access and data management privileges that can be authorised only by the project Chief Investigator (CI).

Data gathered by the researchers from clinical assessments will be entered into a REDCap database accessible to authorised users at the sites (i.e. the local research team will have access to identifiable data just for that site). We will use pseudonyms for users in the central data repository.

Paper copies of questionnaires will be destroyed using confidential waste services at participating sites at the end of the study.

### 7.2 Data protection and confidentiality

The University of Manchester (UoM) will sponsor this multi-site study, which is led by UoM researchers. Prof Sandra Bucci will act as data custodian for this study. Researchers based at UoM, at all collaborating Higher Education Institutions and all study sites will gather, process and securely store data gathered for study purposes (including study data and personal data), in line with UoM policies/procedures. All investigators and study site staff will comply with the requirements of the Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Each study participant will be assigned a unique study identification number at the start of the assessment process. Participant names will be removed from all study data and interview transcripts, which will then be identified by the study ID number only. Personal data (name, address, audio-recordings, consent forms, etc.) will be securely stored separately from de-identified study data:

- Personal data (e.g. name, address, audio-recordings) will be stored on secure University/NHS electronic storage (e.g. secure server) according to local IG procedures. Although consent forms will generally be stored electronically (as just described), participants may opt to complete a paper consent form. Hard copies of signed consent forms will be kept in lockable storage and research and personal data will be stored separately. Consent forms (whether electronic or paper) will not contain the participant's study id number in their content or as part of the electronic document naming convention.
- De-identified data will be on the AWS cloud computing platform, managed by a University of Manchester-approved IT supplier.
- A record sheet linking participant identity, contact details and study identification number for all participants will be kept at each site.

All study data including assessments, ASM data and passively collected data will be stored in the University of Manchester in a secure data service built on the AWS cloud computing platform with ISO27001 certification. Data collected from participants via the smartphone and smartwatch will be wirelessly uploaded to the server; data from the Fitbit will be pulled from FitBit's servers. Data gathered by the research workers from clinical assessments and case note reviews will be entered into a REDCap database accessible to authorised users at the sites (i.e. the local research team will have access to identifiable data just for that site). We will use pseudonyms for users in the central data repository. Data will be kept secure at all times and maintained in accordance with the requirements of GDPR and archived according to GCP regulations. A data management plan will be produced and reviewed by expert research data librarians and updated at least once a year.

The follow-up exit interview (and informed consent, if the participant opts for audio recorded consent rather than another consent format) will be audio recorded using either:

- an encrypted digital audio recorder;
- an online meeting platform (Zoom/Teams; not NHS NearMe, which cannot record meetings).

Participants will be informed that recording the interview via an online platform means that their personal data will be processed by Microsoft/Zoom. This may mean that their personal data is transferred to a country outside of the European Economic Area, some of which have not yet been determined by the United Kingdom to have an adequate level of data protection. However, appropriate legal mechanisms to ensure these transfers are compliant with the Data Protection Act 2018 and the UK General Data Protection Regulation are in place.

We will follow University of Manchester guidance for audio recordings for research purposes (https://documents.manchester.ac.uk/display.aspx?DocID=38446). Audio recordings are personal data and will be processed and stored accordingly. As soon as possible after the interview has finished, the researcher will transfer the audio recording of the interview to a secure server at the relevant site (stored according to local IG procedures) and then remove it from the recording device or online meeting platform system. Audio recordings of informed consent and of qualitative interviews will be stored separately in different folders according to local IG procedures. Transcription may be carried out by the study team, by an approved individual based at the University of Manchester (outside the research team), or by an external transcription service. Anyone outside the research team will sign a confidentiality agreement before accessing the data and will not have access to other personal data (e.g. name, address). Where an external transcription service is used, this must be on the list of services approved by the University of Manchester, and audio files will be transferred using a secure

file transfer system (also approved by the University of Manchester). We will then use the secure file transfer system to transfer these transcripts to The University of Manchester for storage.

Only the research team will have direct access to personal information and study data. However, study data and material may be looked at by individuals from the University of Manchester, from regulatory authorities, from the local HEI site or from the NHS Trust/Board, for monitoring and auditing purposes. This may include access to personal information. Confidentiality of information provided during the research may also be broken if a participant is assessed to be at risk to/from themselves/others (or discloses significant bad practice); participants will be informed of this procedure prior to giving consent.

De-identified data will be safely stored for up to 20 years. Consent forms (and consent audio recordings) will be kept as essential documents for 2 years after the end of the study but other personally identifiable information such as contact details will be deleted as soon as they are no longer required.

Where relevant (only at certain study sites), participants who would like to receive payment electronically (electronic gift voucher) will be asked to consent to their email address to be sent to the university/NHS finance department. Their email address will then be used to send them the electronic voucher directly, and may then be stored in the university/NHS finance system for up to 7 years (for audit purposes). Other payment options will be available for participants who prefer not to consent to this.

### 7.3 Additional security measures

There are several measures we will employ to protect personally identifiable data. Any data stored on the phone by the participant will be encrypted.

*Software security features*

- **App:** The app will utilise the smartphone features to provide additional security include phone locking and unlocking and encrypted data storage.
- **Servers: ASM and PSM** data will be stored in t a secure data service built on the AWS cloud platform with ISO27001 certification. The system will be managed by a University of Manchester approved IT supplier. This system will be penetration tested prior to participant onboarding.
- **Participant data (app):** Only ASM and PSM related data will be transferred from the app to the server A pseudonymised identifier will be used to identify each participant. Only the research team will know the link between this identifier and the actual participant. This link will not be stored anywhere in the system and the software team will only have access to the pseudonymised identifiers.

Three general principles of information security (confidentiality, integrity and availability) will be followed in the design and implementation of the CONNECT app. All data transmitted to and from the study servers will be encrypted. In cases where participant data are downloaded from the CONNECT sites, these data will be securely encrypted with a pass phrase of appropriate length and complexity. Data transfers are secured by using standard web security protocols. Uploading data to a central server in real time enables study data to be captured and so protects against data loss, such as a phone which can be lost or stolen. This removes the need for personal data storage on the device. The purpose of the server in this case is secure data storage.

