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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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SCHOLARONE™
Manuscripts

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3 **A Study Protocol for the Hummingbird Study, an Open-label, Multicenter**
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6 **Exploratory Trial to Assess the Acceptance and Performance of a Digital**
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8 **Medicine System in Adults With Schizophrenia, Schizoaffective Disorder, or**
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11 **First-Episode Psychosis**
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16 Running title: Study protocol for DMS use in schizophrenia in the UK
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20 Authors:

21
22 J. Corey Fowler, PhD,¹ Nathan Cope, PhD,² Jonathan Knights, PhD,¹ Peter Phiri, PhD,³ Andrew
23 Makin, MD,⁴ Tim Peters-Strickland, MD,¹ Shanaya Rathod, DM, MRCPsych³
24
25

26
27 Affiliations:

28
29 ¹Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, USA; ²Otsuka
30 Pharmaceutical Europe Ltd., Wexham, UK; ³Southern Health NHS Foundation Trust,
31 Southampton, UK; ⁴Otsuka Europe Development and Commercialisation Ltd., Wexham, UK
32
33
34

35
36 E-mail addresses:

37 corey.fowler@otsuka-us.com, NCope@otsuka-europe.com, Jonathan.Knights@otsuka-us.com,
38 Peter.Phiri@southernhealth.nhs.uk, AMakin@otsuka-europe.com, [tim.peters-strickland@otsuka-](mailto:tim.peters-strickland@otsuka-us.com)
39 [us.com](mailto:tim.peters-strickland@otsuka-us.com), shanayarathod@nhs.net
40
41
42
43

44 Address correspondence to: J. Corey Fowler, PhD

45
46 corey.fowler@otsuka-us.com

47 Associate Director, Global Clinical Development

48 Otsuka Pharmaceutical Development & Commercialization, Inc.

49 508 Carnegie Center Blvd, Suite 300

50 Princeton, NJ 08540, USA

51 +1 919 475 4823
52
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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

1
2
3 endpoints will be the proportion of days with good patch coverage and ingestion adherence,
4
5 respectively.
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10 Ethics and Dissemination: Approval for this study was obtained from London - City & East
11 Research Ethics Committee. Results will be disseminated through peer-reviewed publications,
12
13 conference presentations, clinical trial repositories, and communications with participants.
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19 ClinicalTrials.gov: NCT03568500
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24 **Keywords**

25 Coproduction, digital medicine, schizoaffective disorder, schizophrenia
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30 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 31
32
33 • This study was codeveloped with input from clinical practitioners, researchers, patients,
34 caregivers, service managers, information governance teams, and clinical commissioning
35 groups to obtain information that will best serve all those involved in the treatment and
36 care of patients with schizophrenia, schizoaffective disorder, and first-episode psychosis.
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42 • The digital medicine system (DMS) uses an integrated, user-friendly system to provide
43 objective feedback on patient medication adherence and physical health parameters, such
44 as activity and rest levels, as well as voluntary subjective entries regarding mood and rest
45 quality, to help support treatment decisions and evaluation.
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51 • Information from the DMS is made readily available to patients, caregivers (with the
52 patient's consent), and physicians to support clinical decision making, proactive
53 intervention, and individualized care in near to real time.
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- 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.

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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

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3 patients with schizophrenia requires a system that provides physicians with objective information
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5 during interim periods between patient visits.
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8 The use of modern technology such as personal digital assistants [19], digital wristwatches [20],
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10 handheld computers [21], and mobile phones [22] to manage schizophrenia has shown success.

11 A digital medicine system (DMS) has been developed as a drug-device combination to
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13 objectively assess and report ingestion of prescription antipsychotics [23]. The DMS has 4 main
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15 components: an ingestible sensor embedded within an inert tablet, a nonmedicated wearable
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17 sensor (patch) worn by the patient, a mobile application (app), and a Web-based dashboard [23].
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19 Upon interaction with stomach fluids, the ingestible sensor is activated and communicates with
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21 the wearable sensor, which sends a signal to a Bluetooth-paired mobile device where it can be
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23 viewed by patients or be subsequently viewed by HCPs and caregivers using secure mobile- and
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25 cloud-based software [23]. The DMS also communicates data on patient activity and rest levels
26
27 as well as subjective data on mood and rest quality. The intention of the DMS is to encourage
28
29 greater patient self-management and behavior change while enabling caregivers and HCPs to
30
31 provide better care and support both within and outside of office visits, further engaging patients
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33 in their ongoing disease management.
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41 In an open-label, 8-week study, 78% of patients and 72% of HCPs reported being somewhat
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43 satisfied, satisfied, or extremely satisfied with the DMS [24]. Findings from another open-label
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45 study showed patients to be actively involved in their treatment, with >70% utilizing call centers
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47 for technological DMS support [25]; the rate of ingestion adherence in this study was 85.6%
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49 [25].
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52 The DMS from the current study (namely the ingestible sensor and the wearable sensor) are
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54 Conformité Européene (CE)–marked for use in Europe as class IIa medical devices (CE 559373),
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3 but studies in European mental health populations have not been performed. Therefore, the
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5 objective of this exploratory study is to assess the acceptance and performance of the DMS
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7 among adult patients with schizophrenia, schizoaffective disorder, or first-episode psychosis and
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9 among HCPs from different care settings in the United Kingdom.
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14 **METHODS AND ANALYSIS**

15 16 17 18 **Study design**

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20 This is a multicenter, 8-week, single-arm, open-label trial to evaluate the acceptance and
21
22 performance of the DMS in adult patients with schizophrenia, schizoaffective disorder, or first-
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24 episode psychosis on an oral atypical antipsychotic medication (aripiprazole, olanzapine,
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26 quetiapine, or risperidone) and in HCPs. The study will take place at 5 institutions in the United
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28 Kingdom: Northumberland, Tyne and Wear National Health Service (NHS) Foundation Trust,
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30 Surrey and Borders Partnership NHS Foundation Trust, Oxford Health NHS Foundation Trust,
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32 South London and Maudsley NHS Foundation Trust, and Southern Health NHS Foundation
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34 Trust. The first patient's first visit occurred in May 2018. Patient recruitment will be targeted to
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36 last approximately 4 months.
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42 **Intervention**

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

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25 This study was designed using coproduction methodology involving NHS staff and patients
26 (Figure 2). The lead site, Southern Health NHS Foundation Trust, held 5 coproduction
27 workshops, and a subset of these workshops was repeated at other study sites to elicit feedback
28 on the study design. These discussions addressed pharmacy items for the CoE product; HCP
29 recruitment strategies; and protocols for identification, recruitment, and interactions with suitable
30 patients and their general practitioners. Throughout the various workshops at the different sites,
31 participants included clinicians, pharmacists, researchers, information governance personnel,
32 psychiatrists, care coordinators, nurses, information technology personnel, commissioners, and
33 patients (Figure 2).
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46 After changes from the coproduction workshops were incorporated, the Patient and Public
47 Involvement and Service User Lead from 2 study sites (Surrey and Borders Partnership NHS
48 Foundation Trust and Northumberland, Tyne, and Wear NHS Foundation Trust) engaged service
49 users to participate in a patient focus group. At these focus groups, attendees provided feedback
50 on the ease of use of, and the ability to perform tasks within, the DMS mobile app (MyCite).
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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
<ul style="list-style-type: none"> ● Willing and able to give written informed consent and adhere to trial procedures ● Able to read and understand English ● Age 18–65 years at the time of informed consent ● 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 ● Cooperative, able to ingest oral medication, willing to complete aspects of the trial, and capable of reporting adverse events (AEs) ● 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 ● Prescription for aripiprazole, olanzapine, quetiapine, or risperidone ● Fulfills ≥ 1 of the following: <ul style="list-style-type: none"> ○ Discharge from a hospital admission (within 7 days of discharge) to an acute intervention team ○ Referral to an acute intervention team before hospital admission ○ Referral from an acute intervention team to a community team ○ Managed by community services ○ Inclusion within early intervention caseload (<3 years from initial symptoms) ○ Healthcare professional (HCP) determines the patient would benefit ● 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
<ul style="list-style-type: none"> ● Any disorder that may affect patient's ability to participate in the trial or interact with a smartphone ● Likely to be incapable of using DMS technology, even with assistance ● History or evidence of a medical condition that would expose patient to undue risk of an AE ● Known allergy to adhesive tape or any component of the patch or co-encapsulation product ● Current incarceration in prison system ● Hospitalization at the time of screening due to mental or physical illness ● HCP recommendation to not participate ● 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

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

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18 The primary endpoint is the proportion of days with good patch coverage during the assessment
19 period, which will be defined as having $\geq 80\%$ patch data available or IEMs detected within each
20 day of the assessment period. The secondary endpoint is ingestion adherence, defined as the
21 proportion of detected IEMs to the total expected IEMs ingested on the assessment days that
22 showed good patch coverage.
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30 The following exploratory endpoints will also be included:
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- 32
33 • The proportion of time during the assessment period that patients wear their patch
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35 • Engagement and satisfaction of patients, HCPs, and caregivers as determined using the
36 Subject Usability and Satisfaction Scale (**Supplemental Figure 1**), the Physician Utility
37 Survey (**Supplemental Figure 2**), and the Caregiver/Support Person Involvement Scale
38 (**Supplemental Figure 3**)
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40 • Personal and social functioning as assessed using the Personal and Social Performance
41 Scale (**Supplemental Figure 4**)
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43 • Patient activation as assessed using the Patient Activation Measure-Mental Health Scale
44 (**Supplemental Figure 5**)
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46 • The proportion of days that patients and HCPs use the app and dashboard, respectively
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- 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

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3 the GDPR. Data from the DMS are encrypted in activity and rest and will be accessed only by
4 role-specific individuals for discrete time periods and functions (eg, technical troubleshooting).

