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# A Study Protocol for the Hummingbird Study, an Open-label, Multicenter Exploratory Trial to Assess the Acceptance and Performance of a Digital Medicine System in Adults With Schizophrenia, Schizoaffective Disorder, or First-Episode Psychosis



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|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2018-025952 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 13-Aug-2018 |
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| Keywords: | Coproduction, digital medicine, schizoaffective disorder, schizophrenia |
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# A Study Protocol for the Hummingbird Study, an Open-label, Multicenter Exploratory Trial to Assess the Acceptance and Performance of a Digital Medicine System in Adults With Schizophrenia, Schizoaffective Disorder, or First-Episode Psychosis

Running title: Study protocol for DMS use in schizophrenia in the UK

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Word count (max 4000 for BMJ Open): 3059 (Intro through conclusion, not including table)

Table count: 1

Figure count: 3 (+5 supplemental)

Reference count: 31

## ABSTRACT FOR PROTOCOL

Introduction: In patients with schizophrenia, medication adherence is important for relapse prevention, and effective adherence monitoring is essential for treatment planning. Digital technology has shown success in schizophrenia assessment and treatment. A digital medicine system (DMS) has been developed to objectively monitor patient adherence and support clinical decision making regarding treatment choices. This study's objective is to assess the acceptance and performance of the DMS in adults with schizophrenia, schizoaffective disorder, or first-episode psychosis and in healthcare professionals (HCPs) in the United Kingdom.

Methods and Analysis: This is a multicenter, 8-week, single-arm, open-label pragmatic trial designed using coproduction methodology. The study will be conducted at 5 National Health Service Foundation Trusts in the United Kingdom. Patients 18 to 65 years old with a diagnosis of schizophrenia, schizoaffective disorder, or first-episode psychosis will be eligible. HCPs (psychiatrists, care coordinators, nurses, pharmacists) researchers, information governance personnel, commissioners, and patients participated in study design and coproduction. The DMS is an integrated system comprising an oral sensor tablet co-encapsulated with an antipsychotic, nonmedicated wearable patch, mobile application (app), and Web-based dashboard. The co-encapsulation product contains aripiprazole, olanzapine, quetiapine, or risperidone, as prescribed by the HCP, with a miniature ingestible event marker (IEM) in tablet. Upon ingestion, the IEM transmits a signal to the patch, which collects ingestion and physical activity data for processing on the patient's smartphone or tablet before transmission to a cloud-based server for viewing by patients, caregivers, and HCPs on secure web portals or mobile apps. Primary and secondary

endpoints will be the proportion of days with good patch coverage and ingestion adherence, respectively.

Ethics and Dissemination: Approval for this study was obtained from London - City & East Research Ethics Committee. Results will be disseminated through peer-reviewed publications, conference presentations, clinical trial repositories, and communications with participants.

ClinicalTrials.gov: NCT03568500

## Keywords

Coproduction, digital medicine, schizoaffective disorder, schizophrenia

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study was codeveloped with input from clinical practitioners, researchers, patients, caregivers, service managers, information governance teams, and clinical commissioning groups to obtain information that will best serve all those involved in the treatment and care of patients with schizophrenia, schizoaffective disorder, and first-episode psychosis.
- The digital medicine system (DMS) uses an integrated, user-friendly system to provide objective feedback on patient medication adherence and physical health parameters, such as activity and rest levels, as well as voluntary subjective entries regarding mood and rest quality, to help support treatment decisions and evaluation.
- Information from the DMS is made readily available to patients, caregivers (with the patient's consent), and physicians to support clinical decision making, proactive intervention, and individualized care in near to real time.

- Possible limitations of this study are the small sample size (N=60), limited generalizability to the broader pool of UK mental health patients and providers, and the relatively short 12-week timeframe.

## INTRODUCTION

Schizophrenia has an enormous social and economic burden worldwide, accounting for 1.1% of total disability-adjusted life-years and 2.7% of years lived with disability [1, 2]. In Europe, the economic impact of schizophrenia and other psychotic disorders and syndromes in 2010 was estimated at €93.9 billion [3]. Because it is a chronic disease, maintenance treatment is often necessary to prevent relapse and preserve quality of life over the long term [4, 5]. Although antipsychotic medications are effective [6-8], poor insight into schizophrenia can increase risk of medication nonadherence [9, 10]. In patients with schizophrenia, the rate of nonadherence to prescribed antipsychotics has been reported to be as high as 74% [11]. Not only is medication nonadherence burdensome to patients and their families, it also increases the likelihood of rehospitalization and relapse [12] and contributes substantially to healthcare costs [13]. In 2005/2006, mean annual psychiatric inpatient and medication costs for patients with schizophrenia in England were estimated to be approximately £3,000 and £2,000 per patient, respectively [14].

Because medication adherence is important to relapse prevention in schizophrenia [15], effective adherence monitoring is an essential part of the treatment plan. Although there are various subjective methods for determining medication adherence, including patient surveys, adherence diaries, and clinician ratings of patient symptoms and medication side effects, these methods have low validity [16]. Blister packs and electronic medication bottle caps can provide an indicator of pill removal or bottle opening and have been shown to improve adherence [17, 18], but neither technology provides an objective marker of pill ingestion or supports remote monitoring by healthcare professionals (HCPs). Optimal adherence monitoring and support for

patients with schizophrenia requires a system that provides physicians with objective information during interim periods between patient visits.

The use of modern technology such as personal digital assistants [19], digital wristwatches [20], handheld computers [21], and mobile phones [22] to manage schizophrenia has shown success. A digital medicine system (DMS) has been developed as a drug-device combination to objectively assess and report ingestion of prescription antipsychotics [23]. The DMS has 4 main components: an ingestible sensor embedded within an inert tablet, a nonmedicated wearable sensor (patch) worn by the patient, a mobile application (app), and a Web-based dashboard [23]. Upon interaction with stomach fluids, the ingestible sensor is activated and communicates with the wearable sensor, which sends a signal to a Bluetooth-paired mobile device where it can be viewed by patients or be subsequently viewed by HCPs and caregivers using secure mobile- and cloud-based software [23]. The DMS also communicates data on patient activity and rest levels as well as subjective data on mood and rest quality. The intention of the DMS is to encourage greater patient self-management and behavior change while enabling caregivers and HCPs to provide better care and support both within and outside of office visits, further engaging patients in their ongoing disease management.

In an open-label, 8-week study, 78% of patients and 72% of HCPs reported being somewhat satisfied, satisfied, or extremely satisfied with the DMS [24]. Findings from another open-label study showed patients to be actively involved in their treatment, with >70% utilizing call centers for technological DMS support [25]; the rate of ingestion adherence in this study was 85.6% [25].

The DMS from the current study (namely the ingestible sensor and the wearable sensor) are Conformité Européene (CE)–marked for use in Europe as class IIa medical devices (CE 559373),

but studies in European mental health populations have not been performed. Therefore, the objective of this exploratory study is to assess the acceptance and performance of the DMS among adult patients with schizophrenia, schizoaffective disorder, or first-episode psychosis and among HCPs from different care settings in the United Kingdom.

## METHODS AND ANALYSIS

### Study design

This is a multicenter, 8-week, single-arm, open-label trial to evaluate the acceptance and performance of the DMS in adult patients with schizophrenia, schizoaffective disorder, or first-episode psychosis on an oral atypical antipsychotic medication (aripiprazole, olanzapine, quetiapine, or risperidone) and in HCPs. The study will take place at 5 institutions in the United Kingdom: Northumberland, Tyne and Wear National Health Service (NHS) Foundation Trust, Surrey and Borders Partnership NHS Foundation Trust, Oxford Health NHS Foundation Trust, South London and Maudsley NHS Foundation Trust, and Southern Health NHS Foundation Trust. The first patient's first visit occurred in May 2018. Patient recruitment will be targeted to last approximately 4 months.

### Intervention

The DMS is an integrated, 4-component system comprising an oral co-encapsulation (CoE) pharmacologic sensor tablet, a Proteus® Patch, a mobile app, and Otsuka Medical dashboard software (**Figure 1**). Each CoE product contains an approved antipsychotic medication (aripiprazole, olanzapine, quetiapine, or risperidone) encapsulated with a miniature ingestible event marker (IEM) in tablet. HCPs will select the medication and dosage based on each

patient's needs. Upon taking the medication, the IEM transmits a signal to the nonmedicated patch that is attached to the patient's skin. The patch collects IEM ingestion and physical activity data, which are then processed by the Patch Analytics Block on the patient's smartphone. Processed data are transferred through the app on the smartphone and sent to a cloud-based server for patient, caregiver, and HCP viewing on Otsuka Medical software through web portals or mobile apps. Patients will have access to the Otsuka Patient Application, caregivers will have access (with patient consent) to the Otsuka Caregiver Web Portal, and HCPs will have access to the Otsuka Healthcare Provider Web Portal.

## Coproduction and patient involvement

This study was designed using coproduction methodology involving NHS staff and patients (**Figure 2**). The lead site, Southern Health NHS Foundation Trust, held 5 coproduction workshops, and a subset of these workshops was repeated at other study sites to elicit feedback on the study design. These discussions addressed pharmacy items for the CoE product; HCP recruitment strategies; and protocols for identification, recruitment, and interactions with suitable patients and their general practitioners. Throughout the various workshops at the different sites, participants included clinicians, pharmacists, researchers, information governance personnel, psychiatrists, care coordinators, nurses, information technology personnel, commissioners, and patients (**Figure 2**).

After changes from the coproduction workshops were incorporated, the Patient and Public Involvement and Service User Lead from 2 study sites (Surrey and Borders Partnership NHS Foundation Trust and Northumberland, Tyne, and Wear NHS Foundation Trust) engaged service users to participate in a patient focus group. At these focus groups, attendees provided feedback on the ease of use of, and the ability to perform tasks within, the DMS mobile app (MyCite).

## Patient selection

Patients for this exploratory study will be identified using database searches conducted at each study site per HCP discretion. Inclusion and exclusion criteria are provided in **Table 1**.

**Table 1. Inclusion and Exclusion Criteria**

| **Inclusion criteria** |
|---|
| • Willing and able to give written informed consent and adhere to trial procedures<br>• Able to read and understand English<br>• Age 18–65 years at the time of informed consent<br>• Possessing a smartphone and able to use it to interact with the digital medicine system (DMS) application **through robust and dependable cellular or wireless internet connections**<br>• Cooperative, able to ingest oral medication, willing to complete aspects of the trial, and capable of reporting adverse events (AEs)<br>• Clinical diagnosis of schizophrenia, schizoaffective disorder (defined by International Classification of Diseases, Tenth Revision, codes F20 and F25), or first-episode psychosis based on case note review<br>• Prescription for aripiprazole, olanzapine, quetiapine, or risperidone<br>• Fulfills ≥1 of the following:<br>  o Discharge from a hospital admission (within 7 days of discharge) to an acute intervention team<br>  o Referral to an acute intervention team before hospital admission<br>  o Referral from an acute intervention team to a community team<br>  o Managed by community services<br>  o Inclusion within early intervention caseload (<3 years from initial symptoms)<br>  o Healthcare professional (HCP) determines the patient would benefit<br>• General medical condition does not pose additional risk<br>• Skin on the anterior chest above the lower edge of the rib cage is free of any dermatologic problem |
| **Exclusion criteria** |
| • Any disorder that may affect patient's ability to participate in the trial or interact with a smartphone<br>• Likely to be incapable of using DMS technology, even with assistance<br>• History or evidence of a medical condition that would expose patient to undue risk of an AE<br>• Known allergy to adhesive tape or any component of the patch or co-encapsulation product<br>• Current incarceration in prison system<br>• Hospitalization at the time of screening due to mental or physical illness<br>• HCP recommendation to not participate<br>• Aversion to taking gelatin capsules |

- Women who are breastfeeding, pregnant, or plan to become pregnant

## Procedures

The study will comprise 3 phases: a screening phase of up to 7 days, an 8-week assessment phase, and a 2-week safety follow-up (**Figure 3**). Screening and baseline may occur at a single visit or at 2 visits separated by up to 7 days. At the screening/baseline visit, patients providing informed consent will receive patches, CoE product, and other supplies and undergo training by the HCPs on required and correct use of the DMS. HCPs will confirm proper patch application to the skin and pairing of the patch with the smartphone app. Patients will be instructed to wear the patch continuously, replacing it every 7 days or as needed during the assessment period. An integrated call center will be available to patients for technical support regarding use of the DMS.

During the subsequent 8-week assessment period, patients will visit their HCP at weeks 4 and 8 (or at early termination) for clinical evaluation and review of DMS data. At the week 4 visit, patients will also obtain a prescription refill. HCPs will be required to monitor and review DMS data at least every 2 weeks, with the option of requesting additional patient visits as needed. HCPs will also have the ability to modify the patient's treatment plan at their discretion. Safety and tolerability will be assessed on an ongoing basis throughout the assessment period and during the subsequent 2-week safety follow-up, during which time a follow-up telephone call will be made to each study participant.

Healthcare utilization record evaluation will occur continuously beginning at the baseline/screening visit and will span a period ranging from 24 weeks before baseline/screening to 24 weeks after screening. All hospital admissions will be recorded and categorized as

"planned," "unplanned," "related," or "unrelated" to psychiatric illness. Characteristics of each HCP encounter will also be recorded, including the nature of the contact; HCP role; whether the visit was planned or unplanned; whether or not the contact was initiated as a result of the DMS; and any medication titration, adherence counseling, education, or lifestyle coaching that occurred.

## Outcomes

The primary endpoint is the proportion of days with good patch coverage during the assessment period, which will be defined as having ≥80% patch data available or IEMs detected within each day of the assessment period. The secondary endpoint is ingestion adherence, defined as the proportion of detected IEMs to the total expected IEMs ingested on the assessment days that showed good patch coverage.

The following exploratory endpoints will also be included:

- The proportion of time during the assessment period that patients wear their patch
- Engagement and satisfaction of patients, HCPs, and caregivers as determined using the Subject Usability and Satisfaction Scale (**Supplemental Figure 1**), the Physician Utility Survey (**Supplemental Figure 2**), and the Caregiver/Support Person Involvement Scale (**Supplemental Figure 3**)
- Personal and social functioning as assessed using the Personal and Social Performance Scale (**Supplemental Figure 4**)
- Patient activation as assessed using the Patient Activation Measure-Mental Health Scale (**Supplemental Figure 5**)
- The proportion of days that patients and HCPs use the app and dashboard, respectively

- The proportion of ingested IEM tablets registered on the digital health data server of the total expected IEM tablets ingested
- Safety variables will include the frequency and severity of serious adverse events and device-related nonserious adverse events, suicidality, and any product quality complaints that may arise. Suicidality will be determined by face-to-face risk assessment according to each study site's standard operating procedure.

## Statistical analysis

A sample size of 60 patients was determined based on an anticipated 25% discontinuation rate, such that ≥45 patients would complete the 8-week assessment period. Data will be analyzed in the intent-to-treat population (ie, all patients who enter the trial and use the DMS). All data will be analyzed using descriptive statistics. Continuous variables will be summarized using mean, median, range, and standard deviation. Categorical variables will be summarized using frequency distributions.

## Data protection

Before initiating participation, informed consent will be obtained from all patients and caregivers. Health information will be de-identified to the fullest possible extent. However, some identifiers or sensitive health information cannot be stripped (eg, psychiatric medical history, participation in a care program approach, presence of a community treatment order, employment status, disabilities, housing arrangements, or armed forces history). Health information will be used to develop and improve the DMS application and user experience. The DMS and associated third-party vendors are compliant with the General Data Protection Regulation (GDPR), and all accessed health information will be maintained in the strictest confidence and in compliance with

the GDPR. Data from the DMS are encrypted in activity and rest and will be accessed only by role-specific individuals for discrete time periods and functions (eg, technical troubleshooting). All data will be completely anonymized for graphical, statistical, and publication purposes.

Research staff from NHS sites will store consent documents, demographic forms, and receipts for reimbursement of travel in locked filing cabinets to which only research staff will have access. Accessing of health data will be compliant with information governance policies of each participating NHS trust.

## ETHICS AND DISSEMINATION

### Ethical considerations

Ethics approval for this study was obtained from London - City & East Research Ethics Committee (REC Ref no. 18/LO/0128), and clinical trial authorization was provided by the Medicines and Healthcare products Regulatory Agency. Written informed consent will be obtained from every participant. Ethical issues will be related to the identification and recruitment of patients, informed consent, and data protection arrangements. The trial will be conducted in compliance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines and Declaration of Helsinki.

### Dissemination of study results

The study results will be disseminated through peer-reviewed publications, national and international conference presentations, and formal clinical trial repositories (eg, ClinicalTrials.gov). The 5 participating NHS sites will be invited to a results launch event. Results will be shared with individuals who participated in the workshops via the respective

trusts. Additionally, follow-up workshops are planned to capture further feedback on next steps for scaling the DMS technology.

## DISCUSSION

Patient adherence to antipsychotic medication is a crucial component of successful maintenance therapy for schizophrenia. Knowledge of patient adherence in the absence of positive treatment outcome is also essential. Subjective means for assessing medication adherence such as clinician evaluation and patient self-report have low validity [16], and most can only be administered during patient-HCP visits. Digital medicine offers a means to monitor patient adherence and obtain objective data throughout treatment, including periods between office visits, which may yield more accurate data. For example, a study evaluating nonadherence rates for antipsychotic medication based on electronic medication bottle caps, which report when pill bottles have been opened [18], showed a 57% nonadherence rate, much higher than that estimated by patient (5%) and provider (7%) report [18]. This study shows the potential of digital medicine to provide continuous objective data that can inform and improve patient adherence and assist in clinical decision making. The DMS improves upon approaches such as electronic medication caps by providing an objective marker of ingestion and not merely a surrogate in addition to other objective and subjective data.

Patient discontinuation is a considerable problem in studies of digital health technology [26]. Studies of early digital health systems for maintenance and counseling of mental disorders reported low completion rates. For example, a study evaluating a 12-week web-based cognitive behavioral therapy intervention for panic disorder had a 1% (12/1161) completion rate [27], and a study evaluating a publicly accessible 5-module web-based cognitive behavioral therapy

program for anxiety and depression had a 0.5% completion rate (97/19,607) [28]. Completion rates may be particularly low in patients with more severe negative symptoms [22]. Despite these historically poor completion rates in studies of digital health platforms, results of a meta-analysis indicate that more than 50% of patients favor managing their mental health through the use of mobile health technology [29], and the use of mobile devices for health management is viewed by patients as normalized and nonstigmatizing [30]. The integrated DMS described here was developed to leverage the advantages of digital technology to positively influence adherence in patients with schizophrenia.

The DMS is a multimodal, user-friendly system that provides medication reminders and measures patient ingestion of prescribed antipsychotic medications. The CoE product, in particular, advances the ability to confirm medication ingestion and to assess adherence on a continuous basis, which can inform whether uncontrolled symptoms may be explained by nonadherence. Information from the DMS is made readily available to patients, caregivers (with the patient's consent), and physicians for supported decision making, proactive intervention, and individualized care. DMS also provides adherence feedback electronically to the patient, HCP, and/or caregiver. Because it can be implemented discreetly, patients may feel destigmatized and assimilate back into society more readily. The DMS also provides feedback on activity and rest levels, which is important given that maintenance of a healthy lifestyle can help address the problems of weight gain and obesity that are related to both medication side effects and sedentary lifestyles [31]. Furthermore, shifts in activity levels may be indicative of altered patient disposition.

This ongoing study was designed using coproduction methodology to incorporate input from patients, caregivers, psychiatrists, pharmacists, nurses, and researchers. For all 5 study sites, a

minimum of 2 engagement/setup meetings were conducted and 2 specific patient focus groups were held to guide protocol development and app design.. The exploratory data collected in this study, although limited to a small number of patients, will help provide a better understanding of the ease of use for patients, HCPs, and caregivers to inform the development of future software or hardware iterations.

## CONCLUSION

In conclusion, this study will examine the usability and acceptance of the DMS by patients with schizophrenia, schizoaffective disorder, or first-episode psychosis, and by caregivers and HCPs in different care settings. The study was meticulously coproduced through the engagement of all stakeholders and, if successful, could be used to support DMS usage in larger cohorts within the United Kingdom and Europe.



## Funding statement

This study is supported by Otsuka Pharmaceutical Development & Commercialization, Inc. Editorial support for development of this manuscript was provided by Eric Comeau, PhD, at C4 MedSolutions, LLC (Yardley, PA), a CHC Group company, and funded by Otsuka Pharmaceutical Development & Commercialization, Inc.

## Competing interests statement

Dr J. Corey Fowler, Dr Jonathan Knights, and Dr Tim Peters-Strickland are employees of Otsuka Pharmaceutical Development & Commercialization. Dr Nathan Cope is an employee of Otsuka Pharmaceutical Europe Ltd. Dr Andrew Makin is an employee of Otsuka Europe Development

and Commercialisation. Dr Peter Phiri has no conflict of interest. Dr Shanaya Rathod has received honoraria from Otsuka and Lundbeck for educational sessions.

## Author contributions

JCF, NC, AM, and TPS made substantial contributions to the design and to the conception of the work. JCF, JK, PP, and SR participated in acquisition of data for the work. JCF, JK, and TPS participated in analysis of the data for the work. JCF, NC, JK, PP, AM, TPS, and SR participated in interpretation of the data for the work, provided intellectual contribution to the manuscript, and approved the final version of the document for submission.

The authors thank patient advisers and NHS staff from all 5 participating sites (Oxford Health NHS Foundation Trust; Northumberland, Tyne and Wear NHS Foundation Trust; Southern Health NHS Foundation Trust; South London and Maudsley NHS Foundation Trust; and Surrey and Borders Partnership NHS Foundation Trust) for their contributions to the study methodology. Editorial support for development of this manuscript was provided by Eric Comeau at C4 MedSolutions, LLC (Yardley, PA, USA), a CHC Group company, and funded by Otsuka Pharmaceutical Development & Commercialization, Inc.

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## Figure Legends

**Figure 1.** Digital medicine system: co-encapsulated antipsychotic medication with miniature ingestible event marker in tablet (MIT) and compatible medical device. DM=digital medicine; HCP=healthcare professional.

**Figure 2.** Description of coproduction workshops with Southern Health NHS Foundation Trust. DMS=digital medicine system; EIP=Early Intervention in Psychosis; IG=information governance; MoSCoW=must have, should have, could have, won't have; NHS=National Health Service; PANSS=Positive and Negative Syndrome Scale; PPI=Patient and Public Involvement program.

**Figure 3**. Study design.

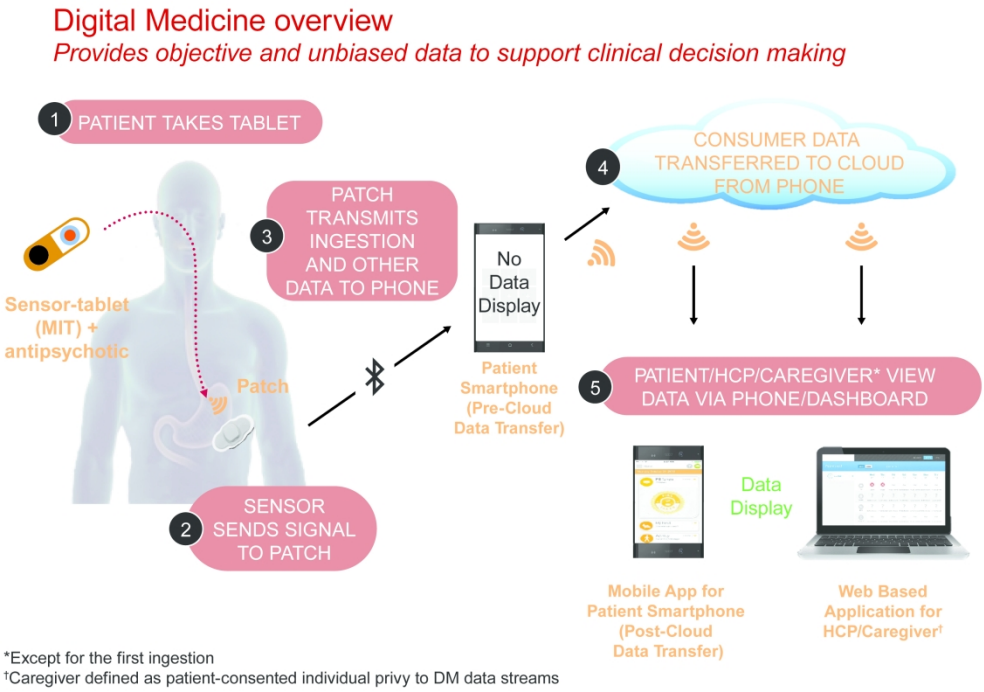



Figure 1. Digital medicine system: co-encapsulated antipsychotic medication with miniature ingestible event marker in tablet (MIT) and compatible medical device. DM=digital medicine; HCP=healthcare professional.