## 7.4 Data handling and record keeping

Data collected via the wrist-worn device will be encrypted and uploaded to a secure server maintained by the sponsor organisation and will be not identifiable by participant name. Data collected via the smartphone will be encrypted and uploaded to secure servers by WIFI or mobile data connection.

The research team will keep legible and accurate documents to ensure thorough documentation of study conduct. The highest degree of confidentiality will be maintained for managing data collected throughout the course of this study; however, to meet legal responsibilities and quality assurance policies, the investigational site will permit authorised representatives of the sponsor, funder and health authorities to examine deidentified records, to satisfy quality assurance reviews, audits and evaluations of study safety and progress.

The non-identifiable data acquired may be transmitted through a computer network, or through the internet, or transferred via removable media to be shared with other members of the CONNECT study team in the UK. This information will be de-identified and will not include anything which could identify participants by name, date of birth or address. Participants will be informed via the PIS and asked to consent to sharing of information.

Regular training sessions will be conducted to ensure research workers are delivering the measures and protocol in a standardised way.

### *7.4.1 Information Governance (IG) & GDPR*

All researchers will receive training in the International Conference on Harmonisation (ICH) Guidelines - Good Clinical Practice before recruitment commences. As the study has various features that are classed by the ICO as high-risk or sensitive data processing (vulnerable individuals, special category data, high volume with >1,000 people recruited, application of a new algorithm), we are obliged under data protection law to complete a Data Protection Impact Assessment (DPIA). We will build in privacy by design by conducting the DPIA from the outset and incorporating privacy considerations into this project in a similar, co-designed way to how it was built into our previous digital mental health apps which we will submit through IRAS for NHS REC Approval. The considerations and outcomes of our qualitative research and PPI work will be recorded in our DPIA. The DPIA will consider the latest standards in data security relevant to clinical data. We will make this DPIA and the other documentation available to NHS recruitment sites to provide accountability and assurance that the study upholds data protection obligations. Our IG and data management expert will guide and develop this process.

## 7.5 Access to data and final study dataset

Direct access will be granted to authorised representatives of the Sponsor, funder and the health authorities to examine deidentified records, to satisfy quality assurance reviews, audits and evaluations of study safety and progress. To add benefit and impact, the data we collect will also be a valuable scientific resource as a platform for downstream research into psychosis, given the breadth, depth, and resolution of the data we will collect. We will ensure that the data can be reused for secondary analysis by publishing schemas and data dictionaries. An anonymised dataset will be created and archived at the University of Manchester. This data will be made available on application to researchers for non-commercial research. Request for data will be subject to approval by a Data Access Committee.

The main dataset that the research will generate will be the de-identified data from ASM, Passive monitoring, clinical assessments, and demographic information. We will obtain consent from participants to share this data with other researchers for secondary analysis in future related research studies (including student research projects), ensuring that participants are fully informed of this before consenting. The de-identified dataset will be securely stored on the University of Manchester Research Data Management System (RDMS) for up to 20 years and then destroyed.

Researchers involved in the study will have direct access to the dataset during the study for the purposes of preparing study reports and publications. Researchers involved in the study who wish to use the data for secondary analysis will be required to make a formal request to the Project Management Group, overseen by the Project Board, including completing a research study proforma detailing the specific research question they wish to address. Researchers external to the study (including student researchers) may also request access to the dataset for secondary analysis via the same route. In all cases, access to the dataset will follow the terms of the funding agreement and proposals for add-on studies must lie within the scope of the aims and objectives of the CONNECT study.

### 7.6 Archiving

Retention periods are subject to the Sponsor's (i.e. University of Manchester) records retention schedule policies. All research data will be kept in anonymised format and retained for 20 years following the end of the study. All final locked datasets will be kept in encrypted files on robust and automatically backed up on University servers. Prof Sandra Bucci will act as data custodian. Local PIs will be responsible for the safe disposal of data collected at participating sites once these are no longer needed. Hard copy data will be safely destroyed using confidential waste management systems, and electronic data will be permanently deleted from computers and servers. At the end of the study, all study data, the Study Master File, and all site files will be forwarded for archiving with the study Sponsor. All data will be stored and processed in accordance with the Data Protection Act (2018).

## 8 Monitoring, Audit and Inspection

### 8.1 Monitoring

A Project Management Group (PMG) will meet monthly and has been established to oversee the running of the project and ensure tasks completed / deadlines met, is chaired by the PI (Professor Bucci) or her nominated Deputy, and comprising study Co-Investigators (including the site PIs and a PPI co-applicant), the project manager, the recruitment site research co-ordinators and postdoctoral researchers.

The Project Board will meet twice a year and comprises the Principal Investigator; the deputy Principal Investigator (being John Ainsworth or his successor) one nominated representative from each academic institution, being Manchester, KCL, Glasgow, Edinburgh, Cardiff, and Sussex and Annabel Walsh on behalf of McPin. All significant operational matters relating to the Project will be decided upon by the Board.

The Research Steering Group will meet twice a year and operates as the key forum through which the funder will be kept up to date about project progress. The RSG will advise the funder when and whether each of the research phases, research outputs or targets of the project have been achieved.

The RSG comprises the Principal Investigator; the deputy Principal Investigator (being John Ainsworth or his successor); at least one independent expert adviser with experience which is relevant to the Project; one representative of the University of Manchester's technology transfer office (in an advisory and non-voting capacity); and two representatives or nominees of The Wellcome Trust.

Thorough training of all research workers at the study onset and subsequent weekly supervision of all research workers throughout their involvement in the study will minimise risk of deviations from protocol. However, accidental deviations from protocol can happen at any time; these will be documented and recorded in a protocol deviations log, which will be saved in the Study Master File. All deviations from protocol will be brought to the attention of the project CI so that corrective actions could be promptly implemented. The protocol deviations log will also be reviewed at regular meetings with the RSG for additional scrutiny and suggestions of corrective actions.

### 8.2 Audit and inspection

The study will also be subject to the audit and monitoring regime of the Sponsor (The University of Manchester), the lead NHS Trust (Greater Manchester Mental Health NHS Trust), and all participating sites including the University of Manchester, the University of Edinburgh, the University of Glasgow, the University of Sussex, Cardiff University and King's College London.