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6 All data will be completely anonymized for graphical, statistical, and publication purposes.
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10 Research staff from NHS sites will store consent documents, demographic forms, and receipts
11 for reimbursement of travel in locked filing cabinets to which only research staff will have
12 access. Accessing of health data will be compliant with information governance policies of each
13 participating NHS trust.
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19 20 21 22 **ETHICS AND DISSEMINATION**

23 24 25 **Ethical considerations**

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28 Ethics approval for this study was obtained from London - City & East Research Ethics
29 Committee (REC Ref no. 18/LO/0128), and clinical trial authorization was provided by the
30 Medicines and Healthcare products Regulatory Agency. Written informed consent will be
31 obtained from every participant. Ethical issues will be related to the identification and
32 recruitment of patients, informed consent, and data protection arrangements. The trial will be
33 conducted in compliance with the International Council for Harmonisation of Technical
34 Requirements for Pharmaceuticals for Human Use guidelines and Declaration of Helsinki.
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45 46 **Dissemination of study results**

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

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12 Patient adherence to antipsychotic medication is a crucial component of successful maintenance
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14 therapy for schizophrenia. Knowledge of patient adherence in the absence of positive treatment
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16 outcome is also essential. Subjective means for assessing medication adherence such as clinician
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18 evaluation and patient self-report have low validity [16], and most can only be administered
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20 during patient-HCP visits. Digital medicine offers a means to monitor patient adherence and
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22 obtain objective data throughout treatment, including periods between office visits, which may
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24 yield more accurate data. For example, a study evaluating nonadherence rates for antipsychotic
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26 medication based on electronic medication bottle caps, which report when pill bottles have been
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28 opened [18], showed a 57% nonadherence rate, much higher than that estimated by patient (5%)
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30 and provider (7%) report [18]. This study shows the potential of digital medicine to provide
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32 continuous objective data that can inform and improve patient adherence and assist in clinical
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34 decision making. The DMS improves upon approaches such as electronic medication caps by
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36 providing an objective marker of ingestion and not merely a surrogate in addition to other
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38 objective and subjective data.
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45 Patient discontinuation is a considerable problem in studies of digital health technology [26].
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47 Studies of early digital health systems for maintenance and counseling of mental disorders
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49 reported low completion rates. For example, a study evaluating a 12-week web-based cognitive
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51 behavioral therapy intervention for panic disorder had a 1% (12/1161) completion rate [27], and
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53 a study evaluating a publicly accessible 5-module web-based cognitive behavioral therapy
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3 program for anxiety and depression had a 0.5% completion rate (97/19,607) [28]. Completion
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5 rates may be particularly low in patients with more severe negative symptoms [22]. Despite these
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7 historically poor completion rates in studies of digital health platforms, results of a meta-analysis
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9 indicate that more than 50% of patients favor managing their mental health through the use of
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11 mobile health technology [29], and the use of mobile devices for health management is viewed
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13 by patients as normalized and nonstigmatizing [30]. The integrated DMS described here was
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15 developed to leverage the advantages of digital technology to positively influence adherence in
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17 patients with schizophrenia.
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22 The DMS is a multimodal, user-friendly system that provides medication reminders and
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24 measures patient ingestion of prescribed antipsychotic medications. The CoE product, in
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26 particular, advances the ability to confirm medication ingestion and to assess adherence on a
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28 continuous basis, which can inform whether uncontrolled symptoms may be explained by
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30 nonadherence. Information from the DMS is made readily available to patients, caregivers (with
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32 the patient's consent), and physicians for supported decision making, proactive intervention, and
33
34 individualized care. DMS also provides adherence feedback electronically to the patient, HCP,
35
36 and/or caregiver. Because it can be implemented discreetly, patients may feel destigmatized and
37
38 assimilate back into society more readily. The DMS also provides feedback on activity and rest
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40 levels, which is important given that maintenance of a healthy lifestyle can help address the
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42 problems of weight gain and obesity that are related to both medication side effects and
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44 sedentary lifestyles [31]. Furthermore, shifts in activity levels may be indicative of altered
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46 patient disposition.
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52 This ongoing study was designed using coproduction methodology to incorporate input from
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54 patients, caregivers, psychiatrists, pharmacists, nurses, and researchers. For all 5 study sites, a
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3 minimum of 2 engagement/setup meetings were conducted and 2 specific patient focus groups
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5 were held to guide protocol development and app design.. The exploratory data collected in this
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7 study, although limited to a small number of patients, will help provide a better understanding of
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9 the ease of use for patients, HCPs, and caregivers to inform the development of future software
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11 or hardware iterations.
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16 **CONCLUSION**

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19 In conclusion, this study will examine the usability and acceptance of the DMS by patients with
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21 schizophrenia, schizoaffective disorder, or first-episode psychosis, and by caregivers and HCPs
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23 in different care settings. The study was meticulously coproduced through the engagement of all
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25 stakeholders and, if successful, could be used to support DMS usage in larger cohorts within the
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27 United Kingdom and Europe.
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34
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36
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38
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40
41 Pharmaceutical Development & Commercialization, Inc.
42
43
44
45

46 **Competing interests statement**

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48
49 Dr J. Corey Fowler, Dr Jonathan Knights, and Dr Tim Peters-Strickland are employees of Otsuka
50
51 Pharmaceutical Development & Commercialization. Dr Nathan Cope is an employee of Otsuka
52
53 Pharmaceutical Europe Ltd. Dr Andrew Makin is an employee of Otsuka Europe Development
54
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3 and Commercialisation. Dr Peter Phiri has no conflict of interest. Dr Shanaya Rathod has
4
5 received honoraria from Otsuka and Lundbeck for educational sessions.
6
7

8 **Author contributions**

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11 JCF, NC, AM, and TPS made substantial contributions to the design and to the conception of the
12
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For peer review only

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.

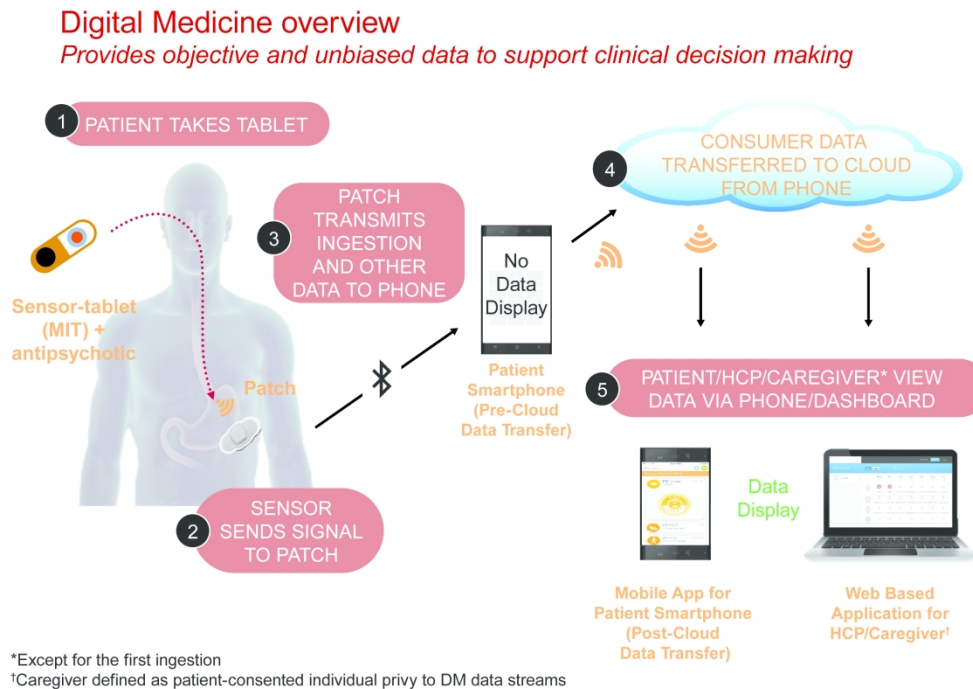


Figure 1. Digital medicine system: co-encapsulated antipsychotic medication with miniature ingestible event marker in tablet (MIT) and compatible medical device. DM=digital medicine; HCP=healthcare professional.