254x177mm (300 x 300 DPI)

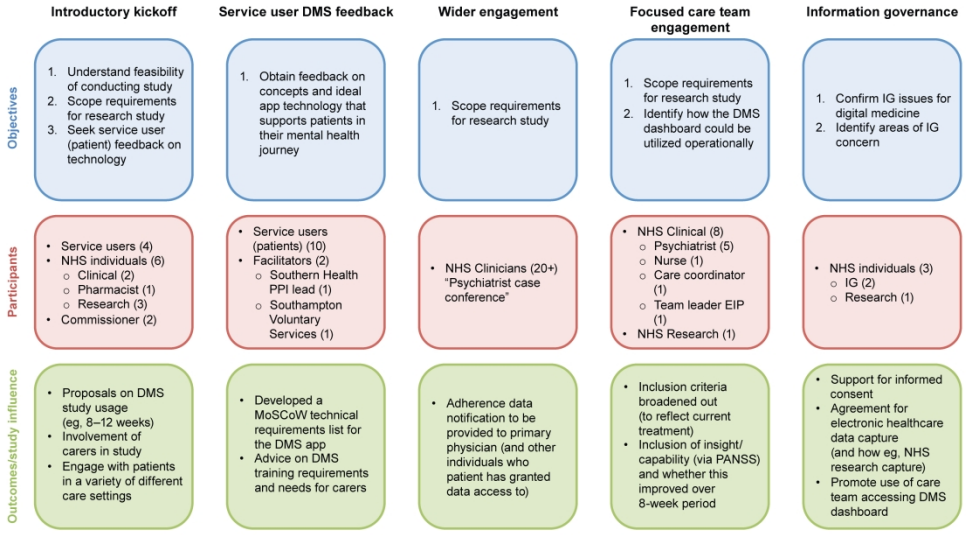
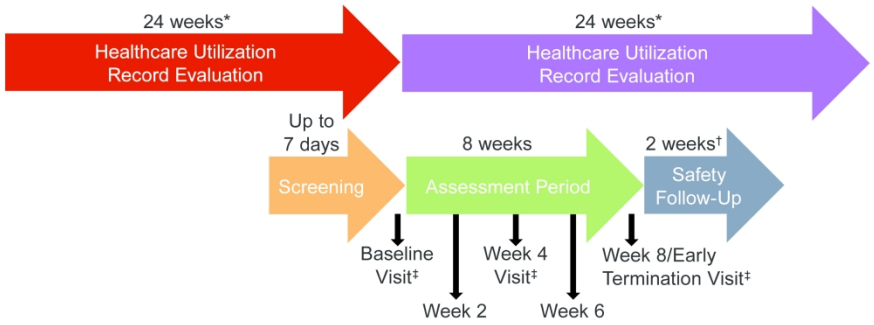



Figure 2. Description of coproduction workshops with Southern Health NHS Foundation Trust. DMS=digital medicine system; EIP=Early Intervention in Psychosis; IG=information governance; MoSCoW=must have, should have, could have, won't have; NHS=National Health Service; PANSS=Positive and Negative Syndrome Scale; PPI=Patient and Public Involvement program.

317x184mm (300 x 300 DPI)




Healthcare professionals (HCPs) will review dashboard at weeks 2, 4, 6, and 8 and make treatment changes at their discretion.
*Healthcare utilization will be recorded 24 weeks before and after baseline visit (for a total of 48 weeks).
†Safety follow-up phone call will occur 2 weeks after week 8/early termination visit.
‡Patient visits will occur at baseline, week 4, and week 8/early termination. Other visits will be at the discretion of the HCP.

Figure 3. Study design.

241x108mm (300 x 300 DPI)

# Supplementary Material

## Supplemental Figure 1. Subject Usability and Satisfaction Scale (Ver 2.0)

**Section A: Usability**

**1. How easy or difficult was it for you to apply the patch on your body?**

| Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**2. How easy or difficult was it to pair the patch with the mobile phone application (app)?**

| Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**3. How easy or difficult was it for you to use the mobile phone application (app)?**

| Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**4. How easy or difficult was it for you to use the Digital Medicine System?**

| Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**5. How well do you agree with the following statement?**

- **In general, I did not mind wearing the patch.**

| Strongly Disagree | Disagree | Somewhat Disagree | Neutral | Somewhat Agree | Agree | Strongly Agree |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | |

**6. Since your last visit, did you receive assistance when changing and pairing the required patches? Yes No**

If yes,

| | Never | Once a month or less | A few times a month | Once a week | A few times a week | Daily |
|---|---|---|---|---|---|---|
| How much assistance did you receive when applying the patches? | | | | | | |
| How much assistance did you receive when syncing the technology? | | | | | | |

If you did receive any help or assistance, who helped or assisted you?
(please place a √ [check] to indicate who helped or assisted you)

| Friend | Hired Caregiver | Relative* | Other** |
|---|---|---|---|
| | | | |

*If a relative helped or assisted you, then please specify their relationship to you (such as wife, husband, father, mother, sister, brother, or whatever else you think is the most appropriate description of the relative who helped you): _____

**If you selected "Other", please specify your relationship to the person who helped you _____

## Section B: Satisfaction

**7. How easy or difficult was it for you to use the entire Digital Medicine System, which includes the patch, pills, and mobile phone application (app)?**

| Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

8. **How helpful or unhelpful was the Digital Medicine System in the management of your condition?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

9. **How helpful or unhelpful was the Digital Medicine System for sharing information with your healthcare professionals to help you understand your treatment plan?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

10. **How helpful or unhelpful was the Digital Medicine System in improving your discussions with your doctor / treatment team?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

11. **Based on your experience, how would you rate your satisfaction with the Digital Medicine System?**

| Extremely Dissatisfied | Dissatisfied | Somewhat Dissatisfied | Neutral | Somewhat Satisfied | Satisfied | Extremely Satisfied |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

12. **How likely would you be to use the Digital Medicine System in the future, if it were available and recommended by your doctor?**

| Extremely Unlikely | Unlikely | Somewhat Unlikely | Neutral | Somewhat Likely | Likely | Extremely Likely |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**Supplemental Figure 2. Physician Utility Survey (Ver 2.0)**

*We ask the Principal Investigator, Physician Investigator, and Trial Coordinator(s) at a clinical site/trust to complete this survey for each patient enrolled. Please answer the below questions based on your overall experience using DMS.*

1. **How easy or difficult was it for you and your patient to apply the patch on the patient's body?**

| | Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| For you | | | | | | | |
| For your patient | | | | | | | |

2. **How easy or difficult was it for you and your patient to sync the patch with the mobile phone application (app)?**

| | Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| For you | | | | | | | |
| For your patient | | | | | | | |

3. **How easy or difficult was it for you and your patient to complete the overall onboarding for the Digital Medicine System?**

| | Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| For you | | | | | | | |
| For your patient | | | | | | | |

4. **Overall, how easy or difficult was it for you and your patient to use the mobile phone application (app)?**

| | Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| For you | | | | | | | |
| For your patient | | | | | | | |

5. **Overall, how easy or difficult was it for you and your patient to use the entire Digital Medicine System, which includes the patch, pills, and mobile phone application (app)?**

| | Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| For you | | | | | | | |
| For your patient | | | | | | | |

6. **How easy or difficult was it for you to use the HCP dashboard?**

| Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**7. If you were in routine clinical practice (ie, in clinical practice without a study protocol), how helpful or unhelpful do you think the Digital Medicine System could be for the following elements of clinical management for this specific patient?**

| | Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Assessment | | | | | | | |
| Clinical Advice/ Recommendations | | | | | | | |
| Treatment Decisions | | | | | | | |

**8. How effective was the Digital Medicine System in aiding decision-making for medication adherence?**

| Extremely Not Effective | Not Effective to Use | Somewhat Not Effective to Use | Neutral | Somewhat Effective to Use | Effective to Use | Extremely Effective to Use |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**9. How helpful or unhelpful was the Digital Medicine System in providing a way to better engage your patients in self-management of their condition?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**10. How helpful or unhelpful was the Digital Medicine System in improving quality of care for your patient?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**11. How helpful or unhelpful was the Digital Medicine System in improving your conversations with your patient about their treatment plan and progress?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**12. How helpful or unhelpful was the Digital Medicine System in the identification of potential lifestyle changes for your patient (eg sleep and exercise)?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**13. Other than during the patient visit(s), did you look at the HCP dashboard at other times? Please select all that apply**

| | Place a √ (check) next to the time you referred to the HCP dashboard |
|---|---|
| No, only during the patient visit | |
| Prior to patient visit (same day as visit) | |
| In between visits | |
| Other: *Please Specify:* _____ | |

**14. What features did you find helpful? Please select all that apply**

| | Place a √ (check) next to the features you found helpful | For the features you have selected, please rank these features from 1 (most helpful) to 7 (least helpful) in order of helpfulness |
|---|---|---|
| Pill ingestion data | | |
| Patient reported reason code for missed doses | | |
| Multiple dose alerts | | |
| Missed dose alerts | | |
| Activity | | |
| Rest | | |
| Patient reported rest quality rating | | |
| Other: *Please Specify:* _____ | | |

**15. Did you set up alerts to be notified of missed doses? Yes/no**

**a. If yes, based on your overall experience, how helpful were the missed dose alerts?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful | Not Applicable – No alerts received |
|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | |
| | | | | | | | |

15a. If you received a missed dose alert what action did you take, if any? (If none, please write N/A) _____

**16. Did you set up alerts to be notified of multiple doses? Yes/no**

**a. If yes, based on your overall experience, how helpful were the multiple dose alerts?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful | Not Applicable – No alerts received |
|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | |
| | | | | | | | |

16a. If you received a multiple dose alert what action did you take, if any? (If none, please write N/A _____

**17. How well do you agree with the following statement?**

**a. Overall, the Digital Medicine System adds value to my practice.**

| Strongly Disagree | Disagree | Somewhat Disagree | Neutral | Somewhat Agree | Agree | Strongly Agree |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**18. Based on your overall experience with this patient, how would you rate your satisfaction with the Digital Medicine System?**

| Extremely Dissatisfied | Dissatisfied | Somewhat Dissatisfied | Neutral | Somewhat Satisfied | Satisfied | Extremely Satisfied |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**Supplemental Figure 3. Caregiver/Support Person Involvement Scale (Ver 2.0)**

**DMS Caregiver/Support Person Involvement Scale**

**1. Are you aware that the study participant/patient is currently participating in the Digital Medicine study (check one)?**

| Yes | No* |
|---|---|
| | |

***If no, stop here and do not answer the rest of the questions on this form.**

**2. Indicate your relationship to the study participant/patient by placing a √ (check).**

| Friend | Hired Caregiver | Relative* | Other** |
|---|---|---|---|
| | | | |

***If you are a relative, please specify relationship to the study participant/patient, e.g., wife, father:**

****If you selected "Other", please specify your relationship to the study participant/patient:**

_____

**3. How much involvement did you provide the subject with regard to taking medication, pairing the patch, applying the patch, and using the app during the course of the study?**

| | Never | Once a month or less | A few times a month | Once a week | A few times a week | Daily |
|---|---|---|---|---|---|---|
| How much overall assistance did you provide the subject during the course of the study? | | | | | | |
| How much assistance did you provide with patch application? | | | | | | |
| How much assistance did you provide with syncing the technology? | | | | | | |
| How much assistance did you provide with using the app? | | | | | | |
| | **Never** | **Once a week** | **A few times a week** | **Nearly every day** | **Daily** | **More than once/day** |
| How much overall assistance did you provide during the past week of the study? | | | | | | |

## Clinical Global Impression Scale

Clinical Global Impression – Severity Scale (CGI-S)

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

0 = Not assessed

1 = Normal, not at all ill

2 = Borderline mentally ill

3 = Mildly ill

4 = Moderately ill

5 = Markedly ill

6 = Severely ill

7 = Among the most extremely ill subjects

**Supplemental Figure 4. Personal and Social Performance Scale**

Original version: Morosini PL, Magliano L, Brambilla L, et al. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand* 2000;101(4):323-9

# Personal and Social Performance Scale (PSP)

The rating is based on four main areas: (a) socially useful activities, including work and study; (b) personal and social relationships; (c) self-care; and (d) disturbing and aggressive behaviors.

Data will be captured in the following format using the PSP descriptions provided below:

| | Absent | Mild | Manifest | Marked | Severe | Very Severe |
|---|---|---|---|---|---|---|
| a. Socially useful activities, including work and study | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| b. Personal and social relationships | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| c. Self-care | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| d. Disturbing and aggressive behaviors | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

The levels of functioning in other areas should be taken into account to adjust the rating inside the decimal level (for instance, from 31 to 40). Suicidal risk is not included in the scale.

| 10-point intervals | PSP descriptions |
|---|---|
| 100–91 | Excellent functioning in all four main areas*. He/she is held in high consideration for his/her good qualities, copes adequately with life problems, is involved in a wide range of interests and activities. |
| 90–81 | Good functioning in all four main areas, presence of only common problems or difficulties. |
| 80–71 | Mild difficulties in 1 or more of areas a–c. |
| 70–61 | Manifest, but not marked difficulties in 1 or more areas a–c, *or* mild difficulties in d. |
| 60–51 | Marked difficulties in 1 of areas a–c, *or* manifest difficulties in d. |
| 50–41 | Marked difficulties in 2 or more, *or* severe difficulties in 1 of areas a–c, with or without manifest difficulties in d. |
| 40–31 | Severe difficulties in 1 *and* marked difficulties in at least 1 of areas a–c, *or* marked difficulties in d. |
| 30–21 | Severe difficulties in 2 of areas a–c, *or* severe difficulties in d, with or without impairment in areas a–c. |
| 20–11 | Severe difficulties in all areas a–d, *or* very severe in d with or without impairment in general areas a–c. If the person reacts to external prompts the suggested scores are 20–16, if not, the suggested scores are 15–11. |
| 10–1 | Lack of autonomy in basic functioning with extreme behaviors but without survival risk (ratings 6–10) or with survival risk, eg, death risk due to malnutrition, dehydration, infections, inability to recognize situation of manifest danger (ratings 5–1). |

| For main areas a–c, the degrees of severity are: | |
|---|---|
| Absent | |
| Mild | Not manifest difficulties, known only to someone who is very familiar with the person. |
| Manifest, but not marked | Difficulties clearly noticeable by everyone, but not interfering substantially with the person's ability to perform his/her role in that area, given the person's socio-cultural context, age, sex and educational levels. |
| Marked | Difficulties heavily interfering with role performance in that area; however, the person is still able to do something without professional or social help, although inadequately and/or occasionally; if helped by someone, he/she may be able reach the previous level of functioning. |
| Severe | Difficulties that make the person unable to perform any role in that area, if not professionally helped, or lead the person to a destructive role; however, there are no survival risks. |
| Very severe | Impairments and difficulties of such intensity to endanger person's survival. |

| For general area d, the degrees of severity are: | |
|---|---|
| Absent | |
| Mild | Mild rudeness, unsociability or whingeing. |
| Manifest, but not marked | Speaking too loudly or speaking to others in a too-familiar manner, or eating in a socially unacceptable manner. |
| Marked | Insulting other in public, breaking or wrecking objects, acting frequently in a socially inappropriate but not dangerous way (eg, stripping in public or urinating in public). |
| Severe | Frequent verbal threats or frequent physical assaults, without intention or possibility of severe injuries. |
| Very severe | Frequent aggressive acts, aimed at or likely to cause severe injuries. |

Occasional is defined as occurring three or more times in the reference period or occurring even less than three times but in circumstances and/or with such a previous history to convince the rater that there is a risk of recurrence in the near future. If the aggressive behavior has been present occasionally, the rating may be decreased by one degree, eg, from severe to marked.

* Main areas: a = socially useful activities, including work and study; b = personal and social relationships; c = self-care; d = disturbing and aggressive behaviors.

**Guidelines for PSP Total Score**

Ratings from 71–100 reflect only mild difficulties.

Ratings from 31–70 reflect manifest disabilities of various degrees.

Ratings from 1–30 reflect functioning so poor that intensive support or supervision is needed.

**Supplemental Figure 5. Patient Activation Measure-Mental Health Scale**

The following questions ask about your feelings regarding your mental healthcare. When you think about mental health and mental health care, how much do you agree or disagree with the following statements? Please circle the answer that you most agree with:

**1.** When all is said and done, I am the person who is responsible for managing my mental health.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**2.** Taking an active role in my own mental health is the most important factor in determining my mental health and ability to function.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**3.** I am confident that I can take actions that will help prevent or minimize some symptoms or problems associated with my mental health condition.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**4.** I know what each of my prescribed mental health medications does.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**5.** I am confident that I can tell when I need to go get mental health care, and when I can handle a mental health problem myself.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**6.** I am confident I can tell my mental health clinician about concerns I have, even when he or she does not ask.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**7.** I am confident that I can follow through on mental health treatments I need to do at home.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**8.** I understand the nature and causes of my mental health condition(s).

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**9.** I know the different treatment options available for my mental health condition(s).

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**10.** I am able to maintain the lifestyle changes I have made for my mental health.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**11.** I know how to prevent further mental health problems.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**12.** I am confident I can figure out solutions when new situations or problems arise with my mental health.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**13.** I am confident that I can maintain lifestyle changes, like diet and exercise, even during times of stress.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

BMJ Open

# A Study Protocol for the Hummingbird Study, a Multicenter Exploratory Trial to Assess the Acceptance and Performance of a Digital Medicine System in Adults With Schizophrenia, Schizoaffective Disorder, or First-Episode Psychosis



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2018-025952.R1 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 04-Mar-2019 |
| Complete List of Authors: | Fowler, J.; Otsuka Pharmaceutical Development & Commercialization, Inc.,<br>Cope, Nathan; Otsuka Pharmaceutical Europe Ltd.<br>Knights, Jonathan; Otsuka Pharmaceutical Development & Commercialization, Inc.<br>Phiri, Peter; Southern Health NHS Foundation Trust<br>Makin, Andrew; Otsuka Europe Development and Commercialisation Ltd.<br>Peters-Strickland, Tim; Otsuka Pharmaceutical Development & Commercialization, Inc.<br>Rathod, Shanaya; Southern Health NHS Foundation Trust, Psychiatry |
| Primary Subject Heading: | Mental health |
| Secondary Subject Heading: | Evidence based practice |
| Keywords: | Coproduction, digital medicine, schizoaffective disorder, schizophrenia |
| | |

# A Study Protocol for the Hummingbird Study, a Multicenter Exploratory Trial to Assess the Acceptance and Performance of a Digital Medicine System in Adults With Schizophrenia, Schizoaffective Disorder, or First-Episode Psychosis

Running title: Study protocol for DMS use in schizophrenia in the UK

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Word count (max 4000 for BMJ Open): 3988 (Intro through conclusion, not including table)

Table count: 1

Figure count: 3 (+5 supplemental)

Reference count: 31

# ABSTRACT

Objectives: In patients with schizophrenia, medication adherence is important for relapse prevention, and effective adherence monitoring is essential for treatment planning. A digital medicine system (DMS) has been developed to objectively monitor patient adherence and support clinical decision-making regarding treatment choices. This study's objective is to assess the acceptance and performance of the DMS in adults with schizophrenia, schizoaffective disorder, or first-episode psychosis and in healthcare professionals (HCPs) in the United Kingdom.

Design: This is a multicenter, 8-week, single-arm, open-label pragmatic trial designed using coproduction methodology.

Setting: The study will be conducted at 5 National Health Service Foundation Trusts in the United Kingdom.

Participants: Patients 18 to 65 years old with a diagnosis of schizophrenia, schizoaffective disorder, or first-episode psychosis will be eligible. HCPs (psychiatrists, care coordinators, nurses, pharmacists) researchers, information governance (IG) personnel, Clinical Commissioning Groups (CCGs), and patients participated in study design and coproduction.

Interventions: The DMS is an integrated system comprising an oral sensor tablet co-encapsulated with an antipsychotic, nonmedicated wearable patch, mobile application (app), and Web-based dashboard. The co-encapsulation product contains aripiprazole, olanzapine, quetiapine, or risperidone, as prescribed by the HCP, with a miniature ingestible event marker (IEM) in tablet. Upon ingestion, the IEM transmits a signal to the patch, which collects ingestion and physical activity data for processing on the patient's smartphone or tablet before transmission to a cloud-based server for viewing by patients, caregivers, and HCPs on secure web portals or mobile apps.

Outcome measures: The primary and secondary endpoints will be the proportion of days with good patch coverage and ingestion adherence, respectively.

Conclusions: This study will provide data on the acceptance and performance of the DMS in UK patients with schizophrenia, schizoaffective disorder, or first-episode psychosis and in caregivers and HCPs.

ClinicalTrials.gov: NCT03568500; EudraCT 2017-004602-17

## Keywords

Coproduction, digital medicine, schizoaffective disorder, schizophrenia

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study was codeveloped with input from clinical practitioners, researchers, patients, caregivers, service managers, IG teams, and clinical commissioning groups to obtain information that will best serve all those involved in the treatment and care of patients with schizophrenia, schizoaffective disorder, and first-episode psychosis.
- The digital medicine system (DMS) uses an integrated, user-friendly system to provide objective feedback on patient medication adherence and physical health parameters, such as activity and rest levels, as well as voluntary subjective entries regarding mood and rest quality, to help support treatment decisions and evaluation.
- Information from the DMS is made readily available to patients, caregivers (with the patient's consent), and physicians to support clinical decision making, proactive intervention, and individualized care in near to real time.
- Possible limitations of this study are the small sample size (N=60), limited generalizability to the broader pool of UK mental health patients and providers, and the

relatively short 12-week timeframe. Although the DMS does require the patient to engage more with their own care, the benefits of increasing their awareness of medication, activity, rest, and mood patters outweighs risks/burden for most patients. The DMS was not developed for all mental health patients, but for a subset of patients who have difficulty with adherence and want to improve their status by self-monitoring with potential for their HCP's to make better clinical decisions based on objective data from the DMS. Patients with poor insight into their illness will likely be a better candidate for a long-acting injectable atypical antipsychotic than this DMS.

# INTRODUCTION

Schizophrenia has an enormous social and economic burden worldwide, accounting for 1.1% of total disability-adjusted life-years and 2.7% of years lived with disability [1, 2]. In Europe, the economic impact of schizophrenia and other psychotic disorders and syndromes in 2010 was estimated at €93.9 billion [3]. Because it is a chronic disease, maintenance treatment is often necessary to prevent relapse and preserve quality of life over the long term [4, 5]. Although antipsychotic medications are effective [6-8], poor insight into schizophrenia can increase risk of medication nonadherence [9, 10]. In patients with schizophrenia, the rate of nonadherence to prescribed antipsychotics has been reported to be as high as 74% [11]. Not only is medication nonadherence burdensome to patients and their families, it also increases the likelihood of rehospitalization and relapse [12] and contributes substantially to healthcare costs [13]. In 2005/2006, mean annual psychiatric inpatient and medication costs for patients with schizophrenia in England were estimated to be approximately £3,000 and £2,000 per patient, respectively [14].

Because medication adherence is important to relapse prevention in schizophrenia [15], effective adherence monitoring is an essential part of the treatment plan. Although there are various subjective methods for determining medication adherence, including patient surveys, adherence diaries, and clinician ratings of patient symptoms and medication side effects, these methods have low validity [16]. Blister packs and electronic medication bottle caps can provide an indicator of pill removal or bottle opening and have been shown to improve adherence [17, 18], but neither technology provides an objective marker of pill ingestion or supports remote monitoring by healthcare professionals (HCPs). Optimal adherence monitoring and support for

patients with schizophrenia requires a system that provides physicians with objective information during interim periods between patient visits.