## 9 Ethical and Regulatory Considerations

### 9.1 Assessment and management of risks

#### *9.1.1 Overall study risk assessment*

The overall study risk assessment (Appendix C) includes details of measures in place to control risks to participants (distress, disclosures of harm to self/others, and exposure to Covid-19 virus) and risks to researchers (distress, lone working, environmental hazards, driving to study meetings/visits, and exposure to Covid-19 virus).

#### *9.1.2. Managing participant distress, risk and disclosures*

During visits, participants will be asked about topics that may be highly sensitive, emotive or distressing topics. There is a small chance that some participants may find the topics upsetting or that they may disclose plans to harm themselves or others. Details of procedures to deal with participant distress and risk disclosures are provided in Appendix H and summarised below.

Participants may become distressed while using the app, phone or wearable device. The CONNECT app will have an emergency contacts section so that, should a participant become distressed while using the app or device, they will be able to contact a relevant organisation. The contact list will include information to out-of-hours emergency contacts (e.g., A&E services; NHS contacts; charity helplines / websites) as well as local organisations that can provide support during business hours. We will also seek consent to contact a participant's care team should the become distressed. We will not, however, monitor the data stream for risk information, to feedback information about a participant's symptom/behaviour pattern, or to intervene in a participant's care.

It is possible that some participants might misinterpret the app to be an emergency device which they can use to communicate information about risk to their care team or to the research team. We will ensure that the app includes a statement that data will not be monitored for information regarding risk and is not an emergency tool. The information sheet will explain that all users should use normal

methods of seeking help in a crisis (e.g. calling NHS contacts, the Samaritans or go to A&E) and this information is reiterated in the CONNECT app.

Researchers will be sensitive to the possibility of participant distress. They will reassure participants that they can decline to answer any questions that they prefer not to answer and that they should only disclose information if they are comfortable doing so. Participants can request a break from the interviews at any point if they wish, and researchers will suggest a break in the event of participant distress. If the participant finds the interview stressful, they are free to discontinue without having to give a reason. All researchers will be sufficiently experienced, trained and supervised to carry out the study protocol. The researcher will check if participants have any concerns and give them an opportunity to discuss these at the end of the visit. We will have a standard protocol for managing any distress that is associated with the completion of measures or study procedures, which we have successfully utilised in several studies and has been developed in collaboration with people with lived experience; this includes telephone contact within 48 hours of assessments to check on participant well-being.

It is also possible that participants may disclose plans to harm themselves or other people during the interview, or that they may disclose information about bad practice (e.g. an NHS staff member who is not following Trust/Board policy and procedure). If such a disclosure occurs, the researcher will pass the relevant information on to the participant's clinical team (or other relevant person in the case of reports of bad practice). Participants will be informed of this procedure regarding the limits of confidentiality prior to giving consent. In cases where information is passed on, the researcher will inform the participant of their intention to do so (as long as this does not put the researcher themselves at immediate risk). All relevant information will be taken into account when making this decision.

Research staff will liaise immediately with clinical staff and services to ensure provision of appropriate support, should risk be identified. We will develop a robust process for informing the clinical team, based on tried-and-tested procedures (which will be further developed in consultation with our advisory groups) we have already employed in other studies of digitally-mediated and face-to-face interventions in this participant group (e.g. the MRC-funded Actissist trial (IRAS Refs: 234090). We will liaise closely with a participant's care co-ordinator and share information relevant to the participants' welfare, clinical support needs and safety. At the point of referral, we will collect the contact details of both the participant's General Practitioner and key contact from the referring service, who will be our primary point of contact for subsequent liaison with the clinical team. Once a participant has consented to taking part in the study, we will swiftly inform the referring clinician from the referring service of the participants' decision to take part in the study and write a letter to the healthcare provider to inform them about participation so that this information can be included in relevant electronic notes accessible to all team members involved in the participant's care. We will follow the study's Safeguarding and Distress Management Protocol included in this application. We will report risks where needed according to the relevant Trust risk reporting procedure.

An essential aim of this project is to determine the feasibility and acceptability of long-term engagement with AMS. By choosing aesthetically appealing, commercially marketed fitness trackers, and by incorporating feedback from our Involvement groups, we hope to minimise stigma and burden for the user and maximise acceptability. However, there may be several factors affecting willingness to use the devices. Participants will be asked to wear the device on their non-dominant wrist for 24 hours a day, ideally taking off only to shower and charge. All devices will be non-invasive, painless, and extremely low risk. They are similar in size and dimension to a watch, manufactured primarily in

rubber, and are marked as lifestyle devices, therefore not denoting participation in a research study, reducing stigmatisation and eliminating the possibility of identifying an individual as a research participant. They have been thoroughly tested and approved for safety by regulatory authorities. Participants may however find them to be uncomfortable or cumbersome. They may forget to charge them, or not know how to charge them. The introductory training provided for all participants will mitigate this risk, along with provision of a 'help' section in the smartphone app, and the availability of contact with the research team. The extent to which participants continue to wear the device, or complete the questionnaires on the CONNECT smartphone app is likely to correlate with their mental health; a decline in mood may show itself through disengagement with the research protocol. Regular review of the data by the research team, alongside practices designed to encourage engagement, may help to identify whether a loss of data is due to potential relapse, or technical/practical issues which can be resolved.

The questionnaires to be completed on the CONNECT app have been well-tested in pilot studies and in other research protocols, however the frequency of assessment and usability of the app may make completion of the questionnaires difficult. A member of the research team will contact the participant once a week for the first 4 weeks, followed by monthly contact (e.g. phone call, text message), to mitigate this risk.

The CONNECT app will generate prompts at certain times of the day. However, participants will be reminded not to answer questions in situations where attention is required, such as when crossing a road or driving. An additional risk is that the activity tracker or smartphone are lost, sold or stolen. We will consider replacing devices on a case-by-case basis. We will encourage participants throughout the study to exercise care in using the devices, emphasising the goals of the study and potential benefits to participants.