254x177mm (300 x 300 DPI)

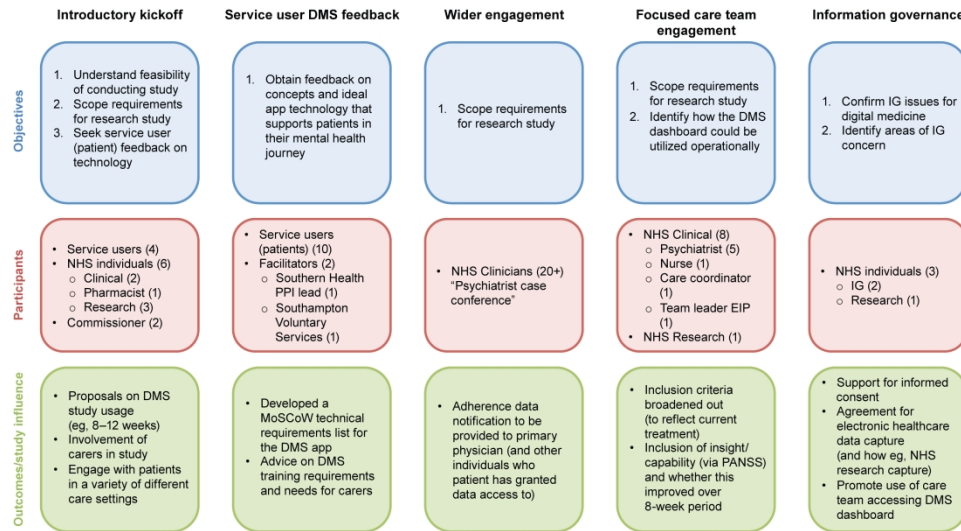
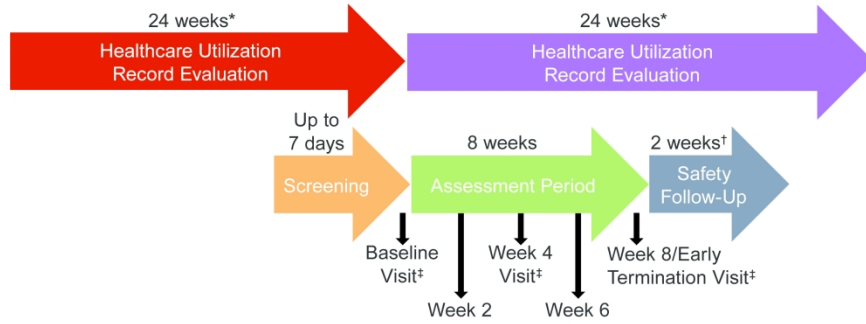


Figure 2. Description of coproduction workshops with Southern Health NHS Foundation Trust. DMS=digital medicine system; EIP=Early Intervention in Psychosis; IG=information governance; MoSCoW=must have, should have, could have, won't have; NHS=National Health Service; PANSS=Positive and Negative Syndrome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

	Extremel y 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)?

	Extremel y 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?

	Extremel y 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)?

	Extremel y 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)?

	Extremel y Difficult	Difficult	Somewhat Difficult	Neutral	Somewhat Easy	Easy	Extremel y 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

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4 **11. How helpful or unhelpful was the Digital Medicine System in improving your conversations with**
5 **your patient about their treatment plan and progress?**
6

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

13 **12. How helpful or unhelpful was the Digital Medicine System in the identification of**
14 **potential lifestyle changes for your patient (eg sleep and exercise)?**
15

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

22 **13. Other than during the patient visit(s), did you look at the HCP dashboard at other**
23 **times? Please select all that apply**
24

	Place a \checkmark (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: <i>Please Specify:</i> _____	

32 **14. What features did you find helpful? Please select all that apply**
33

	Place a \checkmark (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: <i>Please Specify:</i> _____		

1
2
3 **15. Did you set up alerts to be notified of missed doses? Yes/no**

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

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

13 15a. If you received a missed dose alert what action did you take, if any? (If none,
14 please write N/A) _____
15

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

- 17 a. If yes, based on your overall experience, how helpful were the multiple dose
18 alerts?
19

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

20 21 22 23 24 25 26
27 16a. If you received a multiple dose alert what action did you take, if any? (If none, please write
28 N/A) _____
29

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

- 31 a. Overall, the Digital Medicine System adds value to my practice.
32

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

33 34 35 36 37 38
39 **18. Based on your overall experience with this patient, how would you rate your satisfaction with the**
40 **Digital Medicine System?**
41

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

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3 **Supplemental Figure 3. Caregiver/Support Person Involvement Scale (Ver 2.0)**
4
5

6 **DMS Caregiver/Support Person Involvement Scale**
7

- 8
9
10 **1. Are you aware that the study participant/patient is currently participating in the Digital**
11 **Medicine study (check one)?**
12

Yes	No*

13
14
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16
17
18 ***If no, stop here and do not answer the rest of the questions on this form.**
19

- 20
21 **2. Indicate your relationship to the study participant/patient by placing a √ (check).**
22

Friend	Hired Caregiver	Relative*	Other**

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28 ***If you are a relative, please specify relationship to the study participant/patient, e.g.,**
29 **wife, father:**
30

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

4 = Moderately ill

1 = Normal, not at all ill

5 = Markedly ill

2 = Borderline mentally ill

6 = Severely ill

3 = Mildly ill

7 = Among the most extremely ill subjects

1
2
3 **Supplemental Figure 4. Personal and Social Performance Scale**
4

5 Original version: Morosini PL, Magliano L, Brambilla L, et al. Development, reliability and
6 acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment
7 Scale (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand* 2000;101(4):323-9
8 Copyright © 2000 John Wiley & Sons, Inc. Reproduced with permission of Blackwell
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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	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. Personal and social relationships	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Self-care	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. Disturbing and aggressive behaviors	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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

1
2
3
4
5 **7. I am confident that I can follow through on mental health treatments I need to do at home.**

6
7 1 2 3 4
8
9 Strongly Disagree Disagree Agree Strongly Agree

10
11
12 **8. I understand the nature and causes of my mental health condition(s).**

13
14 1 2 3 4
15
16 Strongly Disagree Disagree Agree Strongly Agree

17
18
19
20 **9. I know the different treatment options available for my mental health condition(s).**

21
22 1 2 3 4
23
24 Strongly Disagree Disagree Agree Strongly Agree

25
26
27
28 **10. I am able to maintain the lifestyle changes I have made for my mental health.**

29
30 1 2 3 4
31
32 Strongly Disagree Disagree Agree Strongly Agree

33
34
35 **11. I know how to prevent further mental health problems.**

36
37 1 2 3 4
38
39 Strongly Disagree Disagree Agree Strongly Agree

40
41
42
43 **12. I am confident I can figure out solutions when new situations or problems arise with my mental health.**

44
45 1 2 3 4
46
47 Strongly Disagree Disagree Agree Strongly Agree

48
49
50
51 **13. I am confident that I can maintain lifestyle changes, like diet and exercise, even during times of stress.**

52
53 1 2 3 4
54
55 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

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Manuscripts

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3 1 **A Study Protocol for the Hummingbird Study, a Multicenter Exploratory**
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6 2 **Trial to Assess the Acceptance and Performance of a Digital Medicine System**
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9 3 **in Adults With Schizophrenia, Schizoaffective Disorder, or First-Episode**
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29 6 Running title: Study protocol for DMS use in schizophrenia in the UK
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8 Authors:

9 J. Corey Fowler, PhD,¹ Nathan Cope, PhD,² Jonathan Knights, PhD,¹ Peter Phiri, PhD,³ Andrew
10 Makin, MD,⁴ Tim Peters-Strickland, MD,¹ Shanaya Rathod, DM, MRCPsych³

12 Affiliations:

13 ¹Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, USA; ²Otsuka
14 Pharmaceutical Europe Ltd., Wexham, UK; ³Southern Health NHS Foundation Trust,
15 Southampton, UK; ⁴Otsuka Europe Development and Commercialisation Ltd., Wexham, UK

17 E-mail addresses:

18 corey.fowler@otsuka-us.com, NCope@otsuka-europe.com, Jonathan.Knights@otsuka-us.com,
19 Peter.Phiri@southernhealth.nhs.uk, AMakin@otsuka-europe.com, [tim.peters-strickland@otsuka-
21 us.com](mailto:tim.peters-strickland@otsuka-
20 us.com), shanayarathod@nhs.net

22 Address correspondence to: J. Corey Fowler, PhD

23 corey.fowler@otsuka-us.com

24 Associate Director, Global Clinical Development

25 Otsuka Pharmaceutical Development & Commercialization, Inc.

26 508 Carnegie Center Blvd, Suite 300

27 Princeton, NJ 08540, USA

28 +1 919 475 4823

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36 **ABSTRACT**

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

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

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

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

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

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

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

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

65 **Keywords**

66 Coproduction, digital medicine, schizoaffective disorder, schizophrenia

67 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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

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1
2
3 81 relatively short 12-week timeframe. Although the DMS does require the patient to
4
5 82 engage more with their own care, the benefits of increasing their awareness of
6
7 83 medication, activity, rest, and mood patters outweighs risks/burden for most patients.
8
9
10 84 The DMS was not developed for all mental health patients, but for a subset of patients
11
12 85 who have difficulty with adherence and want to improve their status by self-monitoring
13
14 86 with potential for their HCP's to make better clinical decisions based on objective data
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16 87 from the DMS. Patients with poor insight into their illness will likely be a better
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19 88 candidate for a long-acting injectable atypical antipsychotic than this DMS.
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90 INTRODUCTION

91 Schizophrenia has an enormous social and economic burden worldwide, accounting for 1.1% of
92 total disability-adjusted life-years and 2.7% of years lived with disability [1, 2]. In Europe, the
93 economic impact of schizophrenia and other psychotic disorders and syndromes in 2010 was
94 estimated at €93.9 billion [3]. Because it is a chronic disease, maintenance treatment is often
95 necessary to prevent relapse and preserve quality of life over the long term [4, 5]. Although
96 antipsychotic medications are effective [6-8], poor insight into schizophrenia can increase risk of
97 medication nonadherence [9, 10]. In patients with schizophrenia, the rate of nonadherence to
98 prescribed antipsychotics has been reported to be as high as 74% [11]. Not only is medication
99 nonadherence burdensome to patients and their families, it also increases the likelihood of
100 rehospitalization and relapse [12] and contributes substantially to healthcare costs [13]. In
101 2005/2006, mean annual psychiatric inpatient and medication costs for patients with
102 schizophrenia in England were estimated to be approximately £3,000 and £2,000 per patient,
103 respectively [14].