The use of modern technology such as personal digital assistants [19], digital wristwatches [20], handheld computers [21], and mobile phones [22] to help people with schizophrenia dealing with their disease has shown success. A digital medicine system (DMS) has been developed as a drug-device combination to objectively assess and report ingestion of prescription antipsychotics [23]. The DMS has 4 main components: an ingestible sensor embedded within an inert tablet, a nonmedicated wearable sensor (patch) worn by the patient, a mobile application (app), and a Web-based dashboard [23]. Upon interaction with stomach fluids, the ingestible sensor is activated and communicates with the wearable sensor, which sends a signal to a Bluetooth-paired mobile device where it can be viewed by patients or be subsequently viewed by HCPs and caregivers using secure mobile- and cloud-based software [23]. The DMS also enables patients to share data on their activity and rest levels as well as subjective data on mood and rest quality, which can be generated while the patient is engaged with the system. The intention of the DMS is to encourage greater patient self-management and behavior change while enabling caregivers and HCPs to provide better care and support both within and outside of office visits, further engaging patients in their ongoing disease management. The data is communicated to the psychiatrist that is connected to the patient on the MyCite platform. Additionally, should the patient choose to share their data, they are able to invite additional healthcare providers, caregivers and/or family or friends. Recipients of the data, through a web-based password protected platform, are able to view this data and assist the patient with their treatment plan, however HCPs can only access the portal for a specific patient once he/she has consented to give them access to their information in the system. It is envisioned that HCPs will be able to use this

data to make more informed clinical decisions such as whether individuals need dose adjustment, medication changes or conversations on lifestyle, adherence or other parameters.

Previous results in the USA have shown in an open-label, 8-week study, 78% (47/60) of patients and 72% (43/60) of HCPs reported being somewhat satisfied, satisfied, or extremely satisfied with the DMS [24]. Findings from another open-label study showed patients to be actively involved in their treatment, with 73.5% (36/49) utilizing call centers for technological DMS support [25]; the rate of ingestion adherence in this study for the 15 patients with schizophrenia was 85.6% [25].

The DMS from the current study (namely the ingestible sensor and the wearable sensor) are Conformité Européene (CE)–marked for use in Europe as class IIa medical devices (CE 559373), but studies in European mental health populations have not been performed. Therefore, the objective of this exploratory study is to assess the acceptance and performance of the DMS among adult patients with schizophrenia, schizoaffective disorder, or first-episode psychosis and among HCPs from different care settings in the United Kingdom. We are particularly interested in assessing the acceptance of the digital medicine technology in individuals from different care settings. Acceptance will be assessed by study completion and, feedback from subjects from patient satisfaction surveys. Furthermore, acceptance will also be evaluated by healthcare providers using the system; this will be assessed by how their clinical decisions altered whilst using the system and through HCP Utility questionnaire evaluations.

In respect to performance, the study will be assessing multiple hardware and software from a varied population. Based on operational feedback of different phones and OS and any technical troubleshooting that occurs, the study will be able to determine areas of the app that need to be enhanced to ensure that the app functions across multiple hardware and operating systems.

Previous studies performed using the DMS were conducted in relatively stable individuals with schizophrenia. For this study, we have broadened out the inclusion criteria and will be assessing the technology in a range of clinical groups from different care settings, such as those individuals managed in the community or on specialized services such as Early Intervention in Psychosis services to determine the performance in these different environments.

The study is not intended to measure and report or make any claims of adherence, but instead, to report the observed ingestions recorded by the DMS. Our goal is to look at the impact of patients' improvements as a result of participation (e.g. reduced need for follow-up care, knowledge of adherence to medication to help physicians decide whether patients are medication compliant or require a long acting injectable or other follow-up care) with the hypothesis that DMS will reduce overall healthcare utilization burden.

## METHODS AND ANALYSIS

### Study design

This is a multicenter, 8-week, single-arm, open-label trial to evaluate the acceptance and performance of the DMS in adult patients with schizophrenia, schizoaffective disorder, or first-episode psychosis on an oral atypical antipsychotic medication (aripiprazole, olanzapine, quetiapine, or risperidone) and in HCPs. Recruitment began the same day that we submitted to CT.gov, 25/MAY. However, we didn't consent our first patient until 11/JUN and dosing occurred on 18/JUN. The study will take place at 5 institutions in the United Kingdom: Northumberland, Tyne and Wear National Health Service (NHS) Foundation Trust, Surrey and Borders Partnership NHS Foundation Trust, Oxford Health NHS Foundation Trust, South London and Maudsley NHS Foundation Trust, and Southern Health NHS Foundation Trust. The

first patient's first visit occurred in May 2018. Patient recruitment will be targeted to last approximately 4 months.

## Patient selection

Patients for this exploratory study will be identified using database searches conducted at each study site per HCP discretion. Inclusion and exclusion criteria are provided in **Table 1**. The degree of clinical stability will be varied across participants that enroll. In short, a fully stable patient population will not be actively recruited, instead a range of clinical populations (crudely based on CGI-S) from different care settings will participate.

**Table 1. Inclusion and Exclusion Criteria**

| **Inclusion criteria** |
|---|
| • Willing and able to give written informed consent and adhere to trial procedures<br>• Able to read and understand English<br>• Age 18–65 years at the time of informed consent<br>• Possessing a smartphone and able to use it to interact with the digital medicine system (DMS) application **through robust and dependable cellular or wireless internet connections (Subjects should have WiFi at home and/or at work, or at the very least have access to free WiFi hot spots. Alternatively, subjects should have a sufficient data plan from their mobile provider and/or coverage on their phone. Such assessments are made during the screening of potential subjects.)**<br>• Cooperative, able to ingest oral medication, willing to complete aspects of the trial, and capable of reporting adverse events (AEs)<br>• Clinical diagnosis of schizophrenia, schizoaffective disorder (defined by International Classification of Diseases, Tenth Revision, codes F20 and F25), or first-episode psychosis based on case note review<br>• Prescription for aripiprazole, olanzapine, quetiapine, or risperidone<br>• Fulfills ≥1 of the following:<br>  ○ Discharge from a hospital admission (within 7 days of discharge) to an acute intervention team<br>  ○ Referral to an acute intervention team before hospital admission<br>  ○ Referral from an acute intervention team to a community team<br>  ○ Managed by community services<br>  ○ Inclusion within early intervention caseload (<3 years from initial symptoms)<br>  ○ Healthcare professional (HCP) determines the patient would benefit<br>• General medical condition does not pose additional risk |

| |
|---|
| • Skin on the anterior chest above the lower edge of the rib cage is free of any dermatologic problem |
| **Exclusion criteria** |
| • Any disorder that may affect patient's ability to participate in the trial or interact with a smartphone<br>• Likely to be incapable of using DMS technology, even with assistance<br>• History or evidence of a medical condition that would expose patient to undue risk of an AE<br>• Known allergy to adhesive tape or any component of the patch or co-encapsulation product<br>• Current incarceration in prison system<br>• Hospitalization at the time of screening due to mental or physical illness<br>• HCP recommendation to not participate<br>• Aversion to taking gelatin capsules<br>• Women who are breastfeeding, pregnant, or plan to become pregnant |

## Intervention

The DMS is an integrated, 4-component system comprising an oral co-encapsulation (CoE) pharmacologic sensor tablet, a Proteus® Patch, a mobile app, and Otsuka Medical dashboard software (**Figure 1**). Each CoE product contains an approved antipsychotic medication (aripiprazole, olanzapine, quetiapine, or risperidone) encapsulated with a miniature ingestible event marker (IEM) in tablet. HCPs will select the medication and dosage based on each patient's needs. Upon taking the medication, the IEM transmits a signal to the nonmedicated patch that is attached to the patient's skin. The patch collects IEM ingestion and physical activity data, which are then processed by the Patch Analytics Block on the patient's smartphone. Processed data are transferred through the app on the smartphone and sent to a cloud-based server for patient, caregiver, and HCP viewing on Otsuka Medical software through web portals or mobile apps. Patients will have access to the Otsuka Patient Application, caregivers will have

access (with patient consent) to the Otsuka Caregiver Web Portal, and HCPs will have access to the Otsuka Healthcare Provider Web Portal.

## Coproduction and patient involvement

This study was designed using coproduction methodology involving NHS staff and patients (**Figure 2**). Coproduction in this protocol is the involvement of people with lived experience of mental illness (diagnosed or otherwise) as equal partners alongside other healthcare stakeholders, in the design and contribution to the protocol. The lead site, Southern Health NHS Foundation Trust, held 5 coproduction workshops, and a subset of these workshops was repeated at other study sites to elicit feedback on the study design. These discussions addressed pharmacy items for the CoE product; HCP recruitment strategies; and protocols for identification, recruitment, and interactions with suitable patients and their general practitioners. Throughout the various workshops at the different sites, participants included clinicians, pharmacists, researchers, IG personnel (refers to the way in which the NHS handles, stores and processes information, in particular personal and sensitive information relating to patients and employees. It was vital to ensure that IG individuals were happy with the privacy and storage features of the digital medicine system), psychiatrists, care coordinators, nurses, information technology personnel, CCGs (clinically led groups within the NHS that are responsible for the planning and commissioning of healthcare services for their local area) , and patients (**Figure 2**).

After changes from the coproduction workshops were incorporated, the Patient and Public Involvement and Service User Lead from 2 study sites (Surrey and Borders Partnership NHS Foundation Trust and Northumberland, Tyne, and Wear NHS Foundation Trust) engaged service users to participate in a patient focus group. The objective of the focus groups was to obtain feedback on the app technology and assess the completion of specific app tasks. The groups

identified issues that may have prevented the completion of key tasks and whether greater explanation would be needed, for instance in ensuring the app could send notifications to patients. Furthermore, general feedback on colour and language was also obtained.

## Procedures

The study will comprise 3 phases: a screening phase of up to 7 days, an 8-week assessment phase, and a 2-week safety follow-up (**Figure 3**). Screening and baseline may occur at a single visit or at 2 visits separated by up to 7 days. At the screening/baseline visit, patients providing informed consent will receive patches, CoE product, and other supplies and undergo training by the HCPs on required and correct use of the DMS. HCPs will confirm proper patch application to the skin and pairing of the patch with the smartphone app when patients commence their usage of the digital medicine system, so called on boarding. These individuals will either be psychiatrists or research assistants for the site. During time in-between the only required site visits at weeks 4 and 8, patients will perform patch changing themselves and be guided, if required, through videos contained within the app. There is a freephone technical support line to assist individuals should they wish. Patients will be instructed to wear the patch continuously, replacing it every 7 days or as needed during the assessment period. An integrated call center will be available to patients for technical support regarding use of the DMS.

During the subsequent 8-week assessment period, patients will visit their HCP at weeks 4 and 8 (or at early termination) for clinical evaluation and review of DMS data. At the week 4 visit, patients will also obtain a prescription refill. HCPs will be required to monitor and review DMS data at least every 2 weeks, with the option of requesting additional patient visits as needed. HCPs will also have the ability to modify the patient's treatment plan at their discretion. Safety

and tolerability will be assessed on an ongoing basis throughout the assessment period and during the subsequent 2-week safety follow-up, during which time a follow-up telephone call will be made to each study participant.

Healthcare utilization record evaluation will occur continuously beginning at the baseline/screening visit and will span a period ranging from 24 weeks before baseline/screening to 24 weeks after screening. All hospital admissions will be recorded and categorized as "planned," "unplanned," "related," or "unrelated" to psychiatric illness. Characteristics of each HCP encounter will also be recorded, including the nature of the contact; HCP role; whether the visit was planned or unplanned; whether or not the contact was initiated as a result of the DMS; and any medication titration, adherence counseling, education, or lifestyle coaching that occurred.

## Outcomes

The primary endpoint is the proportion of days with good patch coverage during the assessment period, which will be defined as having ≥80% patch data available or IEMs detected within each day of the assessment period. The secondary endpoint is ingestion adherence, defined as the proportion of detected IEMs to the total expected IEMs ingested on the assessment days that showed good patch coverage.

The following exploratory endpoints will also be included:

- The proportion of time during the assessment period that patients wear their patch
- Engagement and satisfaction of patients, HCPs, and caregivers as determined using the Subject Usability and Satisfaction Scale (**Supplemental Figure 1**), the Physician Utility

Survey (**Supplemental Figure 2**), and the Caregiver/Support Person Involvement Scale (**Supplemental Figure 3**)

- Personal and social functioning as assessed using the Personal and Social Performance Scale (**Supplemental Figure 4**)
- Patient activation as assessed using the Patient Activation Measure-Mental Health Scale (**Supplemental Figure 5**)
- The proportion of days that patients and HCPs use the app and dashboard, respectively
- The proportion of ingested IEM tablets registered on the digital health data server of the total expected IEM tablets ingested
- Safety variables will include the frequency and severity of serious adverse events and device-related nonserious adverse events, suicidality, and any product quality complaints that may arise. Suicidality will be determined by face-to-face risk assessment according to each study site's standard operating procedure.

## Statistical analysis

A sample size of 60 patients was determined based on an anticipated 25% discontinuation rate, such that ≥45 patients would complete the 8-week assessment period. The study described is a feasibility study with no comparisons and no formal power calculations. The sample size was chosen to contain roughly 20 patients per indication and align with historical studies performed in the USA. The discontinuation rate is assumed based on similar discontinuations for other psychiatry studies and the fact that an actively clinical stable population is not being recruited. Data will be analyzed in the intent-to-treat population (ie, all patients who enter the trial and use the DMS). All data will be analyzed using descriptive statistics. Continuous variables will be

summarized using mean, median, range, and standard deviation. Categorical variables will be summarized using frequency distributions.

## Data protection

Before initiating participation, informed consent will be obtained from all patients and caregivers. Health information will be de-identified to the fullest possible extent. However, some identifiers or sensitive health information cannot be stripped (eg, psychiatric medical history, participation in a care program approach, presence of a community treatment order, employment status, disabilities, housing arrangements, or armed forces history). Health information will be used to develop and improve the DMS application and user experience. The DMS and associated third-party vendors are compliant with the General Data Protection Regulation (GDPR), and all accessed health information will be maintained in the strictest confidence and in compliance with the GDPR. Data from the DMS are encrypted in activity and rest and will be accessed only by role-specific individuals for discrete time periods and functions (eg, technical troubleshooting). All data will be completely anonymized for graphical, statistical, and publication purposes.

Research staff from NHS sites will store consent documents, demographic forms, and receipts for reimbursement of travel in locked filing cabinets to which only research staff will have access. Accessing of health data will be compliant with IG policies of each participating NHS trust.

## Ethical considerations

Ethics approval for this study was o

btained from London - City & East Research Ethics Committee (REC Ref no. 18/LO/0128), and clinical trial authorization was provided by the Medicines and Healthcare products Regulatory

Agency. Written informed consent will be obtained from every participant. Ethical issues will be related to the identification and recruitment of patients, informed consent, and data protection arrangements. The trial will be conducted in compliance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines and Declaration of Helsinki.

### Dissemination of study results

The study results will be disseminated through peer-reviewed publications, national and international conference presentations, and formal clinical trial repositories (eg, ClinicalTrials.gov). The 5 participating NHS sites will be invited to a results launch event. Results will be shared with individuals who participated in the workshops via the respective trusts. Additionally, follow-up workshops are planned to capture further feedback on next steps for scaling the DMS technology.

## DISCUSSION

Patient adherence to antipsychotic medication is a crucial component of successful maintenance therapy for schizophrenia. Knowledge of patient adherence in the absence of positive treatment outcome is also essential. Subjective means for assessing medication adherence such as clinician evaluation and patient self-report have low validity [16], and most can only be administered during patient-HCP visits. Digital medicine offers a means to monitor patient adherence and obtain objective data throughout treatment, including periods between office visits, which may yield more accurate data. For example, a study evaluating nonadherence rates for antipsychotic medication based on electronic medication bottle caps, which report when pill bottles have been opened [18], showed a 57% nonadherence rate, much higher than that estimated by patient (5%)

and provider (7%) report [18]. Electronic medication bottle caps are used as the current gold-standard surrogate for 'objective' adherence data. Few reports in this space exist and the need for more robust objective adherence data is supported through this discrepancy and the limitations of electronic medication bottle caps as an 'objective' measure, given it only measures an intermediate step in the ingestion process. This study shows the potential of digital medicine to provide continuous objective data that can inform and improve patient adherence and assist in clinical decision making. The DMS improves upon approaches such as electronic medication caps by providing an objective marker of ingestion and not merely a surrogate in addition to other objective and subjective data.

Patient discontinuation is a considerable problem in studies of digital health technology [26]. Studies of early digital health systems for maintenance and counseling of mental disorders reported low completion rates. For example, a study evaluating a 12-week web-based cognitive behavioral therapy intervention for panic disorder had a 1% (12/1161) completion rate [27], and a study evaluating a publicly accessible 5-module web-based cognitive behavioral therapy program for anxiety and depression had a 0.5% completion rate (97/19,607) [28]. Completion rates may be particularly low in patients with more severe negative symptoms [22]. Despite these historically poor completion rates in studies of digital health platforms, results of a meta-analysis indicate that more than 50% of patients favor managing their mental health through the use of mobile health technology [29], and the use of mobile devices for health management is viewed by patients as normalized and nonstigmatizing [30]. The integrated DMS described here was developed to leverage the advantages of digital technology to positively influence adherence in patients with schizophrenia.

The DMS is a multimodal, user-friendly system that provides medication reminders and measures patient ingestion of prescribed antipsychotic medications. The CoE product, in particular, advances the ability to confirm medication ingestion and to assess adherence on a continuous basis, which can inform whether uncontrolled symptoms may be explained by nonadherence. Information from the DMS is made readily available to patients, caregivers (with the patient's consent), and physicians for supported decision making, proactive intervention, and individualized care. DMS also provides adherence feedback electronically to the patient, HCP, and/or caregiver. The DMS provides this feedback discreetly, through user-owned and operated applications and a patch that is not readily visible as it is worn on the torso underneath clothing, reducing any potential stigmatization if it (the patch) was visible. The DMS also provides feedback on activity and rest levels, which is important given that maintenance of a healthy lifestyle can help address the problems of weight gain and obesity that are related to both medication side effects and sedentary lifestyles [31]. Furthermore, shifts in activity levels may be indicative of altered patient disposition.

This ongoing study was designed using coproduction methodology to incorporate input from patients, caregivers, psychiatrists, pharmacists, nurses, and researchers. For all 5 study sites, a minimum of 2 engagement/setup meetings were conducted and 2 specific patient focus groups were held to guide protocol development and app design. The exploratory data collected in this study, although limited to a small number of patients, will help provide a better understanding of the ease of use for patients, HCPs, and caregivers to inform the development of future software or hardware iterations.

Given the level of unfamiliarity with digital medicine systems, conducting clinical trials in this space requires a higher level of stakeholder management and alignment, especially when the trial

is being held in a new environment. Whether it's a new country, a new healthcare system, or a new set of investigators, formal buy-in and input is critical to participation. The protocol outlines one way of managing and aligning stakeholders in such an environment - the UK mental health system. Additionally, and increasingly important within mental health services and interventions in the UK, is the involvement of end–users, so called service users who have lived experience of mental health. The methods paper describes a robust engagement strategy using such individuals in mental health research.

Digital health interventions require significant clinician and patient engagement. The protocol describes an approach to ensure that service users of a digital medicine intervention can assist with protocol design and system input e.g. approach and appropriate language

## CONCLUSION

In conclusion, this study will examine the usability and acceptance of the DMS by patients with schizophrenia, schizoaffective disorder, or first-episode psychosis, and by caregivers and HCPs in different care settings. The study was meticulously coproduced through the engagement of all stakeholders and, if successful, could be used to support DMS usage in larger cohorts within the United Kingdom and Europe.

## Funding statement

This study is supported by Otsuka Pharmaceutical Development & Commercialization, Inc. Editorial support for development of this manuscript was provided by Eric Comeau, PhD, at C4 MedSolutions, LLC (Yardley, PA), a CHC Group company, and funded by Otsuka Pharmaceutical Development & Commercialization, Inc.

## Competing interests statement

Dr J. Corey Fowler, Dr Jonathan Knights, and Dr Tim Peters-Strickland are employees of Otsuka Pharmaceutical Development & Commercialization. Dr Nathan Cope is an employee of Otsuka Pharmaceutical Europe Ltd. Dr Andrew Makin is an employee of Otsuka Europe Development and Commercialisation. Dr Peter Phiri has no conflict of interest. Dr Shanaya Rathod has received honoraria from Otsuka and Lundbeck for educational sessions.

## Author contributions

JCF, NC, JK, PP, AM, TP-S and SR contributed to study conception and design as well as data collection, analysis, and interpretation; JCF, NC, JK, PP, AM, TP-S and SR were responsible for review and critical revision of the manuscript; and JCF, NC, JK, PP, AM, TP-S and SR gave final approval to submit for publication.

## Acknowledgements

The authors thank patient advisers and NHS staff from all 5 participating sites (Oxford Health NHS Foundation Trust; Northumberland, Tyne and Wear NHS Foundation Trust; Southern Health NHS Foundation Trust; South London and Maudsley NHS Foundation Trust; and Surrey and Borders Partnership NHS Foundation Trust) for their contributions to the study methodology. Editorial support for development of this manuscript was provided by Eric Comeau at C4 MedSolutions, LLC (Yardley, PA, USA), a CHC Group company, and funded by Otsuka Pharmaceutical Development & Commercialization, Inc.

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## Figure Legends

**Figure 1.** Digital medicine system: co-encapsulated antipsychotic medication with miniature ingestible event marker in tablet (MIT) and compatible medical device. DM=digital medicine; HCP=healthcare professional. Image reprinted from article in npg Digital Medicine [In Press].

**Figure 2.** Description of coproduction workshops with Southern Health NHS Foundation Trust. DMS=digital medicine system; EIP=Early Intervention in Psychosis; IG=information governance; MoSCoW=must have, should have, could have, won't have; NHS=National Health Service; PANSS=Positive and Negative Syndrome Scale; PPI=Patient and Public Involvement program.

**Figure 3**. Study design.

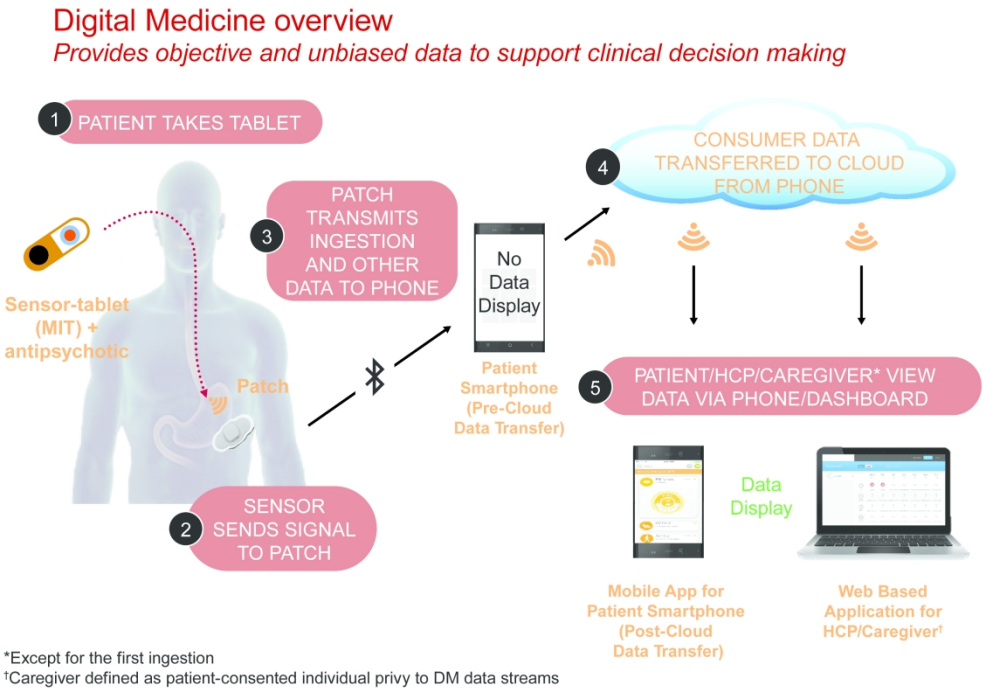



Figure 1. Digital medicine system: co-encapsulated antipsychotic medication with miniature ingestible event marker in tablet (MIT) and compatible medical device. DM=digital medicine; HCP=healthcare professional.