We have ensured the highest standards of data security are in place. Robust data security measures will be implemented throughout the study, in full compliance with national policies and relevant data management and IG policies and procedures of the participating Universities. All study data including assessments, ASM data and passively collected data will be stored on a secure cloud-hosting with Amazon Web Services (AWS) supported by a University of Manchester approved IT supplier; this is a secure data service with ISO27001 certification. Three general principles of information security (confidentiality, integrity and availability) will be followed in the design and implementation of the CONNECT app. All data transmitted to and from the study servers will be encrypted over https with strong ciphers as detailed in the Approved Cryptographic Algorithms Good Practice Guidelines (NHS, 2012 and Australian Equivalence). Cipher suites will be implemented in compliance with Section 6 ("Preferred uses of cryptographic algorithms in security protocols") of the Good Practice Guidelines. In cases where participant data are downloaded from the CONNECT sites, these data will be securely encrypted with a pass phrase of appropriate length and complexity. Data transfers are secured by using standards web security protocols. Uploading data to a central server in real time enables study data to be captured and so protects against data loss such as a phone, which can be lost or stolen. This removes the need for personal data storage on the device. The purpose of the server in this case is secure data storage. Interviews will be conducted using recording devices enabling encryption at the point of data collection, to provide additional data security. All interviews will be anonymised at the point of transcription, and all identifying details removed. Each study participant will be assigned a unique study identification number at the start of the assessment process. Participant names will be removed from all study data and interview transcripts, which will then be identified by the study ID

number only. Personal data (name, address, audio-recordings, consent forms, etc) will be securely stored separately from de-identified study data.

We do not anticipate that participation will increase the risk of relapse, nor of their being other significant risks of harm to the user. Participants may not necessarily be in contact with healthcare services during the study, but for those that are, their relationships with their care teams will not be impacted.

No treatment will be withheld as it would be unethical to restrict the therapeutic options of the clinical teams participating.

This study will be conducted per the Declaration of Helsinki and Good Clinical Practice, adhering to principles outlined in the NHS Research Governance Framework for Health and Social Care (30 October 2020).

### *9.1.3 Managing risks to researchers*

In terms of risk of researcher distress, the questions the researchers will be asking in the visits may include highly sensitive, emotive or distressing topics. However, if the researchers do feel distressed, a debrief meeting with their line manager or a senior member of the research team with whom they feel comfortable discussing this with will be arranged. The research assistants will also receive appropriate training in distress management from their local NHS Trust/Board and/or an experienced clinician.

Conducting face-to-face recruitment visits at a participant's home presents potential risks to the researcher's physical safety. This includes risks of violence or aggression from individuals who may be present at NHS services, or at a participant's home, as well as other environmental risks presented by travelling to or meeting at such locations. Full details of measures to control these risks are given in Appendix C. In brief:

- Risk assessment*: The researcher will obtain an up-to-date risk assessment from the care coordinator before meeting the participant in person in their home (using the standard study risk assessment form which includes details of environmental risks from attending the participant's home). If meeting the participant alone in their home poses too great a risk, either a joint visit will be conducted (e.g. with another researcher or a clinician), the meeting will be held at an NHS service, or the meeting will be conducted via phone or using an online meeting platform.*
- Safety check*: During a visit the researcher will leave contact details and a proposed time for the end of the appointment with a member of the research team. An arrangement will be made for the researcher to phone the research team on leaving the participant's home, or the person undertaking the safety check will phone at the proposed end time if they have not heard from the researcher. If attempts to contact the researcher are unsuccessful, a pre-arranged escalation procedure will be acted upon (see Appendix H, Distress, risk management and safeguarding protocol).*
- Timing*: All meetings will be conducted during working hours when clinical and supervisory support is available. Meetings at NHS services will be only conducted during usual working hours, when other staff will be nearby (i.e. lone working at NHS services will be avoided).*
- Reducing environmental risks*: The researcher will ensure that they plan their route in advance and park in a well-lit area. If pets appear to present a risk, the researcher will request that they be moved to another room.*

- Training*: Researchers should be trained in relevant techniques (e.g. breakaway) and familiar with all study procedures intended to mitigate risks of lone working.*
- The relevant NHS or university lone working policy will be followed at all times.

#### *9.1.4 Use of smartphone and wearable devices*

Commercially available wrist-worn devices will be used to measure various behavioural parameters using sensors on a smartphone and wearable devices. All devices considered are non-invasive, painless, and extremely low risk. They are similar in size and dimension to a watch, manufactured primarily in rubber, and are marked as lifestyle devices, therefore not denoting participation in a research study, reducing stigmatisation and eliminating the possibility of identifying an individual as a research participant. Once a participant has received a wearable device at enrolment, they are not anticipated to change device during the course of the study.

### 9.2 REC and & other regulatory review and reports

#### *9.2.1 REC review and reports*

Before the start of the study, a favourable opinion will be sought from an NHS REC for the study protocol and its appendices. During the study, researchers will abide by the following:

- Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site.
- All correspondence with the REC will be retained.
- The Chief Investigator will produce annual reports as required by the REC and will notify the REC of the end of the study. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.
- Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

#### *9.2.2 Other regulatory approvals*

Before sites begin to enrol participants into the study, HRA approval will be sought for each NHS site. The Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place (HRA approval and site capacity and capability approval).

The sponsor and the University of Manchester regulatory approvals advisor have reviewed and assessed the study.

The app is not a medical device as described in the MHRA decision tool. Whether an app (or other piece of software) is a medical device depends on the intended purpose. The purpose of the CONNECT app is to collect data. It is not intended to prevent or treat a medical condition.

#### *9.2.3. Amendments*

When an amendment to the study is needed, the Chief Investigator or designee will ensure that the current procedure for obtaining approval for amendments are followed.

Once approved, the Chief Investigator or designee will notify sites of amendments and will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

The amended version of the study protocol (and any other amended documents) will be added to the study site file to ensure that the most up to date approved documentation is used at all sites.