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

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3 112 patients with schizophrenia requires a system that provides physicians with objective information
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5 113 during interim periods between patient visits.
6
7
8 114 The use of modern technology such as personal digital assistants [19], digital wristwatches [20],
9
10 115 handheld computers [21], and mobile phones [22] to help people with schizophrenia dealing with
11
12 116 their disease has shown success. A digital medicine system (DMS) has been developed as a drug-
13
14 117 device combination to objectively assess and report ingestion of prescription antipsychotics [23].
15
16 118 The DMS has 4 main components: an ingestible sensor embedded within an inert tablet, a
17
18 119 nonmedicated wearable sensor (patch) worn by the patient, a mobile application (app), and a
19
20 120 Web-based dashboard [23]. Upon interaction with stomach fluids, the ingestible sensor is
21
22 121 activated and communicates with the wearable sensor, which sends a signal to a Bluetooth-paired
23
24 122 mobile device where it can be viewed by patients or be subsequently viewed by HCPs and
25
26 123 caregivers using secure mobile- and cloud-based software [23]. The DMS also enables patients
27
28 124 to share data on their activity and rest levels as well as subjective data on mood and rest quality,
29
30 125 which can be generated while the patient is engaged with the system. The intention of the DMS
31
32 126 is to encourage greater patient self-management and behavior change while enabling caregivers
33
34 127 and HCPs to provide better care and support both within and outside of office visits, further
35
36 128 engaging patients in their ongoing disease management. The data is communicated to the
37
38 129 psychiatrist that is connected to the patient on the MyCite platform. Additionally, should the
39
40 130 patient choose to share their data, they are able to invite additional healthcare providers,
41
42 131 caregivers and/or family or friends. Recipients of the data, through a web-based password
43
44 132 protected platform, are able to view this data and assist the patient with their treatment plan,
45
46 133 however HCPs can only access the portal for a specific patient once he/she has consented to give
47
48 134 them access to their information in the system. It is envisioned that HCPs will be able to use this
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3 135 data to make more informed clinical decisions such as whether individuals need dose adjustment,
4
5 136 medication changes or conversations on lifestyle, adherence or other parameters.
6
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8 137 Previous results in the USA have shown in an open-label, 8-week study, 78% (47/60) of patients
9
10 138 and 72% (43/60) of HCPs reported being somewhat satisfied, satisfied, or extremely satisfied
11
12 139 with the DMS [24]. Findings from another open-label study showed patients to be actively
13
14 140 involved in their treatment, with 73.5% (36/49) utilizing call centers for technological DMS
15
16 141 support [25]; the rate of ingestion adherence in this study for the 15 patients with schizophrenia
17
18 142 was 85.6% [25].
19
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21
22

23 143 The DMS from the current study (namely the ingestible sensor and the wearable sensor) are
24
25 144 Conformité Européene (CE)–marked for use in Europe as class IIa medical devices (CE 559373),
26
27 145 but studies in European mental health populations have not been performed. Therefore, the
28
29 146 objective of this exploratory study is to assess the acceptance and performance of the DMS
30
31 147 among adult patients with schizophrenia, schizoaffective disorder, or first-episode psychosis and
32
33 148 among HCPs from different care settings in the United Kingdom. We are particularly interested
34
35 149 in assessing the acceptance of the digital medicine technology in individuals from different care
36
37 150 settings. Acceptance will be assessed by study completion and, feedback from subjects from
38
39 151 patient satisfaction surveys. Furthermore, acceptance will also be evaluated by healthcare
40
41 152 providers using the system; this will be assessed by how their clinical decisions altered whilst
42
43 153 using the system and through HCP Utility questionnaire evaluations.
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49 154 In respect to performance, the study will be assessing multiple hardware and software from a
50
51 155 varied population. Based on operational feedback of different phones and OS and any technical
52
53 156 troubleshooting that occurs, the study will be able to determine areas of the app that need to be
54
55 157 enhanced to ensure that the app functions across multiple hardware and operating systems.
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3 158 Previous studies performed using the DMS were conducted in relatively stable individuals with
4
5 159 schizophrenia. For this study, we have broadened out the inclusion criteria and will be assessing
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7
8 160 the technology in a range of clinical groups from different care settings, such as those individuals
9
10 161 managed in the community or on specialized services such as Early Intervention in Psychosis
11
12 162 services to determine the performance in these different environments.
13
14

15 163 The study is not intended to measure and report or make any claims of adherence, but instead, to
16
17 164 report the observed ingestions recorded by the DMS. Our goal is to look at the impact of
18
19
20 165 patients' improvements as a result of participation (e.g. reduced need for follow-up care,
21
22 166 knowledge of adherence to medication to help physicians decide whether patients are medication
23
24 167 compliant or require a long acting injectable or other follow-up care) with the hypothesis that
25
26 168 DMS will reduce overall healthcare utilization burden.
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31 169 **METHODS AND ANALYSIS**

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35 170 **Study design**

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37 171 This is a multicenter, 8-week, single-arm, open-label trial to evaluate the acceptance and
38
39 172 performance of the DMS in adult patients with schizophrenia, schizoaffective disorder, or first-
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42 173 episode psychosis on an oral atypical antipsychotic medication (aripiprazole, olanzapine,
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44 174 quetiapine, or risperidone) and in HCPs. Recruitment began the same day that we submitted to
45
46 175 CT.gov, 25/MAY. However, we didn't consent our first patient until 11/JUN and dosing
47
48 176 occurred on 18/JUN. The study will take place at 5 institutions in the United Kingdom:
49
50 177 Northumberland, Tyne and Wear National Health Service (NHS) Foundation Trust, Surrey and
51
52
53 178 Borders Partnership NHS Foundation Trust, Oxford Health NHS Foundation Trust, South
54
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56 179 London and Maudsley NHS Foundation Trust, and Southern Health NHS Foundation Trust. The
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180 first patient's first visit occurred in May 2018. Patient recruitment will be targeted to last
181 approximately 4 months.

182 Patient selection

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

188 **Table 1. Inclusion and Exclusion Criteria**

Inclusion criteria
<ul style="list-style-type: none"> • Willing and able to give written informed consent and adhere to trial procedures • Able to read and understand English • Age 18–65 years at the time of informed consent • 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.) • Cooperative, able to ingest oral medication, willing to complete aspects of the trial, and capable of reporting adverse events (AEs) • 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 • Prescription for aripiprazole, olanzapine, quetiapine, or risperidone • Fulfills ≥ 1 of the following: <ul style="list-style-type: none"> ○ Discharge from a hospital admission (within 7 days of discharge) to an acute intervention team ○ Referral to an acute intervention team before hospital admission ○ Referral from an acute intervention team to a community team ○ Managed by community services ○ Inclusion within early intervention caseload (<3 years from initial symptoms) ○ Healthcare professional (HCP) determines the patient would benefit • General medical condition does not pose additional risk

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- 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
- Likely to be incapable of using DMS technology, even with assistance
- History or evidence of a medical condition that would expose patient to undue risk of an AE
- Known allergy to adhesive tape or any component of the patch or co-encapsulation product
- Current incarceration in prison system
- Hospitalization at the time of screening due to mental or physical illness
- HCP recommendation to not participate
- Aversion to taking gelatin capsules
- Women who are breastfeeding, pregnant, or plan to become pregnant

189

Intervention

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

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

204 **Coproduction and patient involvement**

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

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

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

228

229 **Procedures**

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

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

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

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

259 **Outcomes**

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

265 The following exploratory endpoints will also be included:

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

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- 269 Survey (**Supplemental Figure 2**), and the Caregiver/Support Person Involvement Scale
270 (**Supplemental Figure 3**)
- 271 • Personal and social functioning as assessed using the Personal and Social Performance
272 Scale (**Supplemental Figure 4**)
 - 273 • Patient activation as assessed using the Patient Activation Measure-Mental Health Scale
274 (**Supplemental Figure 5**)
 - 275 • The proportion of days that patients and HCPs use the app and dashboard, respectively
 - 276 • The proportion of ingested IEM tablets registered on the digital health data server of the
277 total expected IEM tablets ingested
 - 278 • Safety variables will include the frequency and severity of serious adverse events and
279 device-related nonserious adverse events, suicidality, and any product quality complaints
280 that may arise. Suicidality will be determined by face-to-face risk assessment according
281 to each study site's standard operating procedure.