254x177mm (300 x 300 DPI)

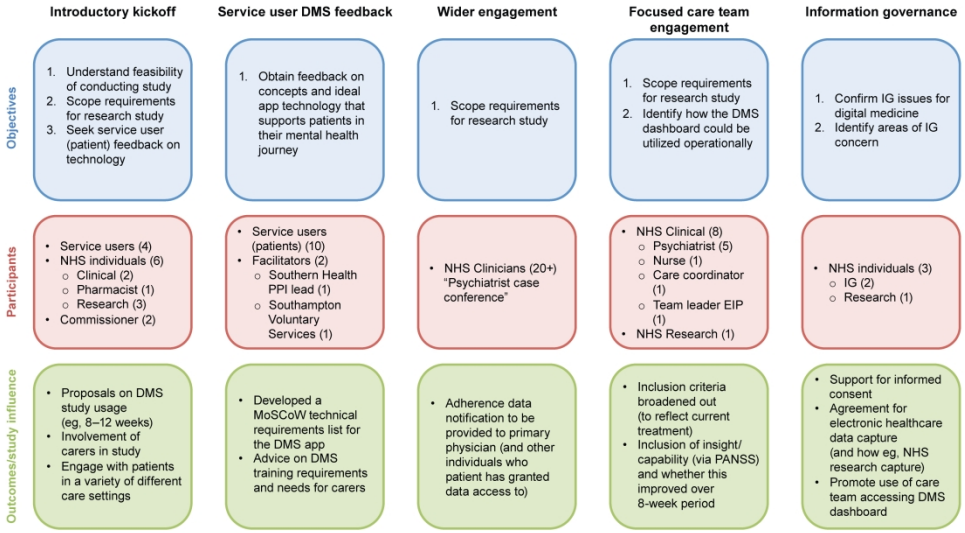
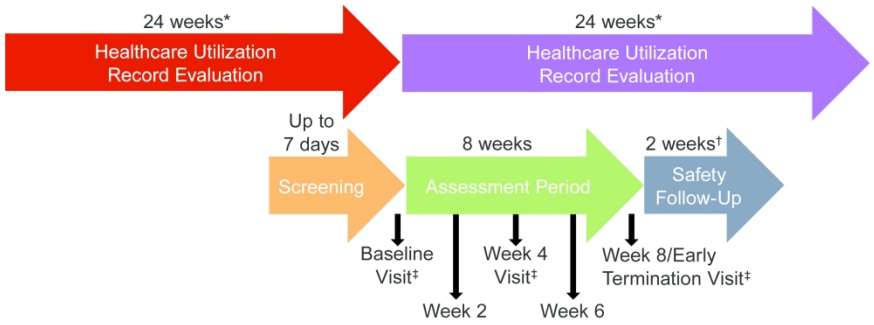



Figure 2. Description of coproduction workshops with Southern Health NHS Foundation Trust. DMS=digital medicine system; EIP=Early Intervention in Psychosis; IG=information governance; MoSCoW=must have, should have, could have, won't have; NHS=National Health Service; PANSS=Positive and Negative Syndrome Scale; PPI=Patient and Public Involvement program.

317x184mm (300 x 300 DPI)




Healthcare professionals (HCPs) will review dashboard at weeks 2, 4, 6, and 8 and make treatment changes at their discretion.
*Healthcare utilization will be recorded 24 weeks before and after baseline visit (for a total of 48 weeks).
†Safety follow-up phone call will occur 2 weeks after week 8/early termination visit.
‡Patient visits will occur at baseline, week 4, and week 8/early termination. Other visits will be at the discretion of the HCP.

Figure 3. Study design.

241x108mm (300 x 300 DPI)

# Supplementary Material

## Supplemental Figure 1. Subject Usability and Satisfaction Scale (Ver 2.0)

**Section A: Usability**

**1. How easy or difficult was it for you to apply the patch on your body?**

| Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**2. How easy or difficult was it to pair the patch with the mobile phone application (app)?**

| Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**3. How easy or difficult was it for you to use the mobile phone application (app)?**

| Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**4. How easy or difficult was it for you to use the Digital Medicine System?**

| Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**5. How well do you agree with the following statement?**

- **In general, I did not mind wearing the patch.**

| Strongly Disagree | Disagree | Somewhat Disagree | Neutral | Somewhat Agree | Agree | Strongly Agree |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | |

**6. Since your last visit, did you receive assistance when changing and pairing the required patches? Yes No**

If yes,

| | Never | Once a month or less | A few times a month | Once a week | A few times a week | Daily |
|---|---|---|---|---|---|---|
| How much assistance did you receive when applying the patches? | | | | | | |
| How much assistance did you receive when syncing the technology? | | | | | | |

If you did receive any help or assistance, who helped or assisted you?
(please place a √ [check] to indicate who helped or assisted you)

| Friend | Hired Caregiver | Relative* | Other** |
|---|---|---|---|
| | | | |

*If a relative helped or assisted you, then please specify their relationship to you (such as wife, husband, father, mother, sister, brother, or whatever else you think is the most appropriate description of the relative who helped you): _____

**If you selected "Other", please specify your relationship to the person who helped you _____

## Section B: Satisfaction

**7. How easy or difficult was it for you to use the entire Digital Medicine System, which includes the patch, pills, and mobile phone application (app)?**

| Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

8. **How helpful or unhelpful was the Digital Medicine System in the management of your condition?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

9. **How helpful or unhelpful was the Digital Medicine System for sharing information with your healthcare professionals to help you understand your treatment plan?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

10. **How helpful or unhelpful was the Digital Medicine System in improving your discussions with your doctor / treatment team?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

11. **Based on your experience, how would you rate your satisfaction with the Digital Medicine System?**

| Extremely Dissatisfied | Dissatisfied | Somewhat Dissatisfied | Neutral | Somewhat Satisfied | Satisfied | Extremely Satisfied |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

12. **How likely would you be to use the Digital Medicine System in the future, if it were available and recommended by your doctor?**

| Extremely Unlikely | Unlikely | Somewhat Unlikely | Neutral | Somewhat Likely | Likely | Extremely Likely |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**Supplemental Figure 2. Physician Utility Survey (Ver 2.0)**

*We ask the Principal Investigator, Physician Investigator, and Trial Coordinator(s) at a clinical site/trust to complete this survey for each patient enrolled. Please answer the below questions based on your overall experience using DMS.*

1. **How easy or difficult was it for you and your patient to apply the patch on the patient's body?**

| | Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| For you | | | | | | | |
| For your patient | | | | | | | |

2. **How easy or difficult was it for you and your patient to sync the patch with the mobile phone application (app)?**

| | Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| For you | | | | | | | |
| For your patient | | | | | | | |

3. **How easy or difficult was it for you and your patient to complete the overall onboarding for the Digital Medicine System?**

| | Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| For you | | | | | | | |
| For your patient | | | | | | | |

4. **Overall, how easy or difficult was it for you and your patient to use the mobile phone application (app)?**

| | Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| For you | | | | | | | |
| For your patient | | | | | | | |

5. **Overall, how easy or difficult was it for you and your patient to use the entire Digital Medicine System, which includes the patch, pills, and mobile phone application (app)?**

| | Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| For you | | | | | | | |
| For your patient | | | | | | | |

6. **How easy or difficult was it for you to use the HCP dashboard?**

| Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**7. If you were in routine clinical practice (ie, in clinical practice without a study protocol), how helpful or unhelpful do you think the Digital Medicine System could be for the following elements of clinical management for this specific patient?**

| | Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Assessment | | | | | | | |
| Clinical Advice/ Recommendations | | | | | | | |
| Treatment Decisions | | | | | | | |

**8. How effective was the Digital Medicine System in aiding decision-making for medication adherence?**

| Extremely Not Effective | Not Effective to Use | Somewhat Not Effective to Use | Neutral | Somewhat Effective to Use | Effective to Use | Extremely Effective to Use |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**9. How helpful or unhelpful was the Digital Medicine System in providing a way to better engage your patients in self-management of their condition?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**10. How helpful or unhelpful was the Digital Medicine System in improving quality of care for your patient?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**11. How helpful or unhelpful was the Digital Medicine System in improving your conversations with your patient about their treatment plan and progress?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**12. How helpful or unhelpful was the Digital Medicine System in the identification of potential lifestyle changes for your patient (eg sleep and exercise)?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**13. Other than during the patient visit(s), did you look at the HCP dashboard at other times? Please select all that apply**

| | Place a √ (check) next to the time you referred to the HCP dashboard |
|---|---|
| No, only during the patient visit | |
| Prior to patient visit (same day as visit) | |
| In between visits | |
| Other: *Please Specify:* _____ | |

**14. What features did you find helpful? Please select all that apply**

| | Place a √ (check) next to the features you found helpful | For the features you have selected, please rank these features from 1 (most helpful) to 7 (least helpful) in order of helpfulness |
|---|---|---|
| Pill ingestion data | | |
| Patient reported reason code for missed doses | | |
| Multiple dose alerts | | |
| Missed dose alerts | | |
| Activity | | |
| Rest | | |
| Patient reported rest quality rating | | |
| Other: *Please Specify:* _____ | | |

**15. Did you set up alerts to be notified of missed doses? Yes/no**

**a. If yes, based on your overall experience, how helpful were the missed dose alerts?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful | Not Applicable – No alerts received |
|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | |
| | | | | | | | |

15a. If you received a missed dose alert what action did you take, if any? (If none, please write N/A) _____

**16. Did you set up alerts to be notified of multiple doses? Yes/no**

**a. If yes, based on your overall experience, how helpful were the multiple dose alerts?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful | Not Applicable – No alerts received |
|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | |
| | | | | | | | |

16a. If you received a multiple dose alert what action did you take, if any? (If none, please write N/A _____

**17. How well do you agree with the following statement?**

**a. Overall, the Digital Medicine System adds value to my practice.**

| Strongly Disagree | Disagree | Somewhat Disagree | Neutral | Somewhat Agree | Agree | Strongly Agree |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**18. Based on your overall experience with this patient, how would you rate your satisfaction with the Digital Medicine System?**

| Extremely Dissatisfied | Dissatisfied | Somewhat Dissatisfied | Neutral | Somewhat Satisfied | Satisfied | Extremely Satisfied |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**Supplemental Figure 3. Caregiver/Support Person Involvement Scale (Ver 2.0)**

**DMS Caregiver/Support Person Involvement Scale**

**1. Are you aware that the study participant/patient is currently participating in the Digital Medicine study (check one)?**

| Yes | No* |
|---|---|
| | |

***If no, stop here and do not answer the rest of the questions on this form.**

**2. Indicate your relationship to the study participant/patient by placing a √ (check).**

| Friend | Hired Caregiver | Relative* | Other** |
|---|---|---|---|
| | | | |

***If you are a relative, please specify relationship to the study participant/patient, e.g., wife, father:**

****If you selected "Other", please specify your relationship to the study participant/patient:**

_____

**3. How much involvement did you provide the subject with regard to taking medication, pairing the patch, applying the patch, and using the app during the course of the study?**

| | Never | Once a month or less | A few times a month | Once a week | A few times a week | Daily |
|---|---|---|---|---|---|---|
| How much overall assistance did you provide the subject during the course of the study? | | | | | | |
| How much assistance did you provide with patch application? | | | | | | |
| How much assistance did you provide with syncing the technology? | | | | | | |
| How much assistance did you provide with using the app? | | | | | | |
| | **Never** | **Once a week** | **A few times a week** | **Nearly every day** | **Daily** | **More than once/day** |
| How much overall assistance did you provide during the past week of the study? | | | | | | |

## Clinical Global Impression Scale

Clinical Global Impression – Severity Scale (CGI-S)

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

0 = Not assessed

1 = Normal, not at all ill

2 = Borderline mentally ill

3 = Mildly ill

4 = Moderately ill

5 = Markedly ill

6 = Severely ill

7 = Among the most extremely ill subjects

**Supplemental Figure 4. Personal and Social Performance Scale**

Original version: Morosini PL, Magliano L, Brambilla L, et al. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand* 2000;101(4):323-9

## Personal and Social Performance Scale (PSP)

The rating is based on four main areas: (a) socially useful activities, including work and study; (b) personal and social relationships; (c) self-care; and (d) disturbing and aggressive behaviors.

Data will be captured in the following format using the PSP descriptions provided below:

| | Absent | Mild | Manifest | Marked | Severe | Very Severe |
|---|---|---|---|---|---|---|
| a. Socially useful activities, including work and study | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| b. Personal and social relationships | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| c. Self-care | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| d. Disturbing and aggressive behaviors | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

The levels of functioning in other areas should be taken into account to adjust the rating inside the decimal level (for instance, from 31 to 40). Suicidal risk is not included in the scale.

| 10-point intervals | PSP descriptions |
|---|---|
| 100–91 | Excellent functioning in all four main areas*. He/she is held in high consideration for his/her good qualities, copes adequately with life problems, is involved in a wide range of interests and activities. |
| 90–81 | Good functioning in all four main areas, presence of only common problems or difficulties. |
| 80–71 | Mild difficulties in 1 or more of areas a–c. |
| 70–61 | Manifest, but not marked difficulties in 1 or more areas a–c, *or* mild difficulties in d. |
| 60–51 | Marked difficulties in 1 of areas a–c, *or* manifest difficulties in d. |
| 50–41 | Marked difficulties in 2 or more, *or* severe difficulties in 1 of areas a–c, with or without manifest difficulties in d. |
| 40–31 | Severe difficulties in 1 *and* marked difficulties in at least 1 of areas a–c, *or* marked difficulties in d. |
| 30–21 | Severe difficulties in 2 of areas a–c, *or* severe difficulties in d, with or without impairment in areas a–c. |
| 20–11 | Severe difficulties in all areas a–d, *or* very severe in d with or without impairment in general areas a–c. If the person reacts to external prompts the suggested scores are 20–16, if not, the suggested scores are 15–11. |
| 10–1 | Lack of autonomy in basic functioning with extreme behaviors but without survival risk (ratings 6–10) or with survival risk, eg, death risk due to malnutrition, dehydration, infections, inability to recognize situation of manifest danger (ratings 5–1). |

| For main areas a–c, the degrees of severity are: | |
|---|---|
| Absent | |
| Mild | Not manifest difficulties, known only to someone who is very familiar with the person. |
| Manifest, but not marked | Difficulties clearly noticeable by everyone, but not interfering substantially with the person's ability to perform his/her role in that area, given the person's socio-cultural context, age, sex and educational levels. |
| Marked | Difficulties heavily interfering with role performance in that area; however, the person is still able to do something without professional or social help, although inadequately and/or occasionally; if helped by someone, he/she may be able reach the previous level of functioning. |
| Severe | Difficulties that make the person unable to perform any role in that area, if not professionally helped, or lead the person to a destructive role; however, there are no survival risks. |
| Very severe | Impairments and difficulties of such intensity to endanger person's survival. |

| For general area d, the degrees of severity are: | |
|---|---|
| Absent | |
| Mild | Mild rudeness, unsociability or whingeing. |
| Manifest, but not marked | Speaking too loudly or speaking to others in a too-familiar manner, or eating in a socially unacceptable manner. |
| Marked | Insulting other in public, breaking or wrecking objects, acting frequently in a socially inappropriate but not dangerous way (eg, stripping in public or urinating in public). |
| Severe | Frequent verbal threats or frequent physical assaults, without intention or possibility of severe injuries. |
| Very severe | Frequent aggressive acts, aimed at or likely to cause severe injuries. |

Occasional is defined as occurring three or more times in the reference period or occurring even less than three times but in circumstances and/or with such a previous history to convince the rater that there is a risk of recurrence in the near future. If the aggressive behavior has been present occasionally, the rating may be decreased by one degree, eg, from severe to marked.

* Main areas: a = socially useful activities, including work and study; b = personal and social relationships; c = self-care; d = disturbing and aggressive behaviors.

**Guidelines for PSP Total Score**

Ratings from 71–100 reflect only mild difficulties.

Ratings from 31–70 reflect manifest disabilities of various degrees.

Ratings from 1–30 reflect functioning so poor that intensive support or supervision is needed.

**Supplemental Figure 5. Patient Activation Measure-Mental Health Scale**

The following questions ask about your feelings regarding your mental healthcare. When you think about mental health and mental health care, how much do you agree or disagree with the following statements? Please circle the answer that you most agree with:

**1.** When all is said and done, I am the person who is responsible for managing my mental health.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**2.** Taking an active role in my own mental health is the most important factor in determining my mental health and ability to function.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**3.** I am confident that I can take actions that will help prevent or minimize some symptoms or problems associated with my mental health condition.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**4.** I know what each of my prescribed mental health medications does.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**5.** I am confident that I can tell when I need to go get mental health care, and when I can handle a mental health problem myself.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**6.** I am confident I can tell my mental health clinician about concerns I have, even when he or she does not ask.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**7.** I am confident that I can follow through on mental health treatments I need to do at home.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**8.** I understand the nature and causes of my mental health condition(s).

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**9.** I know the different treatment options available for my mental health condition(s).

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**10.** I am able to maintain the lifestyle changes I have made for my mental health.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**11.** I know how to prevent further mental health problems.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**12.** I am confident I can figure out solutions when new situations or problems arise with my mental health.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**13.** I am confident that I can maintain lifestyle changes, like diet and exercise, even during times of stress.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | Page 1 Line 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | Page 4 Line 64 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | Provided on ClinicalTrials.gov |
| Protocol version | 3 | Date and version identifier | Page 1 of protocol |
| Funding | 4 | Sources and types of financial, material, and other support | Page 20 Line 396 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | Page 21 Line 408 |
| | 5b | Name and contact information for the trial sponsor | Page 1 Line 22 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | Page 21 Line 407 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | Page 21 Line 407 |

**Introduction**

| | | | |
|---|---|---|---|
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | Page 7 Line 137 |
| | 6b | Explanation for choice of comparators | *N/A* |
| Objectives | 7 | Specific objectives or hypotheses | Page 9 Line 163 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | Page 9 Line 170 |

**Methods: Participants, interventions, and outcomes**

| | | | |
|---|---|---|---|
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | Page 9 Line 176 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | Page 10 Line 188 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | Page 11 Line 190 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | Page 18 Line 343 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | Page 19 Line 358 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | As listed on each drug label |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | Page 14 Line 265 |

| | | | |
|---|---|---|---|
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | Figure 3 |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | Page 15 Line 282 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | Page 13 Line 249 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | N/A |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | N/A |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | N/A |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | N/A |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | N/A |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | Protocol Page 81 |

| | | | |
|---|---|---|---|
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | Page 14 Line 259 |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | Protocol Page 73 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | Protocol Page 73 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | Page 15 Line 282 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | Page 15 Line 282 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | N/A Pragmatic Trial - Safety of Interventions is Established |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | N/A |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | Protocol Page 66 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | Protocol Page 81 |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | Page 16 Line 309 |

| | | | |
|---|---|---|---|
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | Updates to ClinicalTrials.gov |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | Page 15 Line 293 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | N/A |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | Page 15 Line 299 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | Page 21 Line 402 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | Page 17 Line 318 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | N/A |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | Protocol page 84 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | Protocol page 84 |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | Not yet determined |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | Protocol Page 107 |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | N/A |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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# A Study Protocol for the Hummingbird Study, a Multicenter Exploratory Trial to Assess the Acceptance and Performance of a Digital Medicine System in Adults With Schizophrenia, Schizoaffective Disorder, or First-Episode Psychosis



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| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2018-025952.R2 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 10-May-2019 |
| Complete List of Authors: | Fowler, J.; Otsuka Pharmaceutical Development & Commercialization, Inc.,<br>Cope, Nathan; Otsuka Pharmaceutical Europe Ltd.<br>Knights, Jonathan; Otsuka Pharmaceutical Development & Commercialization, Inc.<br>Phiri, Peter; Southern Health NHS Foundation Trust<br>Makin, Andrew; Otsuka Europe Development and Commercialisation Ltd.<br>Peters-Strickland, Tim; Otsuka Pharmaceutical Development & Commercialization, Inc.<br>Rathod, Shanaya; Southern Health NHS Foundation Trust, Psychiatry |
| Primary Subject Heading: | Mental health |
| Secondary Subject Heading: | Evidence based practice |
| Keywords: | Coproduction, digital medicine, schizoaffective disorder, schizophrenia |
| | |

# A Study Protocol for the Hummingbird Study, a Multicenter Exploratory Trial to Assess the Acceptance and Performance of a Digital Medicine System in Adults With Schizophrenia, Schizoaffective Disorder, or First-Episode Psychosis

Running title: Study protocol for DMS use in schizophrenia in the UK

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Word count (max 4000 for BMJ Open): 3988 (Intro through conclusion, not including table)

Table count: 1

Figure count: 3 (+6 supplemental)

Reference count: 31

# ABSTRACT

Objectives: In patients with schizophrenia, medication adherence is important for relapse prevention, and effective adherence monitoring is essential for treatment planning. A digital medicine system (DMS) has been developed to objectively monitor patient adherence and support clinical decision-making regarding treatment choices. This study's objective is to assess the acceptance and performance of the DMS in adults with schizophrenia, schizoaffective disorder, or first-episode psychosis and in healthcare professionals (HCPs) in the United Kingdom.

Design: This is a multicenter, 8-week, single-arm, open-label pragmatic trial designed using coproduction methodology.

Setting: The study will be conducted at 5 National Health Service Foundation Trusts in the United Kingdom.

Participants: Patients 18 to 65 years old with a diagnosis of schizophrenia, schizoaffective disorder, or first-episode psychosis will be eligible. HCPs (psychiatrists, care coordinators, nurses, pharmacists) researchers, information governance (IG) personnel, Clinical Commissioning Groups (CCGs), and patients participated in study design and coproduction.

Interventions: The DMS is an integrated system comprising an oral sensor tablet co-encapsulated with an antipsychotic, nonmedicated wearable patch, mobile application (app), and Web-based dashboard. The co-encapsulation product contains aripiprazole, olanzapine, quetiapine, or risperidone, as prescribed by the HCP, with a miniature ingestible event marker (IEM) in tablet. Upon ingestion, the IEM transmits a signal to the patch, which collects ingestion and physical activity data for processing on the patient's smartphone or tablet before transmission to a cloud-based server for viewing by patients, caregivers, and HCPs on secure web portals or mobile apps.

Outcome measures: The primary and secondary endpoints will be the proportion of days with good patch coverage and ingestion adherence, respectively.

Conclusions: This study will provide data on the acceptance and performance of the DMS in UK patients with schizophrenia, schizoaffective disorder, or first-episode psychosis and in caregivers and HCPs.

ClinicalTrials.gov: NCT03568500; EudraCT 2017-004602-17

## Keywords

Coproduction, digital medicine, schizoaffective disorder, schizophrenia

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- Although a PRECIS-2 assessment tool was not used during the design of the study the authors feel that based on a retrospective PRECIS-2 analysis (refer to supplemental materials for this analysis) this study does meet the criteria for a pragmatic study.
- This study was codeveloped with input from clinical practitioners, researchers, patients, caregivers, service managers, IG teams, and clinical commissioning groups to obtain information that will best serve all those involved in the treatment and care of patients with schizophrenia, schizoaffective disorder, and first-episode psychosis.
- The digital medicine system (DMS) uses an integrated, user-friendly system to provide objective feedback on patient medication adherence and physical health parameters, such as activity and rest levels, as well as voluntary subjective entries regarding mood and rest quality, to help support treatment decisions and evaluation.

- Information from the DMS is made readily available to patients, caregivers (with the patient's consent), and physicians to support clinical decision making, proactive intervention, and individualized care in near to real time.
- Possible limitations of this study are the small sample size (N=60), limited generalizability to the broader pool of UK mental health patients and providers, and the relatively short 12-week timeframe. Although the DMS does require the patient to engage more with their own care, the benefits of increasing their awareness of medication, activity, rest, and mood patterns may outweigh risks/burden for most patients. The DMS was not developed for all mental health patients, but for a subset of patients who realize they have difficulty with adherence and want to improve their status by self-monitoring with potential for their HCP's to make better clinical decisions based on objective data from the DMS. Patients with poor insight into their illness will likely be a better candidate for a long-acting injectable atypical antipsychotic than this DMS.

# INTRODUCTION

Schizophrenia has an enormous social and economic burden worldwide, accounting for 1.1% of total disability-adjusted life-years and 2.7% of years lived with disability [1, 2]. In Europe, the economic impact of schizophrenia and other psychotic disorders and syndromes in 2010 was estimated at €93.9 billion [3]. Because schizophrenia is a chronic disease, maintenance treatment is often necessary to prevent relapse and preserve quality of life over the long term [4, 5]. Although antipsychotic medications are effective [6-8], poor insight into schizophrenia can increase risk of medication nonadherence [9, 10]. In patients with schizophrenia, the rate of nonadherence to prescribed antipsychotics has been reported to be as high as 74% [11]. Not only is medication nonadherence burdensome to patients and their families, it also increases the likelihood of rehospitalization and relapse [12] and contributes substantially to healthcare costs [13]. In 2005/2006, mean annual psychiatric inpatient and medication costs for patients with schizophrenia in England were estimated to be approximately £3,000 and £2,000 per patient, respectively [14].