### 9.3 Peer review

The CONNECT study has undergone rigorous scientific review as part of the Wellcome Trust Innovation Flagship funding scheme process. The Wellcome Trust has reviewed multiple iterations of the project and convened an international expert panel interview with members from the study team. All members of the study team have reviewed and approved the protocol, as well as the CONNECT advisory groups, which includes experts by experience, technical platform and data security experts, analytics, clinical pathways and regulation. Senior academics from The University of Manchester, independent to the study team, have also reviewed the project, as well as an IG expert at The University of Manchester. The application has been peer reviewed, and approved by, the funder. Important documents such as the Safeguarding and Distress Management Protocol, protocol, and participant facing documents have been independently reviewed by lived experience colleagues.

### 9.4 Public and Patient Involvement (PPI)

People with lived experience of psychosis have been involved in the study design and will be involved in study management, analysis and dissemination. *A study co-investigator with lived experience of psychosis (Annabel Walsh, McPin Foundation) will lead the study patient and public involvement (PPI) group and is a member of the Project Management Group and Project Board. We have three levels of PPI:*

*i.* Involvement Network *(IN), who will be invited to undertake ad hoc, bespoke work on the study as needed;*
*ii.* Lived Experience Advisory Panel *(LEAP), which is smaller group of lived experience members from the Involvement Network; and*
*iii.* Expert Reference Group (ERG*) comprising a range of stakeholders and experts who will meet throughout the programme of work to advise on project design, management, dissemination.*

Specific examples of PPI input at each stage include:

- Study design: qualitative interview topic guide, participant information sheet, consent form, research protocol, study procedures, newsletter, engagement strategy, IRAS form and other ethics documents.
- Management: PPI contributors will meet during the study to advise on study management. e.g., recruitment strategy.
- Analysis of results: members with lived experience of psychosis will assist in the qualitative analysis and assessment of predictor variables, supported by colleagues from the McPin Foundation.
- Dissemination: PPI contributors will co-produce a lay summary of the results and present at conferences and other meetings as far as is possible.

Our PPI contributors have already made a significant contribution to the study, including reviewing the information sheet, consent form, study protocol, ethics documents and IRAS form, ethical consideration of the study and elements of the study design and processes, including risk and safeguarding.

PPI contributors will be financially reimbursed for time spent contributing to the research, in line with NIHR guidelines. PPI contributors will be listed collectively or individually in publications as authors wherever possible. An acknowledgement for PPI contributions will be given in academic and other publications.

### 9.5 Protocol compliance

Accidental protocol deviations can happen at any time. They will be adequately documented and reported to the Chief Investigator and Sponsor immediately. Deviations from the protocol that recur frequently are not acceptable, will require immediate action, and could potentially be classified as a serious breach. The sponsor will be notified immediately of any case where a serious breach (i.e. a breach which is likely to effect to a significant degree the safety or physical or mental integrity of the participants of the study; or the scientific value of the study) occurs.

### 9.6 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

No potential competing interest was reported by Dr Matteo Cella, Dr Matthew Sperrin, Dr Glen Martin, Professor Gill Haddock, Professor Til Wykes, Professor Niels Peek, Professor Richard Emsley, Professor Richard Drake, Professor Matthias Schwannauer and our PPI partner McPin.

Professor Sandra Bucci, Professor Shôn Lewis, and Professor John Ainsworth are Directors and shareholders of CareLoop Health Ltd, a University of Manchester startup company which develops and markets digital therapeutics for schizophrenia. CareLoop Health Ltd owns the commercial rights to the active symptom monitoring app and platform used in this study.

Prof Andrew Gumley was Chief Investigator of the NIHR funded EMPOWER trial which has informed the design of the CONNECT study including active data capture, fear of recurrence assessment and relapse definition.

Prof Kathryn Greenwood is the Sussex lead for Akrivia Health which runs the Clinical Record Interactive Search (CRIS) data systems across the UK. There are no financial links.

Prof James Walters holds a research grant from Takeda Pharmaceuticals to develop novel drug targets using genetic data.

### 9.7 Indemnity

The University of Manchester will arrange insurance for research involving human subjects that provides cover for legal liabilities arising from its actions or those of its staff or supervised students in relation to study management, design and conduct (subject to policy terms and conditions).

For protocol authors with substantive NHS employment contracts, indemnity in relation to study design will be provided through NHS schemes. Where the participants are NHS patients, indemnity in relation to study conduct will be provided through the NHS schemes or through professional indemnity.

Non NHS sites will have their own insurance in place to cover indemnity in relation to the conduct of the study by their employees.

### 9.8 Adverse events

Details of recording and reporting of all adverse events will be contained in a SOP for Adverse Events. To comply with Standards for Good Clinical Practice (GCP), it is important that all researchers are aware of the different definitions related to adverse events in research and how to record, report and review each of these specific occurrences. Adverse events are reportable from the time of study enrolment, defined as the time at which, following recruitment, a participant signs and dates the informed consent form.

An adverse event (AE) is defined by the HRA as any untoward occurrence or worsening of an unintended sign, symptoms or disease that occurs during participation, regardless of any relation to participation. AEs will be recorded and initially assessed for severity and seriousness by site researchers. Level of severity will be categorised as mild, moderate and severe, which reflect the impact of the event on the person at the time. There is a distinction between 'severe' and 'serious'. Seriousness is the criterion for defining regulatory reporting obligations. An adverse event will be classified as serious if it results in: death, injury or permanent impairment to a body structure or body function; serious deterioration in the health of the subject; or foetal distress, foetal death, or a congenital abnormality or birth defect. However, in this study any AE rated as 'severe' will automatically be classified as a SAE and will be reported immediately to the PI. Urgent actions concerning participant and staff safety, communication with others, and clinical care will be immediately addressed by the PI. SAEs will be further reviewed for unexpectedness and relatedness to the investigational device and/or study procedures by the PI.

If an SAE is thought to be related to participation in the study, it will be reported to the Research Ethics Committee within 15 days using the National Research Ethics Service template, signed by the chief investigator. Other AEs will be reported in the Annual Progress Report to the ethics committee and copied to the sponsor.

An Adverse Event Log file will be created to systematically record occurrences, with reference to an a priori defined list of anticipated and unanticipated adverse events.

All deaths will be reported to the sponsor within 24 hours irrespective of whether the death is related to taking part in the study or an unrelated event.