282 **Statistical analysis**

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

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

293 **Data protection**

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

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

309 **Ethical considerations**

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

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

318 **Dissemination of study results**

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

325 **DISCUSSION**

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

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2
3 335 and provider (7%) report [18]. Electronic medication bottle caps are used as the current gold-
4
5 336 standard surrogate for ‘objective’ adherence data. Few reports in this space exist and the need for
6
7 337 more robust objective adherence data is supported through this discrepancy and the limitations of
8
9 338 electronic medication bottle caps as an ‘objective’ measure, given it only measures an
10
11 339 intermediate step in the ingestion process. This study shows the potential of digital medicine to
12
13 340 provide continuous objective data that can inform and improve patient adherence and assist in
14
15 341 clinical decision making. The DMS improves upon approaches such as electronic medication
16
17 342 caps by providing an objective marker of ingestion and not merely a surrogate in addition to
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19 343 other objective and subjective data.
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24 344 Patient discontinuation is a considerable problem in studies of digital health technology [26].
25
26 345 Studies of early digital health systems for maintenance and counseling of mental disorders
27
28 346 reported low completion rates. For example, a study evaluating a 12-week web-based cognitive
29
30 347 behavioral therapy intervention for panic disorder had a 1% (12/1161) completion rate [27], and
31
32 348 a study evaluating a publicly accessible 5-module web-based cognitive behavioral therapy
33
34 349 program for anxiety and depression had a 0.5% completion rate (97/19,607) [28]. Completion
35
36 350 rates may be particularly low in patients with more severe negative symptoms [22]. Despite these
37
38 351 historically poor completion rates in studies of digital health platforms, results of a meta-analysis
39
40 352 indicate that more than 50% of patients favor managing their mental health through the use of
41
42 353 mobile health technology [29], and the use of mobile devices for health management is viewed
43
44 354 by patients as normalized and nonstigmatizing [30]. The integrated DMS described here was
45
46 355 developed to leverage the advantages of digital technology to positively influence adherence in
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48 356 patients with schizophrenia.
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3 357 The DMS is a multimodal, user-friendly system that provides medication reminders and
4
5 358 measures patient ingestion of prescribed antipsychotic medications. The CoE product, in
6
7 359 particular, advances the ability to confirm medication ingestion and to assess adherence on a
8
9 360 continuous basis, which can inform whether uncontrolled symptoms may be explained by
10
11 361 nonadherence. Information from the DMS is made readily available to patients, caregivers (with
12
13 362 the patient's consent), and physicians for supported decision making, proactive intervention, and
14
15 363 individualized care. DMS also provides adherence feedback electronically to the patient, HCP,
16
17 364 and/or caregiver. The DMS provides this feedback discreetly, through user-owned and operated
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19 365 applications and a patch that is not readily visible as it is worn on the torso underneath clothing,
20
21 366 reducing any potential stigmatization if it (the patch) was visible. The DMS also provides
22
23 367 feedback on activity and rest levels, which is important given that maintenance of a healthy
24
25 368 lifestyle can help address the problems of weight gain and obesity that are related to both
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27 369 medication side effects and sedentary lifestyles [31]. Furthermore, shifts in activity levels may be
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29 370 indicative of altered patient disposition.
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36 371 This ongoing study was designed using coproduction methodology to incorporate input from
37
38 372 patients, caregivers, psychiatrists, pharmacists, nurses, and researchers. For all 5 study sites, a
39
40 373 minimum of 2 engagement/setup meetings were conducted and 2 specific patient focus groups
41
42 374 were held to guide protocol development and app design. The exploratory data collected in this
43
44 375 study, although limited to a small number of patients, will help provide a better understanding of
45
46 376 the ease of use for patients, HCPs, and caregivers to inform the development of future software
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48 377 or hardware iterations.
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53 378 Given the level of unfamiliarity with digital medicine systems, conducting clinical trials in this
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55 379 space requires a higher level of stakeholder management and alignment, especially when the trial
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3 380 is being held in a new environment. Whether it's a new country, a new healthcare system, or a
4
5 381 new set of investigators, formal buy-in and input is critical to participation. The protocol outlines
6
7 382 one way of managing and aligning stakeholders in such an environment - the UK mental health
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9 383 system. Additionally, and increasingly important within mental health services and interventions
10
11 384 in the UK, is the involvement of end-users, so called service users who have lived experience of
12
13 385 mental health. The methods paper describes a robust engagement strategy using such individuals
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15 386 in mental health research.
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20 387 Digital health interventions require significant clinician and patient engagement. The protocol
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22 388 describes an approach to ensure that service users of a digital medicine intervention can assist
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24 389 with protocol design and system input e.g. approach and appropriate language
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29 390 **CONCLUSION**

30
31 391 In conclusion, this study will examine the usability and acceptance of the DMS by patients with
32
33 392 schizophrenia, schizoaffective disorder, or first-episode psychosis, and by caregivers and HCPs
34
35 393 in different care settings. The study was meticulously coproduced through the engagement of all
36
37 394 stakeholders and, if successful, could be used to support DMS usage in larger cohorts within the
38
39 395 United Kingdom and Europe.
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45 397 **Funding statement**

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49
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51
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54 401 Pharmaceutical Development & Commercialization, Inc.
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402 **Competing interests statement**

403 Dr J. Corey Fowler, Dr Jonathan Knights, and Dr Tim Peters-Strickland are employees of Otsuka
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408 **Author contributions**

409 JCF, NC, JK, PP, AM, TP-S and SR contributed to study conception and design as well as data
410 collection, analysis, and interpretation; JCF, NC, JK, PP, AM, TP-S and SR were responsible for
411 review and critical revision of the manuscript; and JCF, NC, JK, PP, AM, TP-S and SR gave
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3 **519 Figure Legends**

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5 **520 Figure 1.** Digital medicine system: co-encapsulated antipsychotic medication with miniature
6
7 **521** ingestible event marker in tablet (MIT) and compatible medical device. DM=digital medicine;
8
9 **522** HCP=healthcare professional. Image reprinted from article in npg Digital Medicine [In Press].
10
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13 **523 Figure 2.** Description of coproduction workshops with Southern Health NHS Foundation Trust.
14
15 **524** DMS=digital medicine system; EIP=Early Intervention in Psychosis; IG=information
16
17 **525** governance; MoSCoW=must have, should have, could have, won't have; NHS=National Health
18
19 **526** Service; PANSS=Positive and Negative Syndrome Scale; PPI=Patient and Public Involvement
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21 **527** program.
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25 **528 Figure 3.** Study design.
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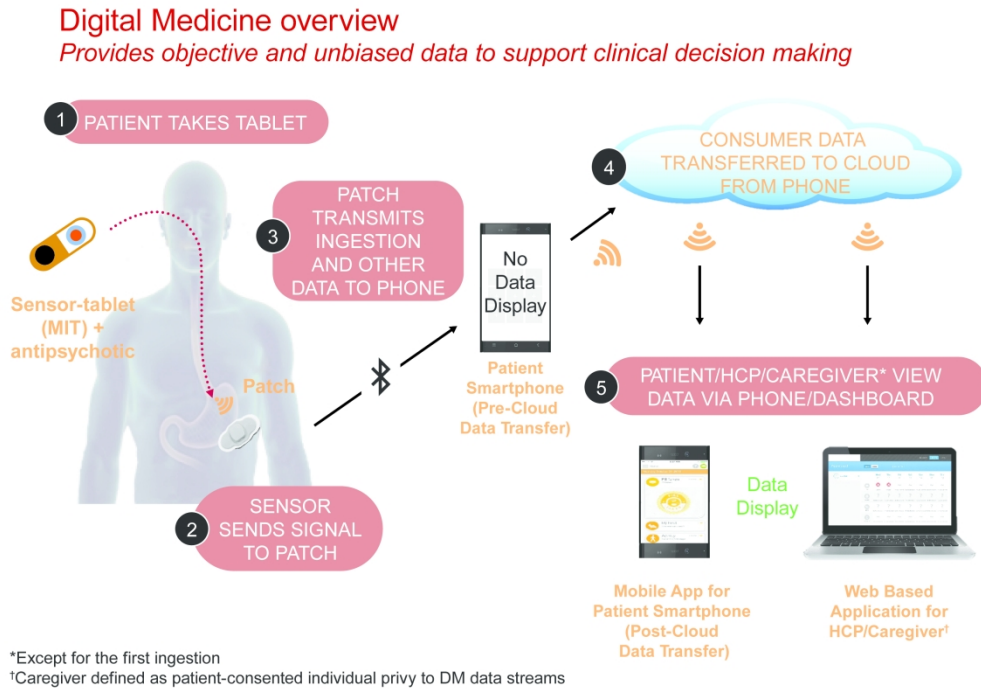


Figure 1. Digital medicine system: co-encapsulated antipsychotic medication with miniature ingestible event marker in tablet (MIT) and compatible medical device. DM=digital medicine; HCP=healthcare professional.

254x177mm (300 x 300 DPI)

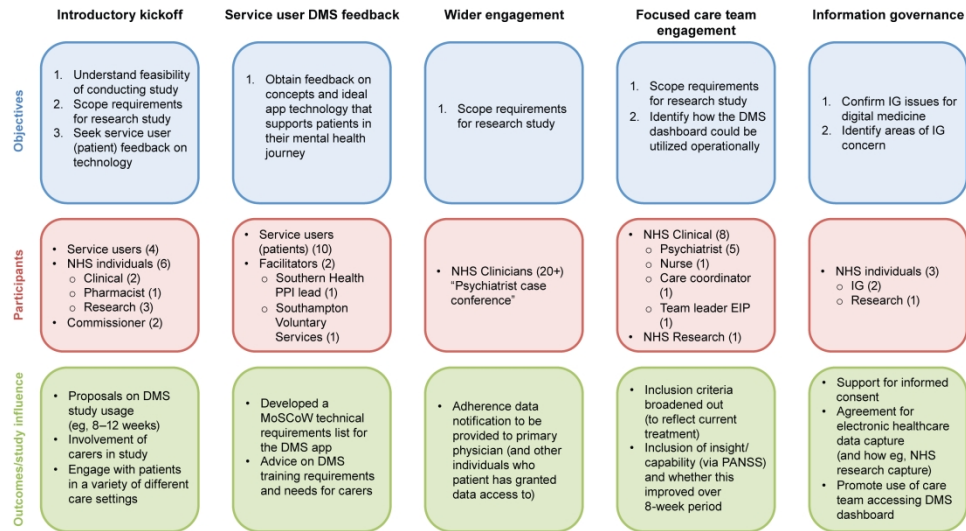
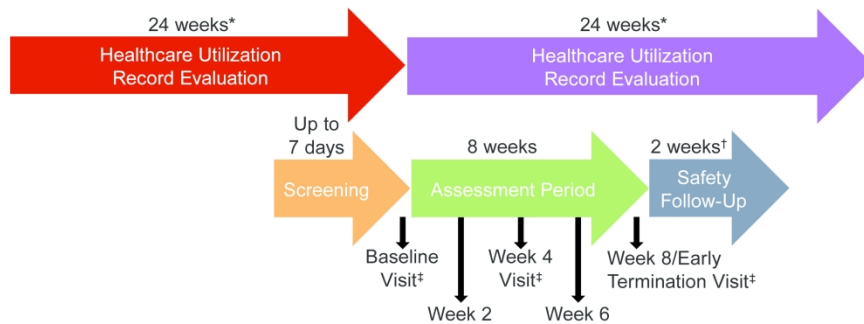


Figure 2. Description of coproduction workshops with Southern Health NHS Foundation Trust. DMS=digital medicine system; EIP=Early Intervention in Psychosis; IG=information governance; MoSCoW=must have, should have, could have, won't have; NHS=National Health Service; PANSS=Positive and Negative Syndrome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

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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?