Because medication adherence is important to relapse prevention in schizophrenia [15], effective adherence monitoring is an essential part of the treatment plan. Although there are various subjective methods for determining medication adherence, including patient surveys, adherence diaries, and clinician ratings of patient symptoms and medication side effects, these methods have low validity [16]. Blister packs and electronic medication bottle caps can provide an indicator of pill removal or bottle opening and have been shown to improve adherence [17, 18], but neither technology provides an objective marker of pill ingestion or supports remote monitoring by healthcare professionals (HCPs). Optimal adherence monitoring and support for

patients with schizophrenia requires a system that provides physicians with objective information during interim periods between patient visits.

The use of modern technology such as personal digital assistants [19], digital wristwatches [20], handheld computers [21], and mobile phones [22] to help people with schizophrenia dealing with their disease has shown success. A digital medicine system (DMS) has been developed as a drug-device combination to objectively assess and report ingestion of prescription antipsychotics [23]. The DMS has 4 main components: an ingestible sensor embedded within an inert tablet, a nonmedicated wearable sensor (patch) worn by the patient, a mobile application (app), and a Web-based dashboard [23]. Upon interaction with stomach fluids, the ingestible sensor is activated and communicates with the wearable sensor, which sends a signal to a Bluetooth-paired mobile device where it can be viewed by patients or be subsequently viewed by HCPs and caregivers using secure mobile- and cloud-based software [23]. The DMS also enables patients to share data on their activity and rest levels as well as subjective data on mood and rest quality, which can be generated while the patient is engaged with the system. The intention of the DMS is to encourage greater patient self-management and behavior change while enabling caregivers and HCPs to provide better care and support both within and outside of office visits, further engaging patients in their ongoing disease management. The data is communicated to the psychiatrist that is connected to the patient on the MyCite platform. Additionally, should the patient choose to share their data, they are able to invite additional healthcare providers, caregivers and/or family or friends. Recipients of the data, through a web-based password protected platform, are able to view this data and assist the patient with their treatment plan, however HCPs can only access the portal for a specific patient once he/she has consented to give them access to their information in the system. It is envisioned that HCPs will be able to use this

data to make more informed clinical decisions such as whether individuals need dose adjustment, medication changes or conversations on lifestyle, adherence or other parameters.

Previous results in the USA have shown in an open-label, 8-week study, 78% (47/60) of patients and 72% (43/60) of HCPs reported being somewhat satisfied, satisfied, or extremely satisfied with the DMS [24]. Findings from another open-label study showed patients to be actively involved in their treatment, with 73.5% (36/49) utilizing call centers for technological DMS support [25]; the rate of ingestion adherence in this study for the 15 patients with schizophrenia was 85.6% [25].

The DMS from the current study (namely the ingestible sensor and the wearable sensor) are Conformité Européene (CE)–marked for use in Europe as class IIa medical devices (CE 559373), but studies in European mental health populations have not been performed. Therefore, the objective of this exploratory study is to assess the acceptance and performance of the DMS among adult patients with schizophrenia, schizoaffective disorder, or first-episode psychosis and among HCPs from different care settings in the United Kingdom. We are particularly interested in assessing the acceptance of the digital medicine technology in individuals from different care settings. Acceptance will be assessed by study completion and, feedback from subjects from patient satisfaction surveys. Furthermore, acceptance will also be evaluated by healthcare providers using the system; this will be assessed by how their clinical decisions altered whilst using the system and through HCP Utility questionnaire evaluations.

In respect to performance, the study will be assessing multiple hardware and software from a varied population. Based on operational feedback of different phones and OS and any technical troubleshooting that occurs, the study will be able to determine areas of the app that need to be enhanced to ensure that the app functions across multiple hardware and operating systems.

Previous studies performed using the DMS were conducted in relatively stable individuals with schizophrenia. For this study, we have broadened the inclusion criteria and will be assessing the technology in a range of clinical groups from different care settings, such as those individuals managed in the community or on specialized services such as Early Intervention in Psychosis services to determine the performance in these different environments.

The study is not intended to measure and report or make any claims of adherence, but instead, to report the observed ingestions recorded by the DMS. Our goal is to look at the impact of patients' improvements as a result of participation (e.g. reduced need for follow-up care, knowledge of adherence to medication to help physicians decide whether patients are medication compliant or require a long acting injectable or other follow-up care) with the hypothesis that DMS will reduce overall healthcare utilization burden by optimizing treatment decisions.

## METHODS AND ANALYSIS

### Study design

This is a multicenter, 8-week, single-arm, open-label trial to evaluate the acceptance and performance of the DMS in adult patients with schizophrenia, schizoaffective disorder, or first-episode psychosis on an oral atypical antipsychotic medication (aripiprazole, olanzapine, quetiapine, or risperidone) and in HCPs. Recruitment began the same day that we submitted to CT.gov, 25/MAY. However, we didn't consent our first patient until 11/JUN and dosing occurred on 18/JUN. The study will take place at 5 institutions in the United Kingdom: Northumberland, Tyne and Wear National Health Service (NHS) Foundation Trust, Surrey and Borders Partnership NHS Foundation Trust, Oxford Health NHS Foundation Trust, South London and Maudsley NHS Foundation Trust, and Southern Health NHS Foundation Trust. The

first patient's first visit occurred in May 2018. Patient recruitment will be targeted to last approximately 4 months.

## Patient selection

Patients for this exploratory study will be identified using database searches conducted at each study site per HCP discretion. Inclusion and exclusion criteria are provided in **Table 1**. The degree of clinical stability will be varied across participants that enroll. In short, a fully stable patient population will not be actively recruited, instead a range of clinical populations (crudely based on Clinical Global Impression – Severity scale (CGI-S)) from different care settings will participate.

**Table 1. Inclusion and Exclusion Criteria**

| **Inclusion criteria** |
|---|
| • Willing and able to give written informed consent and adhere to trial procedures<br>• Able to read and understand English<br>• Age 18–65 years at the time of informed consent<br>• Possessing a smartphone and able to use it to interact with the digital medicine system (DMS) application **through robust and dependable cellular or wireless internet connections (Subjects should have WiFi at home and/or at work, or at the very least have access to free WiFi hot spots. Alternatively, subjects should have a sufficient data plan from their mobile provider and/or coverage on their phone. Such assessments are made during the screening of potential subjects.)**<br>• Cooperative, able to ingest oral medication, willing to complete aspects of the trial, and capable of reporting adverse events (AEs)<br>• Clinical diagnosis of schizophrenia, schizoaffective disorder (defined by International Classification of Diseases, Tenth Revision, codes F20 and F25), or first-episode psychosis based on case note review<br>• Prescription for aripiprazole, olanzapine, quetiapine, or risperidone<br>• Fulfills ≥1 of the following:<br>  ○ Discharge from a hospital admission (within 7 days of discharge) to an acute intervention team<br>  ○ Referral to an acute intervention team before hospital admission<br>  ○ Referral from an acute intervention team to a community team<br>  ○ Managed by community services<br>  ○ Inclusion within early intervention caseload (<3 years from initial symptoms)<br>  ○ Healthcare professional (HCP) determines the patient would benefit<br>• General medical condition does not pose additional risk |

| |
|---|
| • Skin on the anterior chest above the lower edge of the rib cage is free of any dermatologic problem |
| **Exclusion criteria** |
| • Any disorder that may affect patient's ability to participate in the trial or interact with a smartphone<br>• Likely to be incapable of using DMS technology, even with assistance<br>• History or evidence of a medical condition that would expose patient to undue risk of an AE<br>• Known allergy to adhesive tape or any component of the patch or co-encapsulation product<br>• Current incarceration in prison system<br>• Hospitalization at the time of screening due to mental or physical illness<br>• HCP recommendation to not participate<br>• Aversion to taking gelatin capsules<br>• Women who are breastfeeding, pregnant, or plan to become pregnant |

## Intervention

The DMS is an integrated, 4-component system comprising an oral co-encapsulation (CoE) pharmacologic sensor tablet, a Proteus® Patch, a mobile app, and Otsuka Medical dashboard software (**Figure 1**). Each CoE product contains an approved antipsychotic medication (aripiprazole, olanzapine, quetiapine, or risperidone) encapsulated with a miniature ingestible event marker (IEM) in tablet. HCPs will select the medication and dosage based on each patient's needs. Upon taking the medication, the IEM transmits a signal to the nonmedicated patch that is attached to the patient's skin. The patch collects IEM ingestion and physical activity data, which are then processed by the Patch Analytics Block on the patient's smartphone. Processed data are transferred through the app on the smartphone and sent to a cloud-based server for patient, caregiver, and HCP viewing on Otsuka Medical software through web portals or mobile apps. Patients will have access to the Otsuka Patient Application, caregivers will have

access (with patient consent) to the Otsuka Caregiver Web Portal, and HCPs will have access to the Otsuka Healthcare Provider Web Portal.

## Patient and Public Involvement Statement

## Coproduction

This study was designed using coproduction methodology involving NHS staff and patients (**Figure 2**). Coproduction in this protocol is the involvement of people with lived experience of mental illness (diagnosed or otherwise) as equal partners alongside other healthcare stakeholders, in the design and contribution to the protocol. The lead site, Southern Health NHS Foundation Trust, held 5 coproduction workshops, and a subset of these workshops was repeated at other study sites to elicit feedback on the study design. At least 2 of these workshops involved patients. The discussions from the workshops addressed pharmacy items for the CoE product; HCP recruitment strategies; and protocols for identification, recruitment, and interactions with suitable patients and their general practitioners. Throughout the various workshops at the different sites, participants included clinicians, pharmacists, researchers, IG personnel (refers to the way in which the NHS handles, stores and processes information, in particular personal and sensitive information relating to patients and employees; it was vital to ensure that IG individuals were happy with the privacy and storage features of the digital medicine system), psychiatrists, care coordinators, nurses, information technology personnel, CCGs (clinically led groups within the NHS that are responsible for the planning and commissioning of healthcare services for their local area), and patients (**Figure 2**).

## Patient Involvement

The Patient and Public Involvement and Service User Lead from 2 study sites (Surrey and Borders Partnership NHS Foundation Trust and Northumberland, Tyne, and Wear NHS Foundation Trust) engaged service users to participate in a patient focus group. The objective of the focus groups was to obtain feedback on the app technology and assess the completion of specific app tasks. The groups identified issues that may have prevented the completion of key tasks and whether greater explanation would be needed, for instance in ensuring the app could send notifications to patients. Furthermore, general feedback on colour and language was also obtained.

## Procedures

The study will comprise 3 phases: a screening phase of up to 7 days, an 8-week assessment phase, and a 2-week safety follow-up (**Figure 3**). Screening and baseline may occur at a single visit or at 2 visits separated by up to 7 days. At the screening/baseline visit, patients providing informed consent will receive patches, CoE product, and other supplies and undergo training by the HCPs on required and correct use of the DMS. HCPs will confirm proper patch application to the skin and pairing of the patch with the smartphone app when patients commence their usage of the digital medicine system, so called on boarding. These individuals will either be psychiatrists or research assistants for the site. During time in-between the only required site visits at weeks 4 and 8, patients will perform patch changing themselves and be guided, if required, through videos contained within the app. There is a freephone technical support line to assist individuals should they wish. Patients will be instructed to wear the patch continuously, replacing it every 7 days or as needed during the assessment period. An integrated call center will be available to patients for technical support regarding use of the DMS.

During the subsequent 8-week assessment period, patients will visit their HCP at weeks 4 and 8 (or at early termination) for clinical evaluation and review of DMS data. At the week 4 visit, patients will also obtain a prescription refill. HCPs will be required to monitor and review DMS data at least every 2 weeks, with the option of requesting additional patient visits as needed. HCPs will also have the ability to modify the patient's treatment plan at their discretion. Safety and tolerability will be assessed on an ongoing basis throughout the assessment period and during the subsequent 2-week safety follow-up, during which time a follow-up telephone call will be made to each study participant.

Healthcare utilization record evaluation will occur continuously beginning at the baseline/screening visit and will span a period ranging from 24 weeks before baseline/screening to 24 weeks after screening. All hospital admissions will be recorded and categorized as "planned," "unplanned," "related," or "unrelated" to psychiatric illness. Characteristics of each HCP encounter will also be recorded, including the nature of the contact; HCP role; whether the visit was planned or unplanned; whether or not the contact was initiated as a result of the DMS; and any medication titration, adherence counseling, education, or lifestyle coaching that occurred.

## Outcomes

The primary endpoint is the proportion of days with good patch coverage during the assessment period, which will be defined as having ≥80% patch data available or IEMs detected within each day of the assessment period. The secondary endpoint is ingestion adherence, defined as the proportion of detected IEMs to the total expected IEMs ingested on the assessment days that showed good patch coverage.

The following exploratory endpoints will also be included:

- The proportion of time during the assessment period that patients wear their patch
- Engagement and satisfaction of patients, HCPs, and caregivers as determined using the Subject Usability and Satisfaction Scale (**Supplemental Figure 1**), the Physician Utility Survey (**Supplemental Figure 2**), and the Caregiver/Support Person Involvement Scale (**Supplemental Figure 3**)
- Personal and social functioning as assessed using the Personal and Social Performance Scale (**Supplemental Figure 4**)
- Patient activation as assessed using the Patient Activation Measure-Mental Health Scale (**Supplemental Figure 5**)
- The proportion of days that patients and HCPs use the app and dashboard, respectively
- The proportion of ingested IEM tablets registered on the digital health data server of the total expected IEM tablets ingested
- Safety variables will include the frequency and severity of serious adverse events and device-related nonserious adverse events, suicidality, and any product quality complaints that may arise. Suicidality will be determined by face-to-face risk assessment according to each study site's standard operating procedure.

## Statistical analysis

A sample size of 60 patients was determined based on an anticipated 25% discontinuation rate, such that ≥45 patients would complete the 8-week assessment period. The study described is a feasibility study with no comparisons and no formal power calculations. The sample size was chosen to contain roughly 20 patients per indication and align with historical studies performed

in the USA. The discontinuation rate is assumed based on similar discontinuations for other psychiatry studies and the fact that an actively clinical stable population is not being recruited. Data will be analyzed in the intent-to-treat population (ie, all patients who enter the trial and use the DMS). All data will be analyzed using descriptive statistics. Continuous variables will be summarized using mean, median, range, and standard deviation. Categorical variables will be summarized using frequency distributions.

## Data protection

Before initiating participation, informed consent will be obtained from all patients and caregivers. Health information will be de-identified to the fullest possible extent. However, some identifiers or sensitive health information cannot be stripped (eg, psychiatric medical history, participation in a care program approach, presence of a community treatment order, employment status, disabilities, housing arrangements, or armed forces history). Health information will be used to develop and improve the DMS application and user experience. The DMS and associated third-party vendors are compliant with the General Data Protection Regulation (GDPR), and all accessed health information will be maintained in the strictest confidence and in compliance with the GDPR. Data from the DMS are encrypted in activity and rest and will be accessed only by role-specific individuals for discrete time periods and functions (eg, technical troubleshooting). All data will be completely anonymized for graphical, statistical, and publication purposes.

Research staff from NHS sites will store consent documents, demographic forms, and receipts for reimbursement of travel in locked filing cabinets to which only research staff will have access. Accessing of health data will be compliant with IG policies of each participating NHS trust.

## Ethical considerations

Ethics approval for this study was o

btained from London - City & East Research Ethics Committee (REC Ref no. 18/LO/0128), and clinical trial authorization was provided by the Medicines and Healthcare products Regulatory Agency. Written informed consent will be obtained from every participant. Ethical issues will be related to the identification and recruitment of patients, informed consent, and data protection arrangements. The trial will be conducted in compliance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines and Declaration of Helsinki.

## Dissemination of study results

The study results will be disseminated through peer-reviewed publications, national and international conference presentations, and formal clinical trial repositories (eg, ClinicalTrials.gov). The 5 participating NHS sites will be invited to a results launch event. Results will be shared with individuals who participated in the workshops via the respective trusts. Additionally, follow-up workshops are planned to capture further feedback on next steps for scaling the DMS technology.

# DISCUSSION

Patient adherence to antipsychotic medication is a crucial component of successful maintenance therapy for schizophrenia. Knowledge of patient adherence in the absence of positive treatment outcome is also essential. Subjective means for assessing medication adherence such as clinician evaluation and patient self-report have low validity [16], and most can only be administered during patient-HCP visits. Digital medicine offers a means to monitor patient adherence and

obtain objective data throughout treatment, including periods between office visits, which may yield more accurate data. For example, a study evaluating nonadherence rates for antipsychotic medication based on electronic medication bottle caps, which report when pill bottles have been opened [18], showed a 57% nonadherence rate, much higher than that estimated by patient (5%) and provider (7%) report [18]. Electronic medication bottle caps are used as the current gold-standard surrogate for 'objective' adherence data. Few reports in this space exist and the need for more robust objective adherence data is supported through this discrepancy and the limitations of electronic medication bottle caps as an 'objective' measure, given it only measures an intermediate step in the ingestion process. This study shows the potential of digital medicine to provide continuous objective data that can inform and improve patient adherence and assist in clinical decision making. The DMS improves upon approaches such as electronic medication caps by providing an objective marker of ingestion and not merely a surrogate in addition to other objective and subjective data.

Patient discontinuation is a considerable problem in studies of digital health technology [26]. Studies of early digital health systems for maintenance and counseling of mental disorders reported low completion rates. For example, a study evaluating a 12-week web-based cognitive behavioral therapy intervention for panic disorder had a 1% (12/1161) completion rate [27], and a study evaluating a publicly accessible 5-module web-based cognitive behavioral therapy program for anxiety and depression had a 0.5% completion rate (97/19,607) [28]. Completion rates may be particularly low in patients with more severe negative symptoms [22]. Despite these historically poor completion rates in studies of digital health platforms, results of a meta-analysis indicate that more than 50% of patients favor managing their mental health through the use of mobile health technology [29], and the use of mobile devices for health management is viewed

by patients as normalized and nonstigmatizing [30]. The integrated DMS described here was developed to leverage the advantages of digital technology to positively influence adherence in patients with schizophrenia.

The DMS is a multimodal, user-friendly system that provides medication reminders and measures patient ingestion of prescribed antipsychotic medications. The CoE product, in particular, advances the ability to confirm medication ingestion and to assess adherence on a continuous basis, which can inform whether uncontrolled symptoms may be explained by nonadherence. Information from the DMS is made readily available to patients, caregivers (with the patient's consent), and physicians for supported decision making, proactive intervention, and individualized care. DMS also provides adherence feedback electronically to the patient, HCP, and/or caregiver. The DMS provides this feedback discreetly, through user-owned and operated applications and a patch that is not readily visible as it is worn on the torso underneath clothing, reducing any potential stigmatization if it (the patch) was visible. The DMS also provides feedback on activity and rest levels, which is important given that maintenance of a healthy lifestyle can help address the problems of weight gain and obesity that are related to both medication side effects and sedentary lifestyles [31]. Furthermore, shifts in activity levels may be indicative of altered patient disposition.

This ongoing study was designed using coproduction methodology to incorporate input from patients, caregivers, psychiatrists, pharmacists, nurses, and researchers. For all 5 study sites, a minimum of 2 engagement/setup meetings were conducted and 2 specific patient focus groups were held to guide protocol development and app design. The exploratory data collected in this study, although limited to a small number of patients, will help provide a better understanding of

the ease of use for patients, HCPs, and caregivers to inform the development of future software or hardware iterations.

Given the level of unfamiliarity with digital medicine systems, conducting clinical trials in this space requires a higher level of stakeholder management and alignment, especially when the trial is being held in a new environment. Whether it's a new country, a new healthcare system, or a new set of investigators, formal buy-in and input is critical to participation. The protocol outlines one way of managing and aligning stakeholders in such an environment - the UK mental health system. Additionally, and increasingly important within mental health services and interventions in the UK, is the involvement of end–users, so called service users who have lived experience of mental health. The methods paper describes a robust engagement strategy using such individuals in mental health research.

Digital health interventions require significant clinician and patient engagement. The protocol describes an approach to ensure that service users of a digital medicine intervention can assist with protocol design and system input e.g. approach and appropriate language

## CONCLUSION

In conclusion, this study will examine the usability and acceptance of the DMS by patients with schizophrenia, schizoaffective disorder, or first-episode psychosis, and by caregivers and HCPs in different care settings. The study was coproduced through the engagement of all stakeholders and, if successful, could be used to support DMS usage in larger cohorts within the United Kingdom and Europe.

## Funding statement

This study is supported by Otsuka Pharmaceutical Development & Commercialization, Inc.

Editorial support for development of this manuscript was provided by Eric Comeau, PhD, at C4 MedSolutions, LLC (Yardley, PA), a CHC Group company, and funded by Otsuka Pharmaceutical Development & Commercialization, Inc.

## Competing interests statement

Dr J. Corey Fowler, Dr Jonathan Knights, and Dr Tim Peters-Strickland are employees of Otsuka Pharmaceutical Development & Commercialization. Dr Nathan Cope is an employee of Otsuka Pharmaceutical Europe Ltd. Dr Andrew Makin is an employee of Otsuka Europe Development and Commercialisation. Dr Peter Phiri has no conflict of interest. Dr Shanaya Rathod has received honoraria from Otsuka and Lundbeck for educational sessions.

## Author contributions

JCF, NC, JK, PP, AM, TP-S and SR contributed to study conception and design as well as data collection, analysis, and interpretation; JCF, NC, JK, PP, AM, TP-S and SR were responsible for review and critical revision of the manuscript; and JCF, NC, JK, PP, AM, TP-S and SR gave final approval to submit for publication.

## Acknowledgements

The authors thank patient advisers and NHS staff from all 5 participating sites (Oxford Health NHS Foundation Trust; Northumberland, Tyne and Wear NHS Foundation Trust; Southern Health NHS Foundation Trust; South London and Maudsley NHS Foundation Trust; and Surrey and Borders Partnership NHS Foundation Trust) for their contributions to the study methodology. Editorial support for development of this manuscript was provided by Eric

Comeau at C4 MedSolutions, LLC (Yardley, PA, USA), a CHC Group company, and funded by Otsuka Pharmaceutical Development & Commercialization, Inc.

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## Figure Legends

**Figure 1.** Digital medicine system: co-encapsulated antipsychotic medication with miniature ingestible event marker in tablet (MIT) and compatible medical device. DM=digital medicine; HCP=healthcare professional. Image reprinted from article in npg Digital Medicine [In Press].

**Figure 2.** Description of coproduction workshops with Southern Health NHS Foundation Trust. DMS=digital medicine system; EIP=Early Intervention in Psychosis; IG=information governance; MoSCoW=must have, should have, could have, won't have; NHS=National Health Service; PANSS=Positive and Negative Syndrome Scale; PPI=Patient and Public Involvement program.

**Figure 3**. Study design.

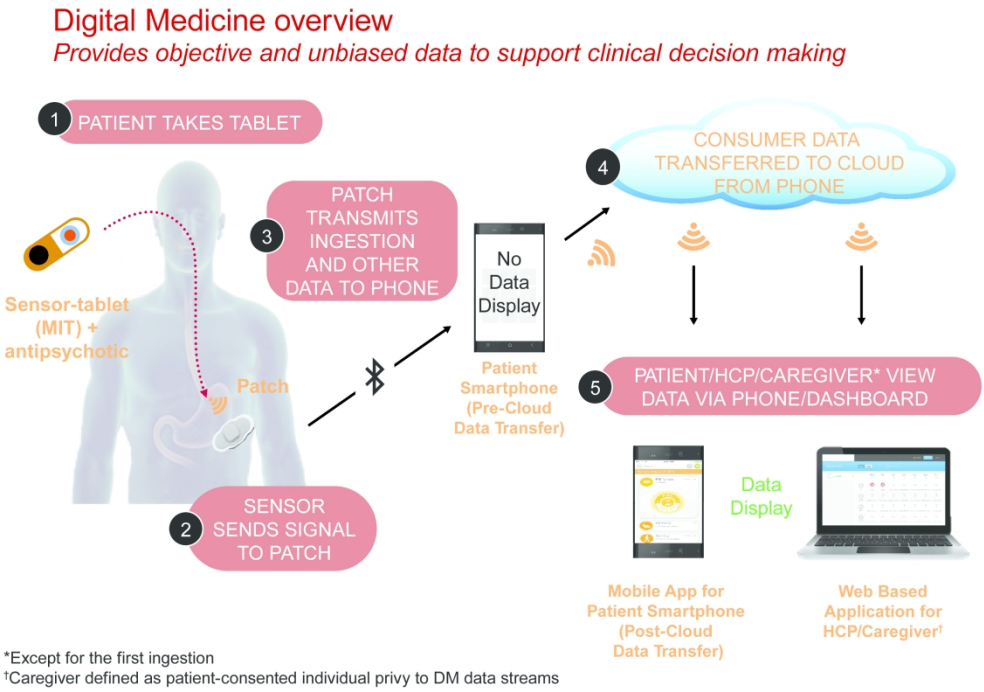



Figure 1. Digital medicine system: co-encapsulated antipsychotic medication with miniature ingestible event marker in tablet (MIT) and compatible medical device. DM=digital medicine; HCP=healthcare professional.