#### *9.8.1 Exemptions to adverse event reporting*

Hospitalisation for elective surgery, a planned hospital admission for a pre-existing condition, or a planned change in medication under supervision without deterioration in health, are not considered to be SAEs and are excluded from SAE reporting (i.e. an Adverse Event Report Form is not required).

The following adverse reactions are expected (anticipated) and do not need an AE Form completed (and therefore do not require reporting):

- Transient / short-lived increased awareness of thoughts resulting in negative emotions (e.g. some distress, tearful) during/on completing an assessment, interview or while using the CONNECT app;
- Irritation/skin rash with wearable strap;
- Some discomfort in having sleep or location data (for example) collected;
- Minor irritation or annoyance reported with app alerts/notifications.

Untoward and unintended responses will therefore NOT include these specified reactions.

Technical glitches such as periodic network outage, other minor technical hitches with the apps, phone loss, phone theft and/or a participant selling the phone are NOT counted as AEs but will be systematically logged in a study spreadsheet. If this does, however, result in a decline in mental state (e.g. phone theft as a result of physical assault) then this will be recorded as an adverse event and the phone theft coded as the trigger (as opposed to the AE itself).

## 10 Dissemination Policy

### 10.1 Overview

It is intended that the results of the study will be reported and disseminated at national and international conferences and in peer-reviewed scientific journals. They will be made available to participants and clinical teams in an accessible format, and on the study website. They will also be accessible in print and digital media and presented at stakeholder events. The data arising from the study will be owned by UoM. On completion of the study, the data will be analysed and tabulated, and a final study report prepared.

We will organise a number of events for stakeholders across sites to identify and share key learning experiences arising from the study and to facilitate scoping and engagement of stakeholders participating in the study.

### 10.2 Authorship eligibility guidelines

No professional writers will be involved in the production of the final project report and other peer-reviewed publications that will result from the research activities conducted as part of the project. Determination of individuals to be involved in the preparation and authorship of publications arising from the study will be based on the International Committee of Medical Journal Editor (ICMJE) guidelines on authorship (*http://www.icmje.org*).

Authorship will be considered separately for each publication arising from the study. In line with ICMJE guidelines, authorship of each publication will be based on the following criteria:

> substantial contribution to: (a) the conception or design of the work; or (b) the acquisition, analysis, or interpretation of data for the work and (c) drafting the work or revising it critically for important intellectual content and (d) final approval of the version to be published and (e) agreement to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Examples of activities contributing to authorship are as follows.

- Conception and design would include development of original ideas behind project, and research design (e.g., deciding inclusion criteria, conditions, measures, overall methodology).
- Acquisition of data includes development of project procedures (e.g., recruitment procedures, assessment procedures and materials, randomisation procedures, risk management procedures, decision making re ethics submissions and amendments). Further clarification regarding procedural activities is included below.
- Analysis, interpretation and write-up would include intellectual contributions to the analysis and interpretation of results.

The individuals involved in the write-up of a publication will usually be those who have been involved in the work (i.e., in conception, design, acquisition of data and/or analysis). An exception to this will be

where an additional author has a particular role to play in joining the team to facilitate the interpretation of findings. However, their role would need to amount to a substantial contribution to the overall manuscript to justify authorship.

When a dataset is reused for publications in addition to the main planned paper(s), the background work for design of the original project and contributions to project management and data acquisition should be factored into those publications. However, background contributions need to be weighted in terms of how much they influence the findings of these publications. This will depend upon how extensive and novel the new conceptualisations and analyses that have been conducted are. In most cases, it is expected that only those very heavily involved in the original project would have background contributions that would carry over to a new publication as 'substantial' solely on that basis.

Every effort will be made to include people with lived experience from the study LEAP and Involvement Network as co-authors on all publications. In every case, an acknowledgement for the Patient and Public Involvement contributions to the study will be made.

## 11. Equipment

All study equipment and research workers are funded by a Wellcome Trust grant awarded to Professor Sandra Bucci at The University of Manchester. Funding will be provided to each site to cover:

- Research worker support to promote recruitment and data collection (supervised and line managed by the site PI, or their delegated team member)
- Funding to purchase the necessary equipment to enable recruitment and data collection activities at the sites, including:
    - Study information material (posters, PIS etc.) and study materials (available electronically)
    - Laptops
    - Smartphone, charger and contract cost for research workers involved in data collections activities
    - Data network charge costs for study participants to take part in the study
- Funds to cover reimbursement for participants time and study related expenses incurred by research participants and research workers over the course of their involvement in the study (e.g. mobile data costs; travel expenses to attend research visits).
- Branded items for publicity

The University of Manchester will provide smartphones and chargers, and wearables and chargers, to each site to give to participants to use in the study.

Smartphones (provided by the site) and wearables remain the property of the study until the participant completes their participation. Participants will be asked to sign a receipt (Appendix K) upon receiving the item/s agreeing that any equipment given to them (smartphone &/or wearable, and chargers) remains the property of the CONNECT study throughout their involvement in the study. Once the phone is the participant's property, the CONNECT study will not be responsible for the phone or its mobile service and data.

In the event that a wearable device or smartphone is lost, or stolen, the site will consider replacing the device on a case-by-case basis. However, participants will be encouraged to exercise care in using the devices, emphasising the goals of the study and the potential benefits to participants.