	Extremel y 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)?

	Extremel y 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?

	Extremel y 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)?

	Extremel y 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)?

	Extremel y Difficult	Difficult	Somewhat Difficult	Neutral	Somewhat Easy	Easy	Extremel y 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 \checkmark (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: <i>Please Specify:</i> _____	

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

	Place a \checkmark (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: <i>Please Specify:</i> _____		

1
2
3 **15. Did you set up alerts to be notified of missed doses? Yes/no**

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

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

13
14 15a. If you received a missed dose alert what action did you take, if any? (If none,
15 please write N/A) _____

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

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

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

26
27 16a. If you received a multiple dose alert what action did you take, if any? (If none, please write
28 N/A) _____

29
30 **17. How well do you agree with the following statement?**

31 **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

38
39 **18. Based on your overall experience with this patient, how would you rate your satisfaction with the**
40 **Digital Medicine System?**

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

1
2
3 **Supplemental Figure 3. Caregiver/Support Person Involvement Scale (Ver 2.0)**
4
5

6 **DMS Caregiver/Support Person Involvement Scale**
7

- 8
9
10 **1. Are you aware that the study participant/patient is currently participating in the Digital**
11 **Medicine study (check one)?**
12

Yes	No*

13
14
15
16
17
18 ***If no, stop here and do not answer the rest of the questions on this form.**
19

- 20
21 **2. Indicate your relationship to the study participant/patient by placing a \surd (check).**
22

Friend	Hired Caregiver	Relative*	Other**

23
24
25
26
27
28 ***If you are a relative, please specify relationship to the study participant/patient, e.g.,**
29 **wife, father:**
30

31 ****If you selected "Other", please specify your relationship to the study**
32 **participant/patient:**
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3 **3. How much involvement did you provide the subject with regard to taking medication,**
4 **pairing the patch, applying the patch, and using the app during the course of the**
5 **study?**
6
7

	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?						

33
34
35
36 **Clinical Global Impression Scale**
37

38
39
40 Clinical Global Impression – Severity Scale (CGI-S)
41

42 Considering your total clinical experience with this particular population, how mentally ill is the
43 patient at this time?
44

45 0 = Not assessed

4 = Moderately ill

46
47 1 = Normal, not at all ill

5 = Markedly ill

48
49 2 = Borderline mentally ill

6 = Severely ill

50
51 3 = Mildly ill

7 = Among the most extremely ill subjects
52
53
54
55
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59
60

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
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For peer review only

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	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. Personal and social relationships	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Self-care	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. Disturbing and aggressive behaviors	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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

1
2
3
4
5 **7. I am confident that I can follow through on mental health treatments I need to do at home.**

6
7 1 2 3 4
8
9 Strongly Disagree Disagree Agree Strongly Agree

10
11
12 **8. I understand the nature and causes of my mental health condition(s).**

13
14 1 2 3 4
15
16 Strongly Disagree Disagree Agree Strongly Agree

17
18
19
20 **9. I know the different treatment options available for my mental health condition(s).**

21
22 1 2 3 4
23
24 Strongly Disagree Disagree Agree Strongly Agree

25
26
27
28 **10. I am able to maintain the lifestyle changes I have made for my mental health.**

29
30 1 2 3 4
31
32 Strongly Disagree Disagree Agree Strongly Agree

33
34
35 **11. I know how to prevent further mental health problems.**

36
37 1 2 3 4
38
39 Strongly Disagree Disagree Agree Strongly Agree

40
41
42
43 **12. I am confident I can figure out solutions when new situations or problems arise with my mental health.**

44
45 1 2 3 4
46
47 Strongly Disagree Disagree Agree Strongly Agree

48
49
50
51 **13. I am confident that I can maintain lifestyle changes, like diet and exercise, even during times of stress.**

52
53 1 2 3 4
54
55 Strongly Disagree Disagree Agree Strongly Agree



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	<u>Page 1 Line 1</u>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	<u>Page 4 Line 64</u>
	2b	All items from the World Health Organization Trial Registration Data Set	Provided on <u>ClinicalTrials.gov</u>
Protocol version	3	Date and version identifier	<u>Page 1 of protocol</u>
Funding	4	Sources and types of financial, material, and other support	<u>Page 20 Line 396</u>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	<u>Page 21 Line 408</u>
	5b	Name and contact information for the trial sponsor	<u>Page 1 Line 22</u>
	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	<u>Page 21 Line 407</u>
	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)	<u>Page 21 Line 407</u>

1 **Introduction**

2

3 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](#)

4

5

6 6b Explanation for choice of comparators [N/A](#)

7

8 Objectives 7 Specific objectives or hypotheses [Page 9 Line 163](#)

9

10 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](#)

11

12

13

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

15

16 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](#)

17

18

19 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](#)

20

21

22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered [Page 11 Line 190](#)

23

24

25 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](#)

26

27

28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) [Page 19 Line 358](#)

29

30

31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial [As listed on each drug label](#)

32

33

34

35 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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1	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)	<u>Figure 3</u>
2				
3				
4	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	<u>Page 15 Line 282</u>
5				
6				
7	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	<u>Page 13 Line 249</u>
8				

9
10 **Methods: Assignment of interventions (for controlled trials)**

11 Allocation:

12				
13				
14	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	<u>N/A</u>
15				
16				
17				
18				
19	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	<u>N/A</u>
20				
21				
22				
23				
24	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	<u>N/A</u>
25				
26				
27	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	<u>N/A</u>
28				
29				
30		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	<u>N/A</u>
31				
32				
33				

34 **Methods: Data collection, management, and analysis**

35				
36	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	<u>Protocol Page 81</u>
37				
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1		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	<u>Page 14 Line 259</u>
2				
3				
4	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	<u>Protocol Page 73</u>
5				
6				
7				
8	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	<u>Protocol Page 73</u>
9				
10				
11		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<u>Page 15 Line 282</u>
12				
13		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)	<u>Page 15 Line 282</u>
14				
15				
16				
17	Methods: Monitoring			
18				
19	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	<u>N/A Pragmatic Trial - Safety of Interventions is Established</u>
20				
21				
22				
23				
24				
25		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	<u>N/A</u>
26				
27				
28	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	<u>Protocol Page 66</u>
29				
30				
31	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	<u>Protocol Page 81</u>
32				
33				
34				
35	Ethics and dissemination			
36				
37	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	<u>Page 16 Line 309</u>
38				
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1	Protocol	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
2	amendments			
3				
4				
5	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
6				
7				
8		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
9				
10				
11	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
12				
13				
14	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 21 Line 402
15				
16				
17				
18	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
19				
20				
21	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
22				
23				
24	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
25				
26				
27				
28				
29		31b	Authorship eligibility guidelines and any intended use of professional writers	Protocol page 84
30				
31		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not yet determined
32				
33	Appendices			
34				
35	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Protocol Page 107
36				
37				
38	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
39				
40				
41				
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For peer review only

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

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29 6 Running title: Study protocol for DMS use in schizophrenia in the UK
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36 8 Authors:

37 9 J. Corey Fowler, PhD,¹ Nathan Cope, PhD,² Jonathan Knights, PhD,¹ Peter Phiri, PhD,³ Andrew
38 10 Makin, MD,⁴ Tim Peters-Strickland, MD,¹ Shanaya Rathod, DM, MRCPsych³
39
40
41
42
43

44 12 Affiliations:

45 13 ¹Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, USA; ²Otsuka
46 14 Pharmaceutical Europe Ltd., Wexham, UK; ³Southern Health NHS Foundation Trust,
47 15 Southampton, UK; ⁴Otsuka Europe Development and Commercialisation Ltd., Wexham, UK
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61 17 E-mail addresses:

62 18 corey.fowler@otsuka-us.com, NCope@otsuka-europe.com, Jonathan.Knights@otsuka-us.com,
63 19 Peter.Phiri@southernhealth.nhs.uk, AMakin@otsuka-europe.com, [tim.peters-strickland@otsuka-
65 21 us.com](mailto:tim.peters-strickland@otsuka-
64 20 us.com), shanayarathod@nhs.net

66 22 Address correspondence to: J. Corey Fowler, PhD

67 23 corey.fowler@otsuka-us.com

68 24 Associate Director, Global Clinical Development

69 25 Otsuka Pharmaceutical Development & Commercialization, Inc.