254x177mm (300 x 300 DPI)

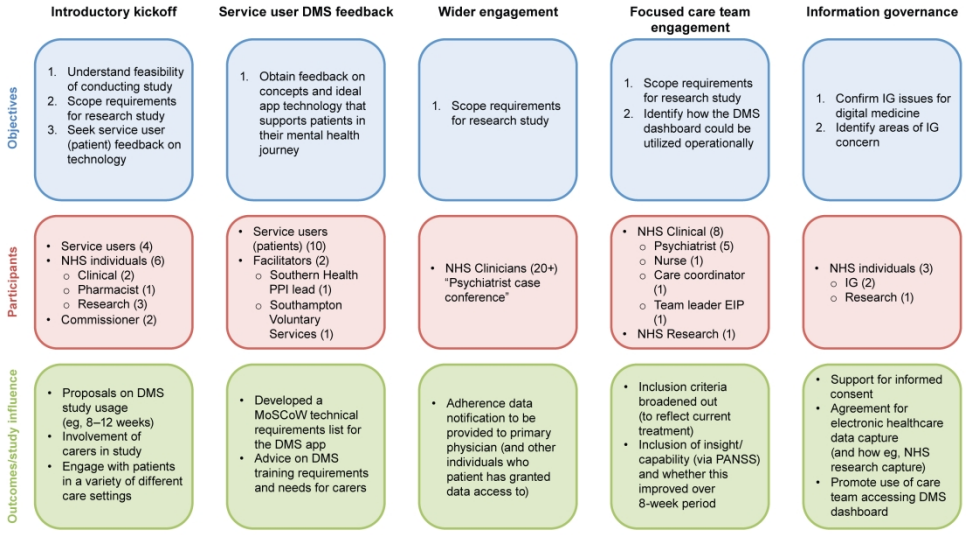
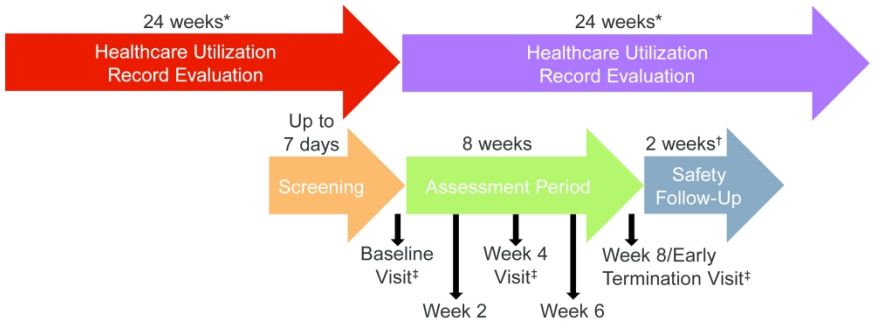



Figure 2. Description of coproduction workshops with Southern Health NHS Foundation Trust. DMS=digital medicine system; EIP=Early Intervention in Psychosis; IG=information governance; MoSCoW=must have, should have, could have, won't have; NHS=National Health Service; PANSS=Positive and Negative Syndrome Scale; PPI=Patient and Public Involvement program.

317x184mm (300 x 300 DPI)




Healthcare professionals (HCPs) will review dashboard at weeks 2, 4, 6, and 8 and make treatment changes at their discretion.
*Healthcare utilization will be recorded 24 weeks before and after baseline visit (for a total of 48 weeks).
†Safety follow-up phone call will occur 2 weeks after week 8/early termination visit.
‡Patient visits will occur at baseline, week 4, and week 8/early termination. Other visits will be at the discretion of the HCP.

Figure 3. Study design.

241x108mm (300 x 300 DPI)

# Supplementary Material

## Supplemental Figure 1. Subject Usability and Satisfaction Scale (Ver 2.0)

**Section A: Usability**

**1. How easy or difficult was it for you to apply the patch on your body?**

| Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**2. How easy or difficult was it to pair the patch with the mobile phone application (app)?**

| Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**3. How easy or difficult was it for you to use the mobile phone application (app)?**

| Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**4. How easy or difficult was it for you to use the Digital Medicine System?**

| Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**5. How well do you agree with the following statement?**

- **In general, I did not mind wearing the patch.**

| Strongly Disagree | Disagree | Somewhat Disagree | Neutral | Somewhat Agree | Agree | Strongly Agree |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | |

**6. Since your last visit, did you receive assistance when changing and pairing the required patches? Yes No**

If yes,

| | Never | Once a month or less | A few times a month | Once a week | A few times a week | Daily |
|---|---|---|---|---|---|---|
| How much assistance did you receive when applying the patches? | | | | | | |
| How much assistance did you receive when syncing the technology? | | | | | | |

If you did receive any help or assistance, who helped or assisted you?
(please place a √ [check] to indicate who helped or assisted you)

| Friend | Hired Caregiver | Relative* | Other** |
|---|---|---|---|
| | | | |

*If a relative helped or assisted you, then please specify their relationship to you (such as wife, husband, father, mother, sister, brother, or whatever else you think is the most appropriate description of the relative who helped you): _____

**If you selected "Other", please specify your relationship to the person who helped you _____

## Section B: Satisfaction

**7. How easy or difficult was it for you to use the entire Digital Medicine System, which includes the patch, pills, and mobile phone application (app)?**

| Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

8. **How helpful or unhelpful was the Digital Medicine System in the management of your condition?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

9. **How helpful or unhelpful was the Digital Medicine System for sharing information with your healthcare professionals to help you understand your treatment plan?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

10. **How helpful or unhelpful was the Digital Medicine System in improving your discussions with your doctor / treatment team?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

11. **Based on your experience, how would you rate your satisfaction with the Digital Medicine System?**

| Extremely Dissatisfied | Dissatisfied | Somewhat Dissatisfied | Neutral | Somewhat Satisfied | Satisfied | Extremely Satisfied |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

12. **How likely would you be to use the Digital Medicine System in the future, if it were available and recommended by your doctor?**

| Extremely Unlikely | Unlikely | Somewhat Unlikely | Neutral | Somewhat Likely | Likely | Extremely Likely |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**Supplemental Figure 2. Physician Utility Survey (Ver 2.0)**

*We ask the Principal Investigator, Physician Investigator, and Trial Coordinator(s) at a clinical site/trust to complete this survey for each patient enrolled. Please answer the below questions based on your overall experience using DMS.*

1. **How easy or difficult was it for you and your patient to apply the patch on the patient's body?**

| | Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| For you | | | | | | | |
| For your patient | | | | | | | |

2. **How easy or difficult was it for you and your patient to sync the patch with the mobile phone application (app)?**

| | Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| For you | | | | | | | |
| For your patient | | | | | | | |

3. **How easy or difficult was it for you and your patient to complete the overall onboarding for the Digital Medicine System?**

| | Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| For you | | | | | | | |
| For your patient | | | | | | | |

4. **Overall, how easy or difficult was it for you and your patient to use the mobile phone application (app)?**

| | Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| For you | | | | | | | |
| For your patient | | | | | | | |

5. **Overall, how easy or difficult was it for you and your patient to use the entire Digital Medicine System, which includes the patch, pills, and mobile phone application (app)?**

| | Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| For you | | | | | | | |
| For your patient | | | | | | | |

6. **How easy or difficult was it for you to use the HCP dashboard?**

| Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**7. If you were in routine clinical practice (ie, in clinical practice without a study protocol), how helpful or unhelpful do you think the Digital Medicine System could be for the following elements of clinical management for this specific patient?**

| | Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Assessment | | | | | | | |
| Clinical Advice/ Recommendations | | | | | | | |
| Treatment Decisions | | | | | | | |

**8. How effective was the Digital Medicine System in aiding decision-making for medication adherence?**

| Extremely Not Effective | Not Effective to Use | Somewhat Not Effective to Use | Neutral | Somewhat Effective to Use | Effective to Use | Extremely Effective to Use |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**9. How helpful or unhelpful was the Digital Medicine System in providing a way to better engage your patients in self-management of their condition?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**10. How helpful or unhelpful was the Digital Medicine System in improving quality of care for your patient?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**11. How helpful or unhelpful was the Digital Medicine System in improving your conversations with your patient about their treatment plan and progress?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**12. How helpful or unhelpful was the Digital Medicine System in the identification of potential lifestyle changes for your patient (eg sleep and exercise)?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**13. Other than during the patient visit(s), did you look at the HCP dashboard at other times? Please select all that apply**

| | Place a √ (check) next to the time you referred to the HCP dashboard |
|---|---|
| No, only during the patient visit | |
| Prior to patient visit (same day as visit) | |
| In between visits | |
| Other: *Please Specify:* _____ | |

**14. What features did you find helpful? Please select all that apply**

| | Place a √ (check) next to the features you found helpful | For the features you have selected, please rank these features from 1 (most helpful) to 7 (least helpful) in order of helpfulness |
|---|---|---|
| Pill ingestion data | | |
| Patient reported reason code for missed doses | | |
| Multiple dose alerts | | |
| Missed dose alerts | | |
| Activity | | |
| Rest | | |
| Patient reported rest quality rating | | |
| Other: *Please Specify:* _____ | | |

**15. Did you set up alerts to be notified of missed doses? Yes/no**

**a. If yes, based on your overall experience, how helpful were the missed dose alerts?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful | Not Applicable – No alerts received |
|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | |
| | | | | | | | |

15a. If you received a missed dose alert what action did you take, if any? (If none, please write N/A) _____

**16. Did you set up alerts to be notified of multiple doses? Yes/no**

**a. If yes, based on your overall experience, how helpful were the multiple dose alerts?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful | Not Applicable – No alerts received |
|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | |
| | | | | | | | |

16a. If you received a multiple dose alert what action did you take, if any? (If none, please write N/A _____

**17. How well do you agree with the following statement?**

**a. Overall, the Digital Medicine System adds value to my practice.**

| Strongly Disagree | Disagree | Somewhat Disagree | Neutral | Somewhat Agree | Agree | Strongly Agree |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**18. Based on your overall experience with this patient, how would you rate your satisfaction with the Digital Medicine System?**

| Extremely Dissatisfied | Dissatisfied | Somewhat Dissatisfied | Neutral | Somewhat Satisfied | Satisfied | Extremely Satisfied |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**Supplemental Figure 3. Caregiver/Support Person Involvement Scale (Ver 2.0)**

**DMS Caregiver/Support Person Involvement Scale**

**1. Are you aware that the study participant/patient is currently participating in the Digital Medicine study (check one)?**

| Yes | No* |
|---|---|
| | |

***If no, stop here and do not answer the rest of the questions on this form.**

**2. Indicate your relationship to the study participant/patient by placing a √ (check).**

| Friend | Hired Caregiver | Relative* | Other** |
|---|---|---|---|
| | | | |

***If you are a relative, please specify relationship to the study participant/patient, e.g., wife, father:**

****If you selected "Other", please specify your relationship to the study participant/patient:**

_____

**3. How much involvement did you provide the subject with regard to taking medication, pairing the patch, applying the patch, and using the app during the course of the study?**

| | Never | Once a month or less | A few times a month | Once a week | A few times a week | Daily |
|---|---|---|---|---|---|---|
| How much overall assistance did you provide the subject during the course of the study? | | | | | | |
| How much assistance did you provide with patch application? | | | | | | |
| How much assistance did you provide with syncing the technology? | | | | | | |
| How much assistance did you provide with using the app? | | | | | | |
| | **Never** | **Once a week** | **A few times a week** | **Nearly every day** | **Daily** | **More than once/day** |
| How much overall assistance did you provide during the past week of the study? | | | | | | |

## Clinical Global Impression Scale

Clinical Global Impression – Severity Scale (CGI-S)

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

0 = Not assessed

1 = Normal, not at all ill

2 = Borderline mentally ill

3 = Mildly ill

4 = Moderately ill

5 = Markedly ill

6 = Severely ill

7 = Among the most extremely ill subjects

**Supplemental Figure 4. Personal and Social Performance Scale**

Original version: Morosini PL, Magliano L, Brambilla L, et al. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand* 2000;101(4):323-9

# Personal and Social Performance Scale (PSP)

The rating is based on four main areas: (a) socially useful activities, including work and study; (b) personal and social relationships; (c) self-care; and (d) disturbing and aggressive behaviors.

Data will be captured in the following format using the PSP descriptions provided below:

| | Absent | Mild | Manifest | Marked | Severe | Very Severe |
|---|---|---|---|---|---|---|
| a. Socially useful activities, including work and study | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| b. Personal and social relationships | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| c. Self-care | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| d. Disturbing and aggressive behaviors | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

The levels of functioning in other areas should be taken into account to adjust the rating inside the decimal level (for instance, from 31 to 40). Suicidal risk is not included in the scale.

| 10-point intervals | PSP descriptions |
|---|---|
| 100–91 | Excellent functioning in all four main areas*. He/she is held in high consideration for his/her good qualities, copes adequately with life problems, is involved in a wide range of interests and activities. |
| 90–81 | Good functioning in all four main areas, presence of only common problems or difficulties. |
| 80–71 | Mild difficulties in 1 or more of areas a–c. |
| 70–61 | Manifest, but not marked difficulties in 1 or more areas a–c, *or* mild difficulties in d. |
| 60–51 | Marked difficulties in 1 of areas a–c, *or* manifest difficulties in d. |
| 50–41 | Marked difficulties in 2 or more, *or* severe difficulties in 1 of areas a–c, with or without manifest difficulties in d. |
| 40–31 | Severe difficulties in 1 *and* marked difficulties in at least 1 of areas a–c, *or* marked difficulties in d. |
| 30–21 | Severe difficulties in 2 of areas a–c, *or* severe difficulties in d, with or without impairment in areas a–c. |
| 20–11 | Severe difficulties in all areas a–d, *or* very severe in d with or without impairment in general areas a–c. If the person reacts to external prompts the suggested scores are 20–16, if not, the suggested scores are 15–11. |
| 10–1 | Lack of autonomy in basic functioning with extreme behaviors but without survival risk (ratings 6–10) or with survival risk, eg, death risk due to malnutrition, dehydration, infections, inability to recognize situation of manifest danger (ratings 5–1). |

| For main areas a–c, the degrees of severity are: | |
|---|---|
| Absent | |
| Mild | Not manifest difficulties, known only to someone who is very familiar with the person. |
| Manifest, but not marked | Difficulties clearly noticeable by everyone, but not interfering substantially with the person's ability to perform his/her role in that area, given the person's socio-cultural context, age, sex and educational levels. |
| Marked | Difficulties heavily interfering with role performance in that area; however, the person is still able to do something without professional or social help, although inadequately and/or occasionally; if helped by someone, he/she may be able reach the previous level of functioning. |
| Severe | Difficulties that make the person unable to perform any role in that area, if not professionally helped, or lead the person to a destructive role; however, there are no survival risks. |
| Very severe | Impairments and difficulties of such intensity to endanger person's survival. |

| For general area d, the degrees of severity are: | |
|---|---|
| Absent | |
| Mild | Mild rudeness, unsociability or whingeing. |
| Manifest, but not marked | Speaking too loudly or speaking to others in a too-familiar manner, or eating in a socially unacceptable manner. |
| Marked | Insulting other in public, breaking or wrecking objects, acting frequently in a socially inappropriate but not dangerous way (eg, stripping in public or urinating in public). |
| Severe | Frequent verbal threats or frequent physical assaults, without intention or possibility of severe injuries. |
| Very severe | Frequent aggressive acts, aimed at or likely to cause severe injuries. |

Occasional is defined as occurring three or more times in the reference period or occurring even less than three times but in circumstances and/or with such a previous history to convince the rater that there is a risk of recurrence in the near future. If the aggressive behavior has been present occasionally, the rating may be decreased by one degree, eg, from severe to marked.

* Main areas: a = socially useful activities, including work and study; b = personal and social relationships; c = self-care; d = disturbing and aggressive behaviors.

**Guidelines for PSP Total Score**

Ratings from 71–100 reflect only mild difficulties.

Ratings from 31–70 reflect manifest disabilities of various degrees.

Ratings from 1–30 reflect functioning so poor that intensive support or supervision is needed.

**Supplemental Figure 5. Patient Activation Measure-Mental Health Scale**

The following questions ask about your feelings regarding your mental healthcare. When you think about mental health and mental health care, how much do you agree or disagree with the following statements? Please circle the answer that you most agree with:

**1.** When all is said and done, I am the person who is responsible for managing my mental health.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**2.** Taking an active role in my own mental health is the most important factor in determining my mental health and ability to function.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**3.** I am confident that I can take actions that will help prevent or minimize some symptoms or problems associated with my mental health condition.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**4.** I know what each of my prescribed mental health medications does.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**5.** I am confident that I can tell when I need to go get mental health care, and when I can handle a mental health problem myself.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**6.** I am confident I can tell my mental health clinician about concerns I have, even when he or she does not ask.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**7.** I am confident that I can follow through on mental health treatments I need to do at home.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**8.** I understand the nature and causes of my mental health condition(s).

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**9.** I know the different treatment options available for my mental health condition(s).

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**10.** I am able to maintain the lifestyle changes I have made for my mental health.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**11.** I know how to prevent further mental health problems.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**12.** I am confident I can figure out solutions when new situations or problems arise with my mental health.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**13.** I am confident that I can maintain lifestyle changes, like diet and exercise, even during times of stress.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

Supplemental Material – PRECIS-2 Tool Assessment

Whilst the PRECIS-2 tool assessment was not completed during the design of the study, when it is designed to be conducted, a post assessment use of the tool confirms the use of the term pragmatic. For example, from the nine PRECIS-2 domains:

Eligibility: Would score 4 (out of 5) since those identified in the study would be those identified in usual care. The study does exclude inpatients, which in the "real world" could in theory participate but we felt the DMS intervention was of limited benefit in this setting since inpatients have observed adherence

Recruitment: would score 4-5 since recruitment is based simply on screening patient caseloads and assessment of patients who may need help with adherence measures. No advertisements have been conducted.

Setting: Would score 4-5 since the care settings used in the study are those in usual care. We have a range of participants from community and specialist mental health services

Organisation: Would likely score 3-4 since although the resource/expertise is largely similar to usual care, the study does use NHS research staff to assist with training and screening, as is commonplace with all clinical studies in the UK

Flexibility (delivery): Would score 3-4 since the study gives patients and HCPs the ability to follow standard of care but does require specific site visit at w4 and w8 (yet one could argue this would occur naturally since the w4 visit is to collect a new prescription (which would occur in

the real world) and the w8 visit is the completion of the study. Patients do not experience any other "forced" visits.

Flexibility (adherence): Would score 3 since following enrolment if patients do not utilise the patch/app the site can contact the patient to found out why they are not engaging and try to encourage; however, this would be the same if the DMS was indeed normal practice; this is the intention of the tool to promote conversations between visits when individuals are not adherent.

Primary outcome: would score 3-4; whilst the outcome may not be obvious to patients, the outcome has been supported from conversations with HCPs and payers. The good patch coverage days are essential to provide insight into medication taking so again, if the intervention become standard, the metric would be used since it would determine whether objective and insightful data was being captured.

Primary analysis: Would score 4 since all individuals will be included in the analysis with all available data.

Based on the above, the average score is approx. 4 which equates to "Rather pragmatic"

The reason why the study is not the top score of 5 (Very pragmatic) is that the intervention itself does cause changes to current care but we are not stating how individuals should respond to these changes. They are free to decide for themselves.


SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | _Page 1 Line 1_ |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | _Page 4 Line 64 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | Provided on ClinicalTrials.gov |
| Protocol version | 3 | Date and version identifier | Page 1 of protocol |
| Funding | 4 | Sources and types of financial, material, and other support | Page 20 Line 396 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | Page 21 Line 408 |
| | 5b | Name and contact information for the trial sponsor | _Page 1 Line 22_ |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | Page 21 Line 407 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | Page 21 Line 407 |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | Page 7 Line 137 |
| | 6b | Explanation for choice of comparators | *N/A* |
| Objectives | 7 | Specific objectives or hypotheses | Page 9 Line 163 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | Page 9 Line 170 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | Page 9 Line 176 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | Page 10 Line 188 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | Page 11 Line 190 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | Page 18 Line 343 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | Page 19 Line 358 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | As listed on each drug label |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | Page 14 Line 265 |

| | | | |
|---|---|---|---|
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | Figure 3 |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | Page 15 Line 282 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | Page 13 Line 249 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | N/A |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | N/A |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | N/A |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | N/A |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | N/A |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | Protocol Page 81 |

| | | | |
|---|---|---|---|
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | Page 14 Line 259 |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | Protocol Page 73 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | Protocol Page 73 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | Page 15 Line 282 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | Page 15 Line 282 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | N/A Pragmatic Trial - Safety of Interventions is Established |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | N/A |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | Protocol Page 66 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | Protocol Page 81 |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | Page 16 Line 309 |

| | | | |
|---|---|---|---|
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | Updates to ClinicalTrials.gov |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | Page 15 Line 293 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | N/A |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | Page 15 Line 299 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | Page 21 Line 402 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | Page 17 Line 318 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | N/A |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | Protocol page 84 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | Protocol page 84 |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | Not yet determined |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | Protocol Page 107 |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | N/A |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. 

BMJ Open

# A Study Protocol for the Hummingbird Study, a Multicenter Exploratory Trial to Assess the Acceptance and Performance of a Digital Medicine System in Adults With Schizophrenia, Schizoaffective Disorder, or First-Episode Psychosis



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2018-025952.R3 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 05-Jun-2019 |
| Complete List of Authors: | Fowler, J.; Otsuka Pharmaceutical Development & Commercialization, Inc.,<br>Cope, Nathan; Otsuka Pharmaceutical Europe Ltd.<br>Knights, Jonathan; Otsuka Pharmaceutical Development & Commercialization, Inc.<br>Phiri, Peter; Southern Health NHS Foundation Trust<br>Makin, Andrew; Otsuka Europe Development and Commercialisation Ltd.<br>Peters-Strickland, Tim; Otsuka Pharmaceutical Development & Commercialization, Inc.<br>Rathod, Shanaya; Southern Health NHS Foundation Trust, Psychiatry |
| Primary Subject Heading: | Mental health |
| Secondary Subject Heading: | Evidence based practice |
| Keywords: | Coproduction, digital medicine, schizoaffective disorder, schizophrenia |
| | |

# A Study Protocol for the Hummingbird Study, a Multicenter Exploratory Trial to Assess the Acceptance and Performance of a Digital Medicine System in Adults With Schizophrenia, Schizoaffective Disorder, or First-Episode Psychosis

Running title: Study protocol for DMS use in schizophrenia in the UK

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Word count (max 4000 for BMJ Open): 3988 (Intro through conclusion, not including table)

Table count: 1

Figure count: 3 (+6 supplemental)

Reference count: 31

# ABSTRACT

**Introduction** In patients with schizophrenia, medication adherence is important for relapse prevention, and effective adherence monitoring is essential for treatment planning. A digital medicine system (DMS) has been developed to objectively monitor patient adherence and support clinical decision-making regarding treatment choices. This study assesses the acceptance and performance of the DMS in adults with schizophrenia, schizoaffective disorder, or first-episode psychosis and in healthcare professionals (HCPs).

**Methods/ analysis** This is a multicenter, 8-week, single-arm, open-label pragmatic trial designed using coproduction methodology. The study will be conducted at 5 National Health Service Foundation Trusts in the United Kingdom. Patients 18 to 65 years old with a diagnosis of schizophrenia, schizoaffective disorder, or first-episode psychosis will be eligible. HCPs (psychiatrists, care coordinators, nurses, pharmacists) researchers, information governance (IG) personnel, Clinical Commissioning Groups (CCGs), and patients participated in study design and coproduction. Intervention employed will be the DMS an integrated system comprising an oral sensor tablet co-encapsulated with an antipsychotic, nonmedicated wearable patch, mobile application (app), and Web-based dashboard. The co-encapsulation product contains aripiprazole, olanzapine, quetiapine, or risperidone, as prescribed by the HCP, with a miniature ingestible event marker (IEM) in tablet. Upon ingestion, the IEM transmits a signal to the patch, which collects ingestion and physical activity data for processing on the patient's smartphone or tablet before transmission to a cloud-based server for viewing by patients, caregivers, and HCPs on secure web portals or mobile apps.