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## 13 Appendices

### 13.0 Appendix 1 - Schedule of Assessments (quarterly assessment schedule)

Participants who provided consent before mid-January 2025 were scheduled to complete clinical assessments post-Baseline every 3 months (i.e., at 3, 6, 9, and 12 months).

| VISIT | BASELINE | ONBOARDING | PHONE CALL (week) | | | | | 3 MONTHS | PHONE CALL (Week) | | 6 MONTHS | PHONE CALL (Week) | | 9 MONTHS | PHONE CALL (week) | | 12 MONTHS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **WEEK** | **1** | **1** | **2** | **3** | **4** | **5** | **9** | **13** | **17** | **21** | **26** | **31** | **35** | **39** | **43** | **47** | **52** |
| **Study Entry/Safety** | | | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | |
| Confirm Consent | | X | | | | | | X | | | X | | | X | | | X |
| Demographics | X | | | | | | | | | | | | | | | | |
| Current Medical/Treatment History | X | | | | | | | X | | | X | | | X | | | X |
| Current treatment | X | | | | | | | X | | | X | | | X | | | X |
| Eligibility Criteria | X | | | | | | | | | | | | | | | | |
| Changes in life circumstances | | | | | | | | X | | | X | | | X | | | X |
| Relapse onset (if applicable) | | | | | | | | X | | | X | | | X | | | X |
| **Clinical Measures** | | | | | | | | | | | | | | | | | |
| CGI-SCH | X | | | | | | | X | | | X | | | X | | | X |
| PSYRATS | X | | | | | | | X | | | X | | | X | | | X |
| CDSS | X | | | | | | | X | | | X | | | X | | | X |
| FORSe | X | | | | | | | X | | | X | | | X | | | X |
| WSAS | X | | | | | | | X | | | X | | | X | | | X |
| DWQ | X | | | | | | | X | | | X | | | X | | | X |
| GAD-7 | | | | | | | | | | | | | | | | | |
| PCWC | X | | | | | | | X | | | X | | | X | | | X |
| EQ-5D-5L | X | | | | | | | X | | | X | | | X | | | X |
| ASSIST -LITE | X | | | | | | | X | | | X | | | X | | | X |

| VISIT | BASELINE | ONBOARDING | PHONE CALL (week) | | | | | 3 MONTHS | PHONE CALL (Week) | | 6 MONTHS | PHONE CALL (Week) | | 9 MONTHS | PHONE CALL (week) | | 12 MONTHS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **WEEK** | **1** | **1** | **2** | **3** | **4** | **5** | **9** | **13** | **17** | **21** | **26** | **31** | **35** | **39** | **43** | **47** | **52** |
| Service Use and clinical information (from EHR) | X | | | | | | | X | | | X | | | X | | | X |
| MARS | X | | | | | | | X | | | X | | | X | | | X |
| **Clinical Measures (cont)** | | | | | | | | | | | | | | | | | |
| Technology satisfaction | | | | | | | | X | | | X | | | | | | X |
| PSSUQ | | | | | | | | X | | | X | | | | | | X |
| **Onboarding** | | | | | | | | | | | | | | | | | |
| Wearable set-up | | X | | | | | | | | | | | | | | | |
| App set-up | | X | | | | | | | | | | | | | | | |
| Training | | X | | | | | | | | | | | | | | | |
| Passive Data Collection | | Continuous Months 1-12 | | | | | | | | | | | | | | | |
| Active Symptom Monitoring | | Continuous Months 1-12 | | | | | | | | | | | | | | | |
| App use | | Continuous Months 1-12 | | | | | | | | | | | | | | | |
| **Technical Support** | | | | | | | | | | | | | | | | | |
| Phone Call | | | X | X | X | X | X | | X | X | | X | X | | X | X | |
| Technical Support | | Continuous Months 1-12 | | | | | | | | | | | | | | | |
| Identify possible relapse | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Record AEs | X | X | X | X | X | X | | X | X | X | X | X | X | X | X | X | X |
| **Qualitative Interviews** | | | | | | | | | | | | | | | | | |
| Debrief | | | | | | | | | | | | | | | | | X |
| Exit Interview* | | | | | | | | | | | | | | | | | X |

* Carried out with a sub-group of participants

## 13.2 Appendix 2 - Schedule of Assessments (4 monthly assessment schedule)

| VISIT | BASELINE | ONBOARDING | PHONE CALL (week) | | | | | | 4 MONTHS | PHONE CALL (Week) | | | 8 MONTHS | PHONE CALL (week) | | | 12 MONTHS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **WEEK** | **1** | **1** | **2** | **3** | **4** | **5** | **9** | **13** | **17** | **21** | **26** | **31** | **35** | **39** | **43** | **47** | **52** |
| **Study Entry/Safety** | | | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | |
| Confirm Consent | | X | | | | | | | X | | | | X | | | | X |
| Demographics | X | | | | | | | | | | | | | | | | |
| Current Medical/Treatment History | X | | | | | | | | X | | | | X | | | | X |
| Current treatment | X | | | | | | | | X | | | | X | | | | X |
| Eligibility Criteria | X | | | | | | | | | | | | | | | | |
| Changes in life circumstances | | | | | | | | | X | | | | X | | | | X |
| Relapse onset (if applicable) | | | | | | | | | X | | | | X | | | | X |
| **Clinical Measures** | | | | | | | | | | | | | | | | | |
| CGI-SCH | X | | | | | | | | X | | | | X | | | | X |
| PSYRATS | X | | | | | | | | X | | | | X | | | | X |
| CDSS | X | | | | | | | | X | | | | X | | | | X |
| FORSe | X | | | | | | | | X | | | | X | | | | X |
| WSAS | X | | | | | | | | X | | | | X | | | | X |
| DWQ | X | | | | | | | | X | | | | X | | | | X |
| GAD-7 | | | | | | | | | | | | | | | | | |
| PCWC | X | | | | | | | | X | | | | X | | | | X |
| EQ-5D-5L | X | | | | | | | | X | | | | X | | | | X |
| ASSIST -LITE | X | | | | | | | | X | | | | X | | | | X |

| VISIT | BASELINE | ONBOARDING | PHONE CALL (week) | | | | | | 4 MONTHS | PHONE CALL (Week) | | | 8 MONTHS | PHONE CALL (week) | | | 12 MONTHS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **WEEK** | **1** | **1** | **2** | **3** | **4** | **5** | **9** | **13** | **17** | 21 | **26** | **31** | **35** | **39** | **43** | **47** | **52** |