70 26 508 Carnegie Center Blvd, Suite 300

71 27 Princeton, NJ 08540, USA

72 28 +1 919 475 4823

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36 **ABSTRACT**

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

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

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

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

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

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

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

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

65 **Keywords**

66 Coproduction, digital medicine, schizoaffective disorder, schizophrenia

67 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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

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3 79 • Information from the DMS is made readily available to patients, caregivers (with the
4
5 patient's consent), and physicians to support clinical decision making, proactive
6 80
7 intervention, and individualized care in near to real time.
8 81
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10 82 • Possible limitations of this study are the small sample size (N=60), limited
11
12 generalizability to the broader pool of UK mental health patients and providers, and the
13 83
14 relatively short 12-week timeframe. Although the DMS does require the patient to
15 84
16 engage more with their own care, the benefits of increasing their awareness of
17 85
18 medication, activity, rest, and mood patterns may outweigh risks/burden for most
19 86
20 patients. The DMS was not developed for all mental health patients, but for a subset of
21 87
22 patients who realize they have difficulty with adherence and want to improve their status
23 88
24 by self-monitoring with potential for their HCP's to make better clinical decisions based
25 89
26 on objective data from the DMS. Patients with poor insight into their illness will likely be
27 90
28 a better candidate for a long-acting injectable atypical antipsychotic than this DMS.
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93 INTRODUCTION

94 Schizophrenia has an enormous social and economic burden worldwide, accounting for 1.1% of
95 total disability-adjusted life-years and 2.7% of years lived with disability [1, 2]. In Europe, the
96 economic impact of schizophrenia and other psychotic disorders and syndromes in 2010 was
97 estimated at €93.9 billion [3]. Because schizophrenia is a chronic disease, maintenance treatment
98 is often necessary to prevent relapse and preserve quality of life over the long term [4, 5].

99 Although antipsychotic medications are effective [6-8], poor insight into schizophrenia can
100 increase risk of medication nonadherence [9, 10]. In patients with schizophrenia, the rate of
101 nonadherence to prescribed antipsychotics has been reported to be as high as 74% [11]. Not only
102 is medication nonadherence burdensome to patients and their families, it also increases the
103 likelihood of rehospitalization and relapse [12] and contributes substantially to healthcare costs
104 [13]. In 2005/2006, mean annual psychiatric inpatient and medication costs for patients with
105 schizophrenia in England were estimated to be approximately £3,000 and £2,000 per patient,
106 respectively [14].

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

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3 115 patients with schizophrenia requires a system that provides physicians with objective information
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5 116 during interim periods between patient visits.
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8 117 The use of modern technology such as personal digital assistants [19], digital wristwatches [20],
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10 118 handheld computers [21], and mobile phones [22] to help people with schizophrenia dealing with
11
12 119 their disease has shown success. A digital medicine system (DMS) has been developed as a drug-
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14 120 device combination to objectively assess and report ingestion of prescription antipsychotics [23].
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17 121 The DMS has 4 main components: an ingestible sensor embedded within an inert tablet, a
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19 122 nonmedicated wearable sensor (patch) worn by the patient, a mobile application (app), and a
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21 123 Web-based dashboard [23]. Upon interaction with stomach fluids, the ingestible sensor is
22
23 124 activated and communicates with the wearable sensor, which sends a signal to a Bluetooth-paired
24
25 125 mobile device where it can be viewed by patients or be subsequently viewed by HCPs and
26
27 126 caregivers using secure mobile- and cloud-based software [23]. The DMS also enables patients
28
29 127 to share data on their activity and rest levels as well as subjective data on mood and rest quality,
30
31 128 which can be generated while the patient is engaged with the system. The intention of the DMS
32
33 129 is to encourage greater patient self-management and behavior change while enabling caregivers
34
35 130 and HCPs to provide better care and support both within and outside of office visits, further
36
37 131 engaging patients in their ongoing disease management. The data is communicated to the
38
39 132 psychiatrist that is connected to the patient on the MyCite platform. Additionally, should the
40
41 133 patient choose to share their data, they are able to invite additional healthcare providers,
42
43 134 caregivers and/or family or friends. Recipients of the data, through a web-based password
44
45 135 protected platform, are able to view this data and assist the patient with their treatment plan,
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47 136 however HCPs can only access the portal for a specific patient once he/she has consented to give
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49 137 them access to their information in the system. It is envisioned that HCPs will be able to use this
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138 data to make more informed clinical decisions such as whether individuals need dose adjustment,
139 medication changes or conversations on lifestyle, adherence or other parameters.

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

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

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

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3 161 Previous studies performed using the DMS were conducted in relatively stable individuals with
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5 162 schizophrenia. For this study, we have broadened the inclusion criteria and will be assessing the
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7 163 technology in a range of clinical groups from different care settings, such as those individuals
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9 164 managed in the community or on specialized services such as Early Intervention in Psychosis
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11 165 services to determine the performance in these different environments.
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14
15 166 The study is not intended to measure and report or make any claims of adherence, but instead, to
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17 167 report the observed ingestions recorded by the DMS. Our goal is to look at the impact of
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19 168 patients' improvements as a result of participation (e.g. reduced need for follow-up care,
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21 169 knowledge of adherence to medication to help physicians decide whether patients are medication
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23 170 compliant or require a long acting injectable or other follow-up care) with the hypothesis that
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25 171 DMS will reduce overall healthcare utilization burden by optimizing treatment decisions.
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31 172 **METHODS AND ANALYSIS**

32 33 34 35 173 **Study design**

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37 174 This is a multicenter, 8-week, single-arm, open-label trial to evaluate the acceptance and
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39 175 performance of the DMS in adult patients with schizophrenia, schizoaffective disorder, or first-
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41 176 episode psychosis on an oral atypical antipsychotic medication (aripiprazole, olanzapine,
42
43 177 quetiapine, or risperidone) and in HCPs. Recruitment began the same day that we submitted to
44
45 178 CT.gov, 25/MAY. However, we didn't consent our first patient until 11/JUN and dosing
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47 179 occurred on 18/JUN. The study will take place at 5 institutions in the United Kingdom:
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49 180 Northumberland, Tyne and Wear National Health Service (NHS) Foundation Trust, Surrey and
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51 181 Borders Partnership NHS Foundation Trust, Oxford Health NHS Foundation Trust, South
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53 182 London and Maudsley NHS Foundation Trust, and Southern Health NHS Foundation Trust. The
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183 first patient's first visit occurred in May 2018. Patient recruitment will be targeted to last
184 approximately 4 months.

185 **Patient selection**

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

192 **Table 1. Inclusion and Exclusion Criteria**

Inclusion criteria
<ul style="list-style-type: none"> • Willing and able to give written informed consent and adhere to trial procedures • Able to read and understand English • Age 18–65 years at the time of informed consent • 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.) • Cooperative, able to ingest oral medication, willing to complete aspects of the trial, and capable of reporting adverse events (AEs) • 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 • Prescription for aripiprazole, olanzapine, quetiapine, or risperidone • Fulfills ≥ 1 of the following: <ul style="list-style-type: none"> ○ Discharge from a hospital admission (within 7 days of discharge) to an acute intervention team ○ Referral to an acute intervention team before hospital admission ○ Referral from an acute intervention team to a community team ○ Managed by community services ○ Inclusion within early intervention caseload (<3 years from initial symptoms) ○ Healthcare professional (HCP) determines the patient would benefit • General medical condition does not pose additional risk

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- 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
- Likely to be incapable of using DMS technology, even with assistance
- History or evidence of a medical condition that would expose patient to undue risk of an AE
- Known allergy to adhesive tape or any component of the patch or co-encapsulation product
- Current incarceration in prison system
- Hospitalization at the time of screening due to mental or physical illness
- HCP recommendation to not participate
- Aversion to taking gelatin capsules
- Women who are breastfeeding, pregnant, or plan to become pregnant

193

Intervention

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

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

208

209 **Patient and Public Involvement Statement**

210 **Coproduction**

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

226

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227 **Patient Involvement**

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

235

236 **Procedures**

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

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

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

266 **Outcomes**

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

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272 The following exploratory endpoints will also be included:

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

289 **Statistical analysis**

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

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3 294 in the USA. The discontinuation rate is assumed based on similar discontinuations for other
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5 295 psychiatry studies and the fact that an actively clinical stable population is not being recruited.
6
7
8 296 Data will be analyzed in the intent-to-treat population (ie, all patients who enter the trial and use
9
10 297 the DMS). All data will be analyzed using descriptive statistics. Continuous variables will be
11
12 298 summarized using mean, median, range, and standard deviation. Categorical variables will be
13
14 299 summarized using frequency distributions.
15
16
17

18 300 **Data protection**

19
20 301 Before initiating participation, informed consent will be obtained from all patients and
21
22 302 caregivers. Health information will be de-identified to the fullest possible extent. However, some
23
24 303 identifiers or sensitive health information cannot be stripped (eg, psychiatric medical history,
25
26 304 participation in a care program approach, presence of a community treatment order, employment
27
28 305 status, disabilities, housing arrangements, or armed forces history). Health information will be
29
30 306 used to develop and improve the DMS application and user experience. The DMS and associated
31
32 307 third-party vendors are compliant with the General Data Protection Regulation (GDPR), and all
33
34 308 accessed health information will be maintained in the strictest confidence and in compliance with
35
36 309 the GDPR. Data from the DMS are encrypted in activity and rest and will be accessed only by
37
38 310 role-specific individuals for discrete time periods and functions (eg, technical troubleshooting).
39
40 311 All data will be completely anonymized for graphical, statistical, and publication purposes.
41
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44 312 Research staff from NHS sites will store consent documents, demographic forms, and receipts
45
46 313 for reimbursement of travel in locked filing cabinets to which only research staff will have
47
48 314 access. Accessing of health data will be compliant with IG policies of each participating NHS
49
50 315 trust.
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316 **Ethical considerations**

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

325 **Dissemination of study results**

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

332 **DISCUSSION**

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

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

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

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

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

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

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

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

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

397 **CONCLUSION**

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

403

404 **Funding statement**

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29
30
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32
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4 526 **Figure Legends**

5 527 **Figure 1.** Digital medicine system: co-encapsulated antipsychotic medication with miniature
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7 528 ingestible event marker in tablet (MIT) and compatible medical device. DM=digital medicine;
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9 529 HCP=healthcare professional. Image reprinted from article in npg Digital Medicine [In Press].