**Ethics and Dissemination** Approval granted by the ethics committee of London-City & East Research Ethics Committee (REC Ref no. 18/LO/0128), and clinical trial authorization was provided by the Medicines and Healthcare products Regulatory Agency. Written informed consent will be obtained from every participant. The trial will be compliant with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines and Declaration of Helsinki.

ClinicalTrials.gov: NCT03568500; EudraCT 2017-004602-17

## Keywords

Coproduction, digital medicine, schizoaffective disorder, schizophrenia

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study was codeveloped with input from clinical practitioners, researchers, patients, caregivers, service managers, IG teams, and clinical commissioning groups to obtain information that will best serve all those involved in the treatment and care of patients with schizophrenia, schizoaffective disorder, and first-episode psychosis.
- The digital medicine system (DMS) uses an integrated, user-friendly system to provide objective feedback on patient medication adherence and physical health parameters, such as activity and rest levels, as well as voluntary subjective entries regarding mood and rest quality, to help support treatment decisions and evaluation.
- Information from the DMS is made readily available to patients, caregivers (with the patient's consent), and physicians to support clinical decision making, proactive intervention, and individualized care in near to real time.

- Possible limitations of this study are the small sample size (N=60), limited generalizability to the broader pool of UK mental health patients and providers, and the relatively short 12-week timeframe.
- The DMS was not developed for all mental health patients, but for a subset of patients who realize they have difficulty with adherence and want to improve their status by self-monitoring with potential for their HCP's to make better clinical decisions based on objective data from the DMS.

# INTRODUCTION

Schizophrenia has an enormous social and economic burden worldwide, accounting for 1.1% of total disability-adjusted life-years and 2.7% of years lived with disability [1, 2]. In Europe, the economic impact of schizophrenia and other psychotic disorders and syndromes in 2010 was estimated at €93.9 billion [3]. Because schizophrenia is a chronic disease, maintenance treatment is often necessary to prevent relapse and preserve quality of life over the long term [4, 5]. Although antipsychotic medications are effective [6-8], poor insight into schizophrenia can increase risk of medication nonadherence [9, 10]. In patients with schizophrenia, the rate of nonadherence to prescribed antipsychotics has been reported to be as high as 74% [11]. Not only is medication nonadherence burdensome to patients and their families, it also increases the likelihood of rehospitalization and relapse [12] and contributes substantially to healthcare costs [13]. In 2005/2006, mean annual psychiatric inpatient and medication costs for patients with schizophrenia in England were estimated to be approximately £3,000 and £2,000 per patient, respectively [14].

Because medication adherence is important to relapse prevention in schizophrenia [15], effective adherence monitoring is an essential part of the treatment plan. Although there are various subjective methods for determining medication adherence, including patient surveys, adherence diaries, and clinician ratings of patient symptoms and medication side effects, these methods have low validity [16]. Blister packs and electronic medication bottle caps can provide an indicator of pill removal or bottle opening and have been shown to improve adherence [17, 18], but neither technology provides an objective marker of pill ingestion or supports remote monitoring by healthcare professionals (HCPs). Optimal adherence monitoring and support for

patients with schizophrenia requires a system that provides physicians with objective information during interim periods between patient visits.

The use of modern technology such as personal digital assistants [19], digital wristwatches [20], handheld computers [21], and mobile phones [22] to help people with schizophrenia dealing with their disease has shown success. A digital medicine system (DMS) has been developed as a drug-device combination to objectively assess and report ingestion of prescription antipsychotics [23]. The DMS has 4 main components: an ingestible sensor embedded within an inert tablet, a nonmedicated wearable sensor (patch) worn by the patient, a mobile application (app), and a Web-based dashboard [23]. Upon interaction with stomach fluids, the ingestible sensor is activated and communicates with the wearable sensor, which sends a signal to a Bluetooth-paired mobile device where it can be viewed by patients or be subsequently viewed by HCPs and caregivers using secure mobile- and cloud-based software [23]. The DMS also enables patients to share data on their activity and rest levels as well as subjective data on mood and rest quality, which can be generated while the patient is engaged with the system. The intention of the DMS is to encourage greater patient self-management and behavior change while enabling caregivers and HCPs to provide better care and support both within and outside of office visits, further engaging patients in their ongoing disease management. The data is communicated to the psychiatrist that is connected to the patient on the MyCite platform. Additionally, should the patient choose to share their data, they are able to invite additional healthcare providers, caregivers and/or family or friends. Recipients of the data, through a web-based password protected platform, are able to view this data and assist the patient with their treatment plan, however HCPs can only access the portal for a specific patient once he/she has consented to give them access to their information in the system. It is envisioned that HCPs will be able to use this

data to make more informed clinical decisions such as whether individuals need dose adjustment, medication changes or conversations on lifestyle, adherence or other parameters.

Previous results in the USA have shown in an open-label, 8-week study, 78% (47/60) of patients and 72% (43/60) of HCPs reported being somewhat satisfied, satisfied, or extremely satisfied with the DMS [24]. Findings from another open-label study showed patients to be actively involved in their treatment, with 73.5% (36/49) utilizing call centers for technological DMS support [25]; the rate of ingestion adherence in this study for the 15 patients with schizophrenia was 85.6% [25].

The DMS from the current study (namely the ingestible sensor and the wearable sensor) are Conformité Européene (CE)–marked for use in Europe as class IIa medical devices (CE 559373), but studies in European mental health populations have not been performed. Therefore, the objective of this exploratory study is to assess the acceptance and performance of the DMS among adult patients with schizophrenia, schizoaffective disorder, or first-episode psychosis and among HCPs from different care settings in the United Kingdom. We are particularly interested in assessing the acceptance of the digital medicine technology in individuals from different care settings. Acceptance will be assessed by study completion and, feedback from subjects from patient satisfaction surveys. Furthermore, acceptance will also be evaluated by healthcare providers using the system; this will be assessed by how their clinical decisions altered whilst using the system and through HCP Utility questionnaire evaluations.

In respect to performance, the study will be assessing multiple hardware and software from a varied population. Based on operational feedback of different phones and OS and any technical troubleshooting that occurs, the study will be able to determine areas of the app that need to be enhanced to ensure that the app functions across multiple hardware and operating systems.

Previous studies performed using the DMS were conducted in relatively stable individuals with schizophrenia. For this study, we have broadened the inclusion criteria and will be assessing the technology in a range of clinical groups from different care settings, such as those individuals managed in the community or on specialized services such as Early Intervention in Psychosis services to determine the performance in these different environments.

The study is not intended to measure and report or make any claims of adherence, but instead, to report the observed ingestions recorded by the DMS. Our goal is to look at the impact of patients' improvements as a result of participation (e.g. reduced need for follow-up care, knowledge of adherence to medication to help physicians decide whether patients are medication compliant or require a long acting injectable or other follow-up care) with the hypothesis that DMS will reduce overall healthcare utilization burden by optimizing treatment decisions.

## METHODS AND ANALYSIS

### Study design

This is a multicenter, 8-week, single-arm, open-label trial to evaluate the acceptance and performance of the DMS in adult patients with schizophrenia, schizoaffective disorder, or first-episode psychosis on an oral atypical antipsychotic medication (aripiprazole, olanzapine, quetiapine, or risperidone) and in HCPs. Recruitment began the same day that we submitted to CT.gov, 25/MAY. However, we didn't consent our first patient until 11/JUN and dosing occurred on 18/JUN. The study will take place at 5 institutions in the United Kingdom: Northumberland, Tyne and Wear National Health Service (NHS) Foundation Trust, Surrey and Borders Partnership NHS Foundation Trust, Oxford Health NHS Foundation Trust, South London and Maudsley NHS Foundation Trust, and Southern Health NHS Foundation Trust. The

first patient's first visit occurred in May 2018. Patient recruitment will be targeted to last approximately 4 months.

## Patient selection

Patients for this exploratory study will be identified using database searches conducted at each study site per HCP discretion. Inclusion and exclusion criteria are provided in **Table 1**. The degree of clinical stability will be varied across participants that enroll. In short, a fully stable patient population will not be actively recruited, instead a range of clinical populations (crudely based on Clinical Global Impression – Severity scale (CGI-S)) from different care settings will participate.

**Table 1. Inclusion and Exclusion Criteria**

| **Inclusion criteria** |
|---|
| • Willing and able to give written informed consent and adhere to trial procedures<br>• Able to read and understand English<br>• Age 18–65 years at the time of informed consent<br>• Possessing a smartphone and able to use it to interact with the digital medicine system (DMS) application **through robust and dependable cellular or wireless internet connections (Subjects should have WiFi at home and/or at work, or at the very least have access to free WiFi hot spots. Alternatively, subjects should have a sufficient data plan from their mobile provider and/or coverage on their phone. Such assessments are made during the screening of potential subjects.)**<br>• Cooperative, able to ingest oral medication, willing to complete aspects of the trial, and capable of reporting adverse events (AEs)<br>• Clinical diagnosis of schizophrenia, schizoaffective disorder (defined by International Classification of Diseases, Tenth Revision, codes F20 and F25), or first-episode psychosis based on case note review<br>• Prescription for aripiprazole, olanzapine, quetiapine, or risperidone<br>• Fulfills ≥1 of the following:<br>  ○ Discharge from a hospital admission (within 7 days of discharge) to an acute intervention team<br>  ○ Referral to an acute intervention team before hospital admission<br>  ○ Referral from an acute intervention team to a community team<br>  ○ Managed by community services<br>  ○ Inclusion within early intervention caseload (<3 years from initial symptoms)<br>  ○ Healthcare professional (HCP) determines the patient would benefit<br>• General medical condition does not pose additional risk |

| |
|---|
| • Skin on the anterior chest above the lower edge of the rib cage is free of any dermatologic problem |
| **Exclusion criteria** |
| • Any disorder that may affect patient's ability to participate in the trial or interact with a smartphone<br>• Likely to be incapable of using DMS technology, even with assistance<br>• History or evidence of a medical condition that would expose patient to undue risk of an AE<br>• Known allergy to adhesive tape or any component of the patch or co-encapsulation product<br>• Current incarceration in prison system<br>• Hospitalization at the time of screening due to mental or physical illness<br>• HCP recommendation to not participate<br>• Aversion to taking gelatin capsules<br>• Women who are breastfeeding, pregnant, or plan to become pregnant |

## Intervention

The DMS is an integrated, 4-component system comprising an oral co-encapsulation (CoE) pharmacologic sensor tablet, a Proteus® Patch, a mobile app, and Otsuka Medical dashboard software (**Figure 1**). Each CoE product contains an approved antipsychotic medication (aripiprazole, olanzapine, quetiapine, or risperidone) encapsulated with a miniature ingestible event marker (IEM) in tablet. HCPs will select the medication and dosage based on each patient's needs. Upon taking the medication, the IEM transmits a signal to the nonmedicated patch that is attached to the patient's skin. The patch collects IEM ingestion and physical activity data, which are then processed by the Patch Analytics Block on the patient's smartphone. Processed data are transferred through the app on the smartphone and sent to a cloud-based server for patient, caregiver, and HCP viewing on Otsuka Medical software through web portals or mobile apps. Patients will have access to the Otsuka Patient Application, caregivers will have

access (with patient consent) to the Otsuka Caregiver Web Portal, and HCPs will have access to the Otsuka Healthcare Provider Web Portal.

## Patient and Public Involvement Statement

### Coproduction

This study was designed using coproduction methodology involving NHS staff and patients (**Figure 2**). Coproduction in this protocol is the involvement of people with lived experience of mental illness (diagnosed or otherwise) as equal partners alongside other healthcare stakeholders, in the design and contribution to the protocol. The lead site, Southern Health NHS Foundation Trust, held 5 coproduction workshops, and a subset of these workshops was repeated at other study sites to elicit feedback on the study design. At least 2 of these workshops involved patients. The discussions from the workshops addressed pharmacy items for the CoE product; HCP recruitment strategies; and protocols for identification, recruitment, and interactions with suitable patients and their general practitioners. Throughout the various workshops at the different sites, participants included clinicians, pharmacists, researchers, IG personnel (refers to the way in which the NHS handles, stores and processes information, in particular personal and sensitive information relating to patients and employees; it was vital to ensure that IG individuals were happy with the privacy and storage features of the digital medicine system), psychiatrists, care coordinators, nurses, information technology personnel, CCGs (clinically led groups within the NHS that are responsible for the planning and commissioning of healthcare services for their local area), and patients (**Figure 2**).

## Patient Involvement

The Patient and Public Involvement and Service User Lead from 2 study sites (Surrey and Borders Partnership NHS Foundation Trust and Northumberland, Tyne, and Wear NHS Foundation Trust) engaged service users to participate in a patient focus group. The objective of the focus groups was to obtain feedback on the app technology and assess the completion of specific app tasks. The groups identified issues that may have prevented the completion of key tasks and whether greater explanation would be needed, for instance in ensuring the app could send notifications to patients. Furthermore, general feedback on colour and language was also obtained.

## Procedures

The study will comprise 3 phases: a screening phase of up to 7 days, an 8-week assessment phase, and a 2-week safety follow-up (**Figure 3**). Screening and baseline may occur at a single visit or at 2 visits separated by up to 7 days. At the screening/baseline visit, patients providing informed consent will receive patches, CoE product, and other supplies and undergo training by the HCPs on required and correct use of the DMS. HCPs will confirm proper patch application to the skin and pairing of the patch with the smartphone app when patients commence their usage of the digital medicine system, so called on boarding. These individuals will either be psychiatrists or research assistants for the site. During time in-between the only required site visits at weeks 4 and 8, patients will perform patch changing themselves and be guided, if required, through videos contained within the app. There is a freephone technical support line to assist individuals should they wish. Patients will be instructed to wear the patch continuously, replacing it every 7 days or as needed during the assessment period. An integrated call center will be available to patients for technical support regarding use of the DMS.

During the subsequent 8-week assessment period, patients will visit their HCP at weeks 4 and 8 (or at early termination) for clinical evaluation and review of DMS data. At the week 4 visit, patients will also obtain a prescription refill. HCPs will be required to monitor and review DMS data at least every 2 weeks, with the option of requesting additional patient visits as needed. HCPs will also have the ability to modify the patient's treatment plan at their discretion. Safety and tolerability will be assessed on an ongoing basis throughout the assessment period and during the subsequent 2-week safety follow-up, during which time a follow-up telephone call will be made to each study participant.

Healthcare utilization record evaluation will occur continuously beginning at the baseline/screening visit and will span a period ranging from 24 weeks before baseline/screening to 24 weeks after screening. All hospital admissions will be recorded and categorized as "planned," "unplanned," "related," or "unrelated" to psychiatric illness. Characteristics of each HCP encounter will also be recorded, including the nature of the contact; HCP role; whether the visit was planned or unplanned; whether or not the contact was initiated as a result of the DMS; and any medication titration, adherence counseling, education, or lifestyle coaching that occurred.

## Outcomes

The primary endpoint is the proportion of days with good patch coverage during the assessment period, which will be defined as having ≥80% patch data available or IEMs detected within each day of the assessment period. The secondary endpoint is ingestion adherence, defined as the proportion of detected IEMs to the total expected IEMs ingested on the assessment days that showed good patch coverage.

The following exploratory endpoints will also be included:

- The proportion of time during the assessment period that patients wear their patch
- Engagement and satisfaction of patients, HCPs, and caregivers as determined using the Subject Usability and Satisfaction Scale (**Supplemental Figure 1**), the Physician Utility Survey (**Supplemental Figure 2**), and the Caregiver/Support Person Involvement Scale (**Supplemental Figure 3**)
- Personal and social functioning as assessed using the Personal and Social Performance Scale (**Supplemental Figure 4**)
- Patient activation as assessed using the Patient Activation Measure-Mental Health Scale (**Supplemental Figure 5**)
- The proportion of days that patients and HCPs use the app and dashboard, respectively
- The proportion of ingested IEM tablets registered on the digital health data server of the total expected IEM tablets ingested
- Safety variables will include the frequency and severity of serious adverse events and device-related nonserious adverse events, suicidality, and any product quality complaints that may arise. Suicidality will be determined by face-to-face risk assessment according to each study site's standard operating procedure.

## Statistical analysis

A sample size of 60 patients was determined based on an anticipated 25% discontinuation rate, such that ≥45 patients would complete the 8-week assessment period. The study described is a feasibility study with no comparisons and no formal power calculations. The sample size was chosen to contain roughly 20 patients per indication and align with historical studies performed

in the USA. The discontinuation rate is assumed based on similar discontinuations for other psychiatry studies and the fact that an actively clinical stable population is not being recruited. Data will be analyzed in the intent-to-treat population (ie, all patients who enter the trial and use the DMS). All data will be analyzed using descriptive statistics. Continuous variables will be summarized using mean, median, range, and standard deviation. Categorical variables will be summarized using frequency distributions.

## Data protection

Before initiating participation, informed consent will be obtained from all patients and caregivers. Health information will be de-identified to the fullest possible extent. However, some identifiers or sensitive health information cannot be stripped (eg, psychiatric medical history, participation in a care program approach, presence of a community treatment order, employment status, disabilities, housing arrangements, or armed forces history). Health information will be used to develop and improve the DMS application and user experience. The DMS and associated third-party vendors are compliant with the General Data Protection Regulation (GDPR), and all accessed health information will be maintained in the strictest confidence and in compliance with the GDPR. Data from the DMS are encrypted in activity and rest and will be accessed only by role-specific individuals for discrete time periods and functions (eg, technical troubleshooting). All data will be completely anonymized for graphical, statistical, and publication purposes.

Research staff from NHS sites will store consent documents, demographic forms, and receipts for reimbursement of travel in locked filing cabinets to which only research staff will have access. Accessing of health data will be compliant with IG policies of each participating NHS trust.

## Ethical considerations

Ethics approval for this study was obtained from London - City & East Research Ethics Committee (REC Ref no. 18/LO/0128), and clinical trial authorization was provided by the Medicines and Healthcare products Regulatory Agency. Written informed consent will be obtained from every participant. Ethical issues will be related to the identification and recruitment of patients, informed consent, and data protection arrangements. The trial will be conducted in compliance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines and Declaration of Helsinki.

## Dissemination of study results

The study results will be disseminated through peer-reviewed publications, national and international conference presentations, and formal clinical trial repositories (eg, ClinicalTrials.gov). The 5 participating NHS sites will be invited to a results launch event. Results will be shared with individuals who participated in the workshops via the respective trusts. Additionally, follow-up workshops are planned to capture further feedback on next steps for scaling the DMS technology.

# DISCUSSION

Patient adherence to antipsychotic medication is a crucial component of successful maintenance therapy for schizophrenia. Knowledge of patient adherence in the absence of positive treatment outcome is also essential. Subjective means for assessing medication adherence such as clinician evaluation and patient self-report have low validity [16], and most can only be administered during patient-HCP visits. Digital medicine offers a means to monitor patient adherence and obtain objective data throughout treatment, including periods between office visits, which may

yield more accurate data. For example, a study evaluating nonadherence rates for antipsychotic medication based on electronic medication bottle caps, which report when pill bottles have been opened [18], showed a 57% nonadherence rate, much higher than that estimated by patient (5%) and provider (7%) report [18]. Electronic medication bottle caps are used as the current gold-standard surrogate for 'objective' adherence data. Few reports in this space exist and the need for more robust objective adherence data is supported through this discrepancy and the limitations of electronic medication bottle caps as an 'objective' measure, given it only measures an intermediate step in the ingestion process. This study shows the potential of digital medicine to provide continuous objective data that can inform and improve patient adherence and assist in clinical decision making. The DMS improves upon approaches such as electronic medication caps by providing an objective marker of ingestion and not merely a surrogate in addition to other objective and subjective data.

Patient discontinuation is a considerable problem in studies of digital health technology [26]. Studies of early digital health systems for maintenance and counseling of mental disorders reported low completion rates. For example, a study evaluating a 12-week web-based cognitive behavioral therapy intervention for panic disorder had a 1% (12/1161) completion rate [27], and a study evaluating a publicly accessible 5-module web-based cognitive behavioral therapy program for anxiety and depression had a 0.5% completion rate (97/19,607) [28]. Completion rates may be particularly low in patients with more severe negative symptoms [22]. Despite these historically poor completion rates in studies of digital health platforms, results of a meta-analysis indicate that more than 50% of patients favor managing their mental health through the use of mobile health technology [29], and the use of mobile devices for health management is viewed by patients as normalized and nonstigmatizing [30]. The integrated DMS described here was

developed to leverage the advantages of digital technology to positively influence adherence in patients with schizophrenia.

The DMS is a multimodal, user-friendly system that provides medication reminders and measures patient ingestion of prescribed antipsychotic medications. The CoE product, in particular, advances the ability to confirm medication ingestion and to assess adherence on a continuous basis, which can inform whether uncontrolled symptoms may be explained by nonadherence. Information from the DMS is made readily available to patients, caregivers (with the patient's consent), and physicians for supported decision making, proactive intervention, and individualized care. DMS also provides adherence feedback electronically to the patient, HCP, and/or caregiver. The DMS provides this feedback discreetly, through user-owned and operated applications and a patch that is not readily visible as it is worn on the torso underneath clothing, reducing any potential stigmatization if it (the patch) was visible. The DMS also provides feedback on activity and rest levels, which is important given that maintenance of a healthy lifestyle can help address the problems of weight gain and obesity that are related to both medication side effects and sedentary lifestyles [31]. Furthermore, shifts in activity levels may be indicative of altered patient disposition.

This ongoing study was designed using coproduction methodology to incorporate input from patients, caregivers, psychiatrists, pharmacists, nurses, and researchers. For all 5 study sites, a minimum of 2 engagement/setup meetings were conducted and 2 specific patient focus groups were held to guide protocol development and app design. Although a PRECIS-2 assessment tool was not used during the design of the study the authors feel that based on a retrospective PRECIS-2 analysis (refer to supplemental materials for this analysis) this study does meet the criteria for a pragmatic study. The exploratory data collected in this study, although limited to a

small number of patients, will help provide a better understanding of the ease of use for patients, HCPs, and caregivers to inform the development of future software or hardware iterations.

Given the level of unfamiliarity with digital medicine systems, conducting clinical trials in this space requires a higher level of stakeholder management and alignment, especially when the trial is being held in a new environment. Whether it's a new country, a new healthcare system, or a new set of investigators, formal buy-in and input is critical to participation. The protocol outlines one way of managing and aligning stakeholders in such an environment - the UK mental health system. Additionally, and increasingly important within mental health services and interventions in the UK, is the involvement of end–users, so called service users who have lived experience of mental health. The methods paper describes a robust engagement strategy using such individuals in mental health research.

Digital health interventions require significant clinician and patient engagement. The protocol describes an approach to ensure that service users of a digital medicine intervention can assist with protocol design and system input e.g. approach and appropriate language

## CONCLUSION

In conclusion, this study will examine the usability and acceptance of the DMS by patients with schizophrenia, schizoaffective disorder, or first-episode psychosis, and by caregivers and HCPs in different care settings. The study was coproduced through the engagement of all stakeholders and, if successful, could be used to support DMS usage in larger cohorts within the United Kingdom and Europe.

## Funding statement

This study is supported by Otsuka Pharmaceutical Development & Commercialization, Inc.

Editorial support for development of this manuscript was provided by Eric Comeau, PhD, at C4 MedSolutions, LLC (Yardley, PA), a CHC Group company, and funded by Otsuka Pharmaceutical Development & Commercialization, Inc.

## Competing interests statement

Dr J. Corey Fowler, Dr Jonathan Knights, and Dr Tim Peters-Strickland are employees of Otsuka Pharmaceutical Development & Commercialization. Dr Nathan Cope is an employee of Otsuka Pharmaceutical Europe Ltd. Dr Andrew Makin is an employee of Otsuka Europe Development and Commercialisation. Dr Peter Phiri has no conflict of interest. Dr Shanaya Rathod has received honoraria from Otsuka and Lundbeck for educational sessions.

## Author contributions

JCF, NC, JK, PP, AM, TP-S and SR contributed to study conception and design as well as data collection, analysis, and interpretation; JCF, NC, JK, PP, AM, TP-S and SR were responsible for review and critical revision of the manuscript; and JCF, NC, JK, PP, AM, TP-S and SR gave final approval to submit for publication.

## Acknowledgements

The authors thank patient advisers and NHS staff from all 5 participating sites (Oxford Health NHS Foundation Trust; Northumberland, Tyne and Wear NHS Foundation Trust; Southern Health NHS Foundation Trust; South London and Maudsley NHS Foundation Trust; and Surrey and Borders Partnership NHS Foundation Trust) for their contributions to the study methodology. Editorial support for development of this manuscript was provided by Eric

Comeau at C4 MedSolutions, LLC (Yardley, PA, USA), a CHC Group company, and funded by Otsuka Pharmaceutical Development & Commercialization, Inc.