| VISIT | BASELINE | ONBOARDING | PHONE CALL (week) | | | | | | 4 MONTHS | PHONE CALL (Week) | | | 8 MONTHS | PHONE CALL (week) | | | 12 MONTHS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Service Use and clinical information (from EHR) | X | | | | | | | | X | | | | X | | | | X |
| MARS | X | | | | | | | | X | | | | X | | | | X |
| **Clinical Measures (cont)** | | | | | | | | | | | | | | | | | |
| Technology satisfaction | | | | | | | | | X | | | | | | | | X |
| PSSUQ | | | | | | | | | X | | | | | | | | X |
| **Onboarding** | | | | | | | | | | | | | | | | | |
| Wearable set-up | | X | | | | | | | | | | | | | | | |
| App set-up | | X | | | | | | | | | | | | | | | |
| Training | | X | | | | | | | | | | | | | | | |
| Passive Data Collection | | Continuous Months 1-12 | | | | | | | | | | | | | | | |
| Active Symptom Monitoring | | Continuous Months 1-12 | | | | | | | | | | | | | | | |
| App use | | Continuous Months 1-12 | | | | | | | | | | | | | | | |
| **Technical Support** | | | | | | | | | | | | | | | | | |
| Phone Call | | | X | X | X | X | X | X | | X | X | X | | X | X | X | |
| Technical Support | | Continuous Months 1-12 | | | | | | | | | | | | | | | |
| Identify possible relapse | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Record AEs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Qualitative Interviews** | | | | | | | | | | | | | | | | | |
| Debrief | | | | | | | | | | | | | | | | | X |
| Exit Interview* | | | | | | | | | | | | | | | | | X |

* Carried out with a sub-group of participants

## 13.3 Appendix 3 - Amendment history

| Amendment No. | Protocol version no. | Date issued | Author(s) of changes | Details of changes made |
|---|---|---|---|---|
| SA1_07_2023 | 3.0 | | Jane Lees, Sandra Bucci | Protocol has been amended to:<br>- reflect the assessments that have been replaced or removed.<br>- remove the upper age limit to increase the range and diversity of participants.<br>- clarify that assessments will take 90 minutes.<br>- clarify that self-report questionnaires can be completed via an online link<br>- indicate the CONNECT dashboard will be checked regularly, rather than every 2 weeks, to allow some flexibility based on researcher workload (section 5.8.1)<br>- remove prompts/follow up phone calls if the participant stops using the system (following PPI feedback) (Section 5.9).<br>- update the qualitative data analysis plan (section 6.5).<br>- clarify how data will be securely stored.<br>- add section 9.8.1 to clarify events/reactions that do not require reporting.<br>- indicate smartphones and wearables for participants will be provided to each site, rather than the funding to purchase them (section 11).<br>- Lead NHS Trust contact and McPin Foundation leads left their roles and will be replaced. |
| SA3_11_2023 | 4.0 | 17.1.24 | Jane Lees, Sandra Bucci | - Included that medical information will be collected from NHS England/NHS Scotland/NHS Wales medical records in order to meet the aims of the study in improving the development of our risk prediction algorithm. This will be optional.<br>- Withdrawing participants can request deletion of all data prior to the pseudo key being deleted, rather than just personally identifying data.<br>- Research workers section removed<br>- One of co-investigators removed |
| SA4_04_2024 | 5.0 | 6.6.24 | Jane Lees, Sandra Bucci | - Updated the process by which participants can seek technical support during the study.<br>- Clarified the inclusion/exclusion criteria following researcher feedback. |

| | | | | |
|---|---|---|---|---|
| SA5_05_2024 | 6.0 | 6.8.24 | Jane Lees, Sandra Bucci | - Where a potential participant is unclear about, for example, the name of their clinical team or clinician or aspects of eligibility (e.g. diagnosis), the researcher they will ask for verbal permission to check their clinical notes to confirm such details, as well as information needed to determine/manage any risk that may arise when arranging a visit to the participant. The potential participant's verbal consent to check these details will be recorded.<br>- The Mental Health Research Network (MHRN) in Scotland facilitates the recruitment of NHS patients by working closely with NHS clinical teams to publicise studies to patients and clinicians through targeted advertising in clinical areas, and directly to the public. Where possible, the Network works with clinicians to identify potential participants, or pre-screens patient databases and reviews clinical records to create shortlists of potential participants for clinical review.<br>- Data will be stored on University/NHS servers according to local information governance procedures. |
| SA08_11_2024 | 8.0 | 21.1.25 | Jane Lees, Sandra Bucci | - Updated exclusion criteria as treatment of relapse takes a variety of forms, so researchers will defer to the treating clinician to decide whether a potential participant has been relapse-free for the past 12 weeks, rather than basing it on discharge from an inpatient ward or crisis team.Some clinical teams, such as Early Intervention Services, do not give formal diagnoses. As such, the inclusion criteria has been updated so that in the absence of a clinical diagnosis of schizophrenia spectrum disorder (ICD10 F20-F29), the treating clinician will be asked to confirm whether a potential participant meets the criteria for a schizophrenia spectrum disorder (ICD10 F20-F29) diagnosis.<br>- Amended the study design so that follow-up assessments are completed every 4 months instead of every 3. |
| SA09_01_2025 | 9.0 | 14.3.25 | Jane Lees, Sandra Bucci | - Removed Samsung Galaxy smartwatch following outcome of nested wearable study<br>- Clarified the previous amendment to the study design and assessment schedule |

| | | | | |
|---|---|---|---|---|
| MA13_06_2025 | 10.0 | 21.7.25 | Jane Lees, Sandra Bucci | - Clarified data will still be extracted from medical records up to the date of a participant's withdrawal |
| SA10_07_2025 | 11.0 | 26.8.25 | Jane Lees<br>Sandra Bucci | Participants can be recruited via SHARE, a register for people in Scotland who are interested in taking part in health research projects. |
| SA11modified_02_2026 | 13.0 | | Jane Lees | Included information on recruitment via the Everyone Included approach at Avon & Wiltshire Mental Health Partnership NHS Trust. |

Protocol amendments will be submitted to the Sponsor for approval prior to submission to the REC committee.

All amendments will be prepared and submitted by the Project Manager (or a delegated research team member).

- SA6_10_2024 was given an unfavourable opinion by the REC committee.
- SA7_11_2024 was withdrawn and re-submitted as part of SA8_11_2024
- SA11_08_2025 and SA11modified_09_2025 were given an unfavourable opinion by the REC committee.