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## Figure Legends

**Figure 1.** Digital medicine system: co-encapsulated antipsychotic medication with miniature ingestible event marker in tablet (MIT) and compatible medical device. DM=digital medicine; HCP=healthcare professional. Image reprinted from article in npg Digital Medicine [In Press].

**Figure 2.** Description of coproduction workshops with Southern Health NHS Foundation Trust. DMS=digital medicine system; EIP=Early Intervention in Psychosis; IG=information governance; MoSCoW=must have, should have, could have, won't have; NHS=National Health Service; PANSS=Positive and Negative Syndrome Scale; PPI=Patient and Public Involvement program.

**Figure 3**. Study design.

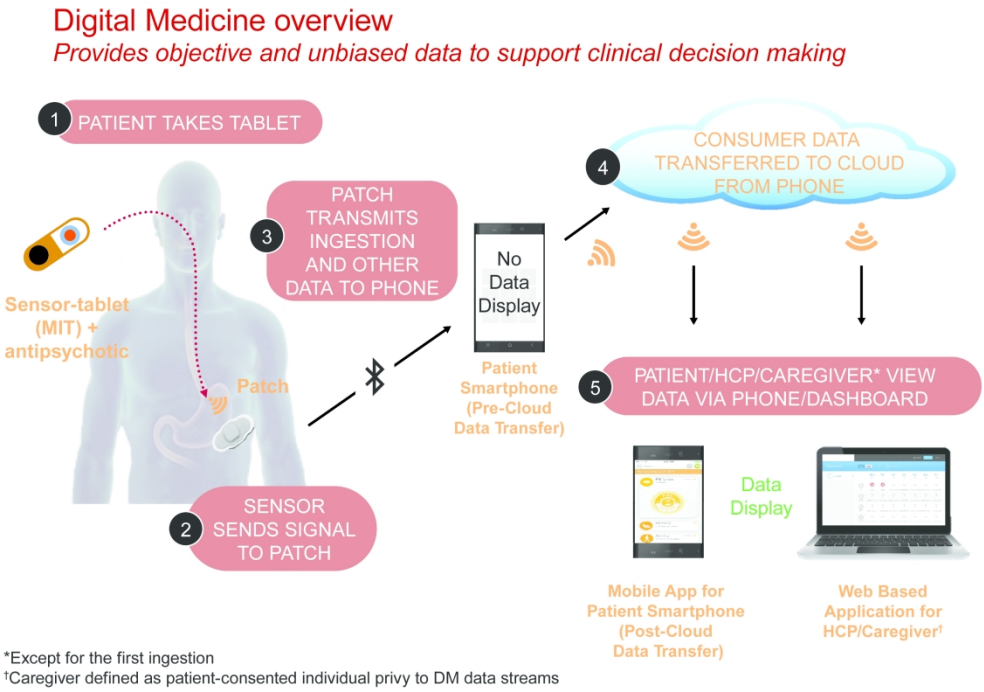



Figure 1. Digital medicine system: co-encapsulated antipsychotic medication with miniature ingestible event marker in tablet (MIT) and compatible medical device. DM=digital medicine; HCP=healthcare professional.

254x177mm (300 x 300 DPI)

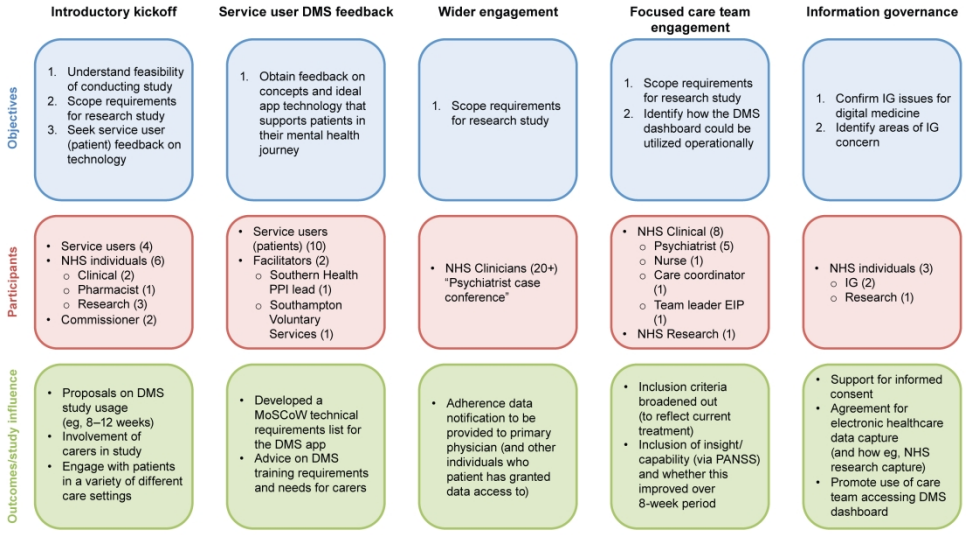
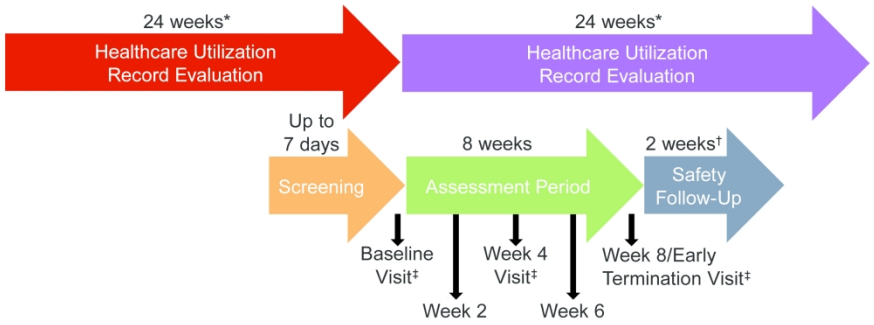



Figure 2. Description of coproduction workshops with Southern Health NHS Foundation Trust. DMS=digital medicine system; EIP=Early Intervention in Psychosis; IG=information governance; MoSCoW=must have, should have, could have, won't have; NHS=National Health Service; PANSS=Positive and Negative Syndrome Scale; PPI=Patient and Public Involvement program.

317x184mm (300 x 300 DPI)




Healthcare professionals (HCPs) will review dashboard at weeks 2, 4, 6, and 8 and make treatment changes at their discretion.
*Healthcare utilization will be recorded 24 weeks before and after baseline visit (for a total of 48 weeks).
†Safety follow-up phone call will occur 2 weeks after week 8/early termination visit.
‡Patient visits will occur at baseline, week 4, and week 8/early termination. Other visits will be at the discretion of the HCP.

Figure 3. Study design.

241x108mm (300 x 300 DPI)

# Supplementary Material

## Supplemental Figure 1. Subject Usability and Satisfaction Scale (Ver 2.0)

**Section A: Usability**

**1. How easy or difficult was it for you to apply the patch on your body?**

| Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**2. How easy or difficult was it to pair the patch with the mobile phone application (app)?**

| Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**3. How easy or difficult was it for you to use the mobile phone application (app)?**

| Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**4. How easy or difficult was it for you to use the Digital Medicine System?**

| Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**5. How well do you agree with the following statement?**

- **In general, I did not mind wearing the patch.**

| Strongly Disagree | Disagree | Somewhat Disagree | Neutral | Somewhat Agree | Agree | Strongly Agree |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | |

**6. Since your last visit, did you receive assistance when changing and pairing the required patches? Yes No**

If yes,

| | Never | Once a month or less | A few times a month | Once a week | A few times a week | Daily |
|---|---|---|---|---|---|---|
| How much assistance did you receive when applying the patches? | | | | | | |
| How much assistance did you receive when syncing the technology? | | | | | | |

If you did receive any help or assistance, who helped or assisted you?
(please place a √ [check] to indicate who helped or assisted you)

| Friend | Hired Caregiver | Relative* | Other** |
|---|---|---|---|
| | | | |

*If a relative helped or assisted you, then please specify their relationship to you (such as wife, husband, father, mother, sister, brother, or whatever else you think is the most appropriate description of the relative who helped you): _____

**If you selected "Other", please specify your relationship to the person who helped you _____

## Section B: Satisfaction

**7. How easy or difficult was it for you to use the entire Digital Medicine System, which includes the patch, pills, and mobile phone application (app)?**

| Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

8. **How helpful or unhelpful was the Digital Medicine System in the management of your condition?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

9. **How helpful or unhelpful was the Digital Medicine System for sharing information with your healthcare professionals to help you understand your treatment plan?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

10. **How helpful or unhelpful was the Digital Medicine System in improving your discussions with your doctor / treatment team?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

11. **Based on your experience, how would you rate your satisfaction with the Digital Medicine System?**

| Extremely Dissatisfied | Dissatisfied | Somewhat Dissatisfied | Neutral | Somewhat Satisfied | Satisfied | Extremely Satisfied |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

12. **How likely would you be to use the Digital Medicine System in the future, if it were available and recommended by your doctor?**

| Extremely Unlikely | Unlikely | Somewhat Unlikely | Neutral | Somewhat Likely | Likely | Extremely Likely |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**Supplemental Figure 2. Physician Utility Survey (Ver 2.0)**

*We ask the Principal Investigator, Physician Investigator, and Trial Coordinator(s) at a clinical site/trust to complete this survey for each patient enrolled. Please answer the below questions based on your overall experience using DMS.*

1. **How easy or difficult was it for you and your patient to apply the patch on the patient's body?**

| | Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| For you | | | | | | | |
| For your patient | | | | | | | |

2. **How easy or difficult was it for you and your patient to sync the patch with the mobile phone application (app)?**

| | Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| For you | | | | | | | |
| For your patient | | | | | | | |

3. **How easy or difficult was it for you and your patient to complete the overall onboarding for the Digital Medicine System?**

| | Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| For you | | | | | | | |
| For your patient | | | | | | | |

4. **Overall, how easy or difficult was it for you and your patient to use the mobile phone application (app)?**

| | Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| For you | | | | | | | |
| For your patient | | | | | | | |

5. **Overall, how easy or difficult was it for you and your patient to use the entire Digital Medicine System, which includes the patch, pills, and mobile phone application (app)?**

| | Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| For you | | | | | | | |
| For your patient | | | | | | | |

6. **How easy or difficult was it for you to use the HCP dashboard?**

| Extremely Difficult | Difficult | Somewhat Difficult | Neutral | Somewhat Easy | Easy | Extremely Easy |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**7. If you were in routine clinical practice (ie, in clinical practice without a study protocol), how helpful or unhelpful do you think the Digital Medicine System could be for the following elements of clinical management for this specific patient?**

| | Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Assessment | | | | | | | |
| Clinical Advice/ Recommendations | | | | | | | |
| Treatment Decisions | | | | | | | |

**8. How effective was the Digital Medicine System in aiding decision-making for medication adherence?**

| Extremely Not Effective | Not Effective to Use | Somewhat Not Effective to Use | Neutral | Somewhat Effective to Use | Effective to Use | Extremely Effective to Use |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**9. How helpful or unhelpful was the Digital Medicine System in providing a way to better engage your patients in self-management of their condition?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**10. How helpful or unhelpful was the Digital Medicine System in improving quality of care for your patient?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**11. How helpful or unhelpful was the Digital Medicine System in improving your conversations with your patient about their treatment plan and progress?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**12. How helpful or unhelpful was the Digital Medicine System in the identification of potential lifestyle changes for your patient (eg sleep and exercise)?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**13. Other than during the patient visit(s), did you look at the HCP dashboard at other times? Please select all that apply**

| | Place a √ (check) next to the time you referred to the HCP dashboard |
|---|---|
| No, only during the patient visit | |
| Prior to patient visit (same day as visit) | |
| In between visits | |
| Other: *Please Specify:* _____ | |

**14. What features did you find helpful? Please select all that apply**

| | Place a √ (check) next to the features you found helpful | For the features you have selected, please rank these features from 1 (most helpful) to 7 (least helpful) in order of helpfulness |
|---|---|---|
| Pill ingestion data | | |
| Patient reported reason code for missed doses | | |
| Multiple dose alerts | | |
| Missed dose alerts | | |
| Activity | | |
| Rest | | |
| Patient reported rest quality rating | | |
| Other: *Please Specify:* _____ | | |

**15. Did you set up alerts to be notified of missed doses? Yes/no**

**a. If yes, based on your overall experience, how helpful were the missed dose alerts?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful | Not Applicable – No alerts received |
|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | |
| | | | | | | | |

15a. If you received a missed dose alert what action did you take, if any? (If none, please write N/A) _____

**16. Did you set up alerts to be notified of multiple doses? Yes/no**

**a. If yes, based on your overall experience, how helpful were the multiple dose alerts?**

| Extremely Unhelpful | Unhelpful | Somewhat Unhelpful | Neutral | Somewhat Helpful | Helpful | Extremely Helpful | Not Applicable – No alerts received |
|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | |
| | | | | | | | |

16a. If you received a multiple dose alert what action did you take, if any? (If none, please write N/A _____

**17. How well do you agree with the following statement?**

**a. Overall, the Digital Medicine System adds value to my practice.**

| Strongly Disagree | Disagree | Somewhat Disagree | Neutral | Somewhat Agree | Agree | Strongly Agree |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**18. Based on your overall experience with this patient, how would you rate your satisfaction with the Digital Medicine System?**

| Extremely Dissatisfied | Dissatisfied | Somewhat Dissatisfied | Neutral | Somewhat Satisfied | Satisfied | Extremely Satisfied |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| | | | | | | |

**Supplemental Figure 3. Caregiver/Support Person Involvement Scale (Ver 2.0)**

**DMS Caregiver/Support Person Involvement Scale**

**1. Are you aware that the study participant/patient is currently participating in the Digital Medicine study (check one)?**

| Yes | No* |
|---|---|
| | |

***If no, stop here and do not answer the rest of the questions on this form.**

**2. Indicate your relationship to the study participant/patient by placing a √ (check).**

| Friend | Hired Caregiver | Relative* | Other** |
|---|---|---|---|
| | | | |

***If you are a relative, please specify relationship to the study participant/patient, e.g., wife, father:**

****If you selected "Other", please specify your relationship to the study participant/patient:**

_____

**3. How much involvement did you provide the subject with regard to taking medication, pairing the patch, applying the patch, and using the app during the course of the study?**

| | Never | Once a month or less | A few times a month | Once a week | A few times a week | Daily |
|---|---|---|---|---|---|---|
| How much overall assistance did you provide the subject during the course of the study? | | | | | | |
| How much assistance did you provide with patch application? | | | | | | |
| How much assistance did you provide with syncing the technology? | | | | | | |
| How much assistance did you provide with using the app? | | | | | | |
| | **Never** | **Once a week** | **A few times a week** | **Nearly every day** | **Daily** | **More than once/day** |
| How much overall assistance did you provide during the past week of the study? | | | | | | |

## Clinical Global Impression Scale

Clinical Global Impression – Severity Scale (CGI-S)

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

0 = Not assessed

1 = Normal, not at all ill

2 = Borderline mentally ill

3 = Mildly ill

4 = Moderately ill

5 = Markedly ill

6 = Severely ill

7 = Among the most extremely ill subjects

**Supplemental Figure 4. Personal and Social Performance Scale**

Original version: Morosini PL, Magliano L, Brambilla L, et al. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand* 2000;101(4):323-9

# Personal and Social Performance Scale (PSP)

The rating is based on four main areas: (a) socially useful activities, including work and study; (b) personal and social relationships; (c) self-care; and (d) disturbing and aggressive behaviors.

Data will be captured in the following format using the PSP descriptions provided below:

| | Absent | Mild | Manifest | Marked | Severe | Very Severe |
|---|---|---|---|---|---|---|
| a. Socially useful activities, including work and study | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| b. Personal and social relationships | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| c. Self-care | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| d. Disturbing and aggressive behaviors | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

The levels of functioning in other areas should be taken into account to adjust the rating inside the decimal level (for instance, from 31 to 40). Suicidal risk is not included in the scale.

| 10-point intervals | PSP descriptions |
|---|---|
| 100–91 | Excellent functioning in all four main areas*. He/she is held in high consideration for his/her good qualities, copes adequately with life problems, is involved in a wide range of interests and activities. |
| 90–81 | Good functioning in all four main areas, presence of only common problems or difficulties. |
| 80–71 | Mild difficulties in 1 or more of areas a–c. |
| 70–61 | Manifest, but not marked difficulties in 1 or more areas a–c, *or* mild difficulties in d. |
| 60–51 | Marked difficulties in 1 of areas a–c, *or* manifest difficulties in d. |
| 50–41 | Marked difficulties in 2 or more, *or* severe difficulties in 1 of areas a–c, with or without manifest difficulties in d. |
| 40–31 | Severe difficulties in 1 *and* marked difficulties in at least 1 of areas a–c, *or* marked difficulties in d. |
| 30–21 | Severe difficulties in 2 of areas a–c, *or* severe difficulties in d, with or without impairment in areas a–c. |
| 20–11 | Severe difficulties in all areas a–d, *or* very severe in d with or without impairment in general areas a–c. If the person reacts to external prompts the suggested scores are 20–16, if not, the suggested scores are 15–11. |
| 10–1 | Lack of autonomy in basic functioning with extreme behaviors but without survival risk (ratings 6–10) or with survival risk, eg, death risk due to malnutrition, dehydration, infections, inability to recognize situation of manifest danger (ratings 5–1). |

| For main areas a–c, the degrees of severity are: | |
|---|---|
| Absent | |
| Mild | Not manifest difficulties, known only to someone who is very familiar with the person. |
| Manifest, but not marked | Difficulties clearly noticeable by everyone, but not interfering substantially with the person's ability to perform his/her role in that area, given the person's socio-cultural context, age, sex and educational levels. |
| Marked | Difficulties heavily interfering with role performance in that area; however, the person is still able to do something without professional or social help, although inadequately and/or occasionally; if helped by someone, he/she may be able reach the previous level of functioning. |
| Severe | Difficulties that make the person unable to perform any role in that area, if not professionally helped, or lead the person to a destructive role; however, there are no survival risks. |
| Very severe | Impairments and difficulties of such intensity to endanger person's survival. |

| For general area d, the degrees of severity are: | |
|---|---|
| Absent | |
| Mild | Mild rudeness, unsociability or whingeing. |
| Manifest, but not marked | Speaking too loudly or speaking to others in a too-familiar manner, or eating in a socially unacceptable manner. |
| Marked | Insulting other in public, breaking or wrecking objects, acting frequently in a socially inappropriate but not dangerous way (eg, stripping in public or urinating in public). |
| Severe | Frequent verbal threats or frequent physical assaults, without intention or possibility of severe injuries. |
| Very severe | Frequent aggressive acts, aimed at or likely to cause severe injuries. |

Occasional is defined as occurring three or more times in the reference period or occurring even less than three times but in circumstances and/or with such a previous history to convince the rater that there is a risk of recurrence in the near future. If the aggressive behavior has been present occasionally, the rating may be decreased by one degree, eg, from severe to marked.

* Main areas: a = socially useful activities, including work and study; b = personal and social relationships; c = self-care; d = disturbing and aggressive behaviors.

**Guidelines for PSP Total Score**

Ratings from 71–100 reflect only mild difficulties.

Ratings from 31–70 reflect manifest disabilities of various degrees.

Ratings from 1–30 reflect functioning so poor that intensive support or supervision is needed.

**Supplemental Figure 5. Patient Activation Measure-Mental Health Scale**

The following questions ask about your feelings regarding your mental healthcare. When you think about mental health and mental health care, how much do you agree or disagree with the following statements? Please circle the answer that you most agree with:

**1.** When all is said and done, I am the person who is responsible for managing my mental health.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**2.** Taking an active role in my own mental health is the most important factor in determining my mental health and ability to function.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**3.** I am confident that I can take actions that will help prevent or minimize some symptoms or problems associated with my mental health condition.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**4.** I know what each of my prescribed mental health medications does.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**5.** I am confident that I can tell when I need to go get mental health care, and when I can handle a mental health problem myself.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**6.** I am confident I can tell my mental health clinician about concerns I have, even when he or she does not ask.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**7.** I am confident that I can follow through on mental health treatments I need to do at home.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**8.** I understand the nature and causes of my mental health condition(s).

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**9.** I know the different treatment options available for my mental health condition(s).

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**10.** I am able to maintain the lifestyle changes I have made for my mental health.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**11.** I know how to prevent further mental health problems.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**12.** I am confident I can figure out solutions when new situations or problems arise with my mental health.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

**13.** I am confident that I can maintain lifestyle changes, like diet and exercise, even during times of stress.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Strongly Disagree | Disagree | Agree | Strongly Agree |

Supplemental Material – PRECIS-2 Tool Assessment

Whilst the PRECIS-2 tool assessment was not completed during the design of the study, when it is designed to be conducted, a post assessment use of the tool confirms the use of the term pragmatic. For example, from the nine PRECIS-2 domains:

Eligibility: Would score 4 (out of 5) since those identified in the study would be those identified in usual care. The study does exclude inpatients, which in the "real world" could in theory participate but we felt the DMS intervention was of limited benefit in this setting since inpatients have observed adherence

Recruitment: would score 4-5 since recruitment is based simply on screening patient caseloads and assessment of patients who may need help with adherence measures. No advertisements have been conducted.

Setting: Would score 4-5 since the care settings used in the study are those in usual care. We have a range of participants from community and specialist mental health services

Organisation: Would likely score 3-4 since although the resource/expertise is largely similar to usual care, the study does use NHS research staff to assist with training and screening, as is commonplace with all clinical studies in the UK

Flexibility (delivery): Would score 3-4 since the study gives patients and HCPs the ability to follow standard of care but does require specific site visit at w4 and w8 (yet one could argue this would occur naturally since the w4 visit is to collect a new prescription (which would occur in

the real world) and the w8 visit is the completion of the study. Patients do not experience any other "forced" visits.

Flexibility (adherence): Would score 3 since following enrolment if patients do not utilise the patch/app the site can contact the patient to found out why they are not engaging and try to encourage; however, this would be the same if the DMS was indeed normal practice; this is the intention of the tool to promote conversations between visits when individuals are not adherent.

Primary outcome: would score 3-4; whilst the outcome may not be obvious to patients, the outcome has been supported from conversations with HCPs and payers. The good patch coverage days are essential to provide insight into medication taking so again, if the intervention become standard, the metric would be used since it would determine whether objective and insightful data was being captured.

Primary analysis: Would score 4 since all individuals will be included in the analysis with all available data.

Based on the above, the average score is approx. 4 which equates to "Rather pragmatic"

The reason why the study is not the top score of 5 (Very pragmatic) is that the intervention itself does cause changes to current care but we are not stating how individuals should respond to these changes. They are free to decide for themselves.


SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | _Page 1 Line 1_ |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | _Page 4 Line 64 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | Provided on ClinicalTrials.gov |
| Protocol version | 3 | Date and version identifier | Page 1 of protocol |
| Funding | 4 | Sources and types of financial, material, and other support | Page 20 Line 396 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | Page 21 Line 408 |
| | 5b | Name and contact information for the trial sponsor | _Page 1 Line 22_ |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | Page 21 Line 407 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | Page 21 Line 407 |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | Page 7 Line 137 |
| | 6b | Explanation for choice of comparators | *N/A* |
| Objectives | 7 | Specific objectives or hypotheses | Page 9 Line 163 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | Page 9 Line 170 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | Page 9 Line 176 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | Page 10 Line 188 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | Page 11 Line 190 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | Page 18 Line 343 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | Page 19 Line 358 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | As listed on each drug label |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | Page 14 Line 265 |

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| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | Figure 3 |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | Page 15 Line 282 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | Page 13 Line 249 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | N/A |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | N/A |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | N/A |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | N/A |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | N/A |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | Protocol Page 81 |

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| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | Page 14 Line 259 |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | Protocol Page 73 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | Protocol Page 73 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | Page 15 Line 282 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | Page 15 Line 282 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | N/A Pragmatic Trial - Safety of Interventions is Established |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | N/A |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | Protocol Page 66 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | Protocol Page 81 |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | Page 16 Line 309 |

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| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | Updates to ClinicalTrials.gov |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | Page 15 Line 293 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | N/A |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | Page 15 Line 299 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | Page 21 Line 402 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | Page 17 Line 318 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | N/A |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | Protocol page 84 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | Protocol page 84 |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | Not yet determined |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | Protocol Page 107 |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | N/A |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. 