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13 530 **Figure 2.** Description of coproduction workshops with Southern Health NHS Foundation Trust.
14
15 531 DMS=digital medicine system; EIP=Early Intervention in Psychosis; IG=information
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17 532 governance; MoSCoW=must have, should have, could have, won't have; NHS=National Health
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19 533 Service; PANSS=Positive and Negative Syndrome Scale; PPI=Patient and Public Involvement
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22 534 program.

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25 535 **Figure 3.** Study design.
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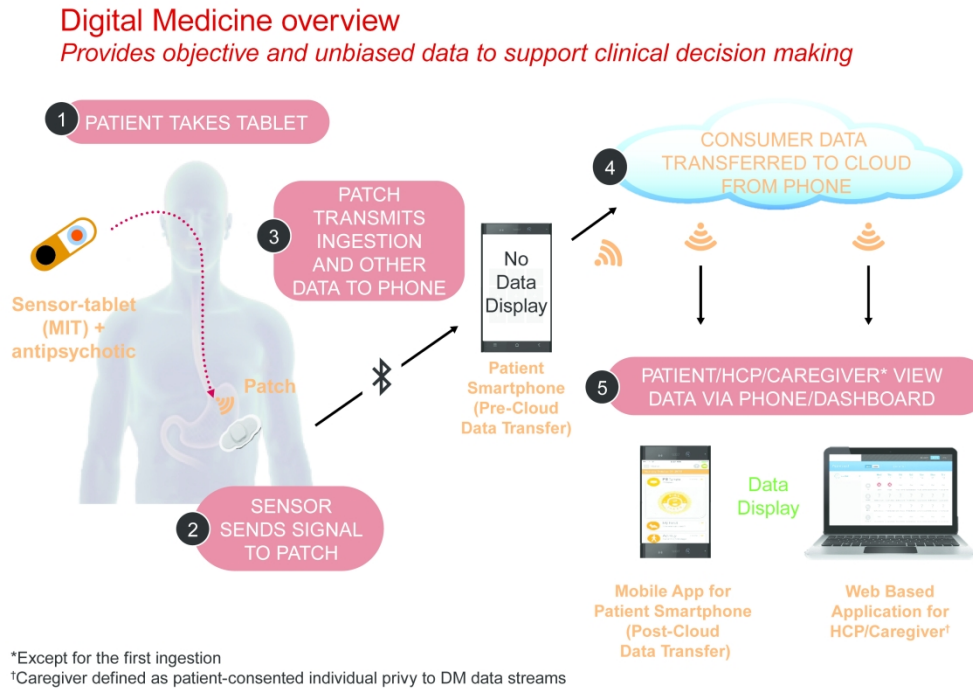


Figure 1. Digital medicine system: co-encapsulated antipsychotic medication with miniature ingestible event marker in tablet (MIT) and compatible medical device. DM=digital medicine; HCP=healthcare professional.

254x177mm (300 x 300 DPI)

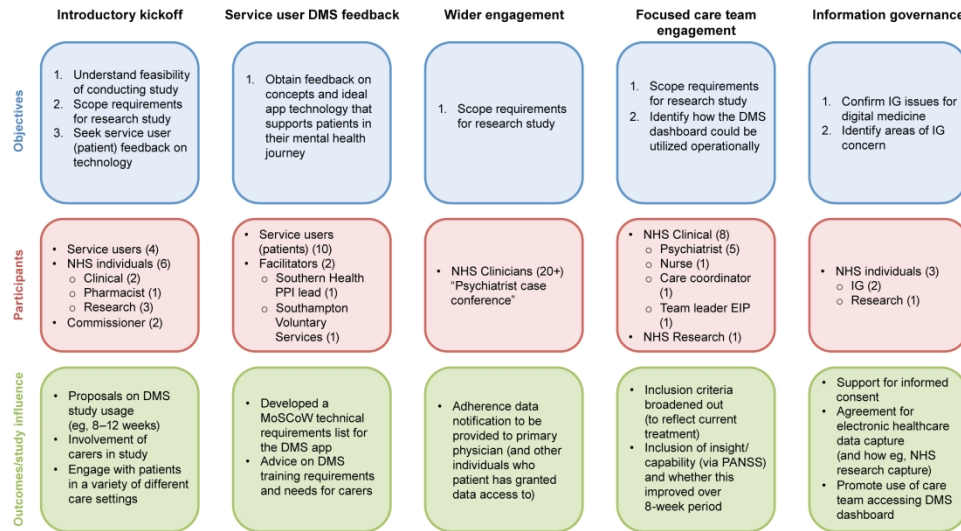
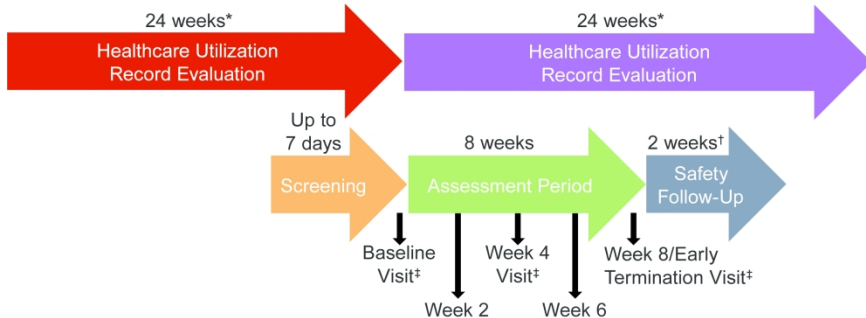


Figure 2. Description of coproduction workshops with Southern Health NHS Foundation Trust. DMS=digital medicine system; EIP=Early Intervention in Psychosis; IG=information governance; MoSCoW=must have, should have, could have, won't have; NHS=National Health Service; PANSS=Positive and Negative Syndrome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

317x184mm (300 x 300 DPI)

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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?

	Extremel y 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)?

	Extremel y 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?

	Extremel y 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)?

	Extremel y 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)?

	Extremel y Difficult	Difficult	Somewhat Difficult	Neutral	Somewhat Easy	Easy	Extremel y 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

1
2
3
4 **11. How helpful or unhelpful was the Digital Medicine System in improving your conversations with**
5 **your patient about their treatment plan and progress?**
6

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

13 **12. How helpful or unhelpful was the Digital Medicine System in the identification of**
14 **potential lifestyle changes for your patient (eg sleep and exercise)?**
15

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

22 **13. Other than during the patient visit(s), did you look at the HCP dashboard at other**
23 **times? Please select all that apply**
24

	Place a \checkmark (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: <i>Please Specify:</i> _____	

32 **14. What features did you find helpful? Please select all that apply**
33

	Place a \checkmark (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: <i>Please Specify:</i> _____		

1
2
3 **15. Did you set up alerts to be notified of missed doses? Yes/no**

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

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

13 15a. If you received a missed dose alert what action did you take, if any? (If none,
14 please write N/A) _____

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

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

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

27 16a. If you received a multiple dose alert what action did you take, if any? (If none, please write
28 N/A) _____

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

31 **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

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

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

1
2
3 **Supplemental Figure 3. Caregiver/Support Person Involvement Scale (Ver 2.0)**
4
5

6 **DMS Caregiver/Support Person Involvement Scale**
7

- 8
9 **1. Are you aware that the study participant/patient is currently participating in the Digital**
10 **Medicine study (check one)?**
11

Yes	No*

12
13
14
15
16
17
18 ***If no, stop here and do not answer the rest of the questions on this form.**
19

- 20
21 **2. Indicate your relationship to the study participant/patient by placing a √ (check).**
22

Friend	Hired Caregiver	Relative*	Other**

23
24
25
26
27
28 ***If you are a relative, please specify relationship to the study participant/patient, e.g.,**
29 **wife, father:**
30

31 ****If you selected "Other", please specify your relationship to the study**
32 **participant/patient:**
33
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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

4 = Moderately ill

1 = Normal, not at all ill

5 = Markedly ill

2 = Borderline mentally ill

6 = Severely ill

3 = Mildly 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
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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	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. Personal and social relationships	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Self-care	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. Disturbing and aggressive behaviors	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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

1
2
3
4
5 **7. I am confident that I can follow through on mental health treatments I need to do at home.**

6
7 1 2 3 4
8
9 Strongly Disagree Disagree Agree Strongly Agree

10
11
12 **8. I understand the nature and causes of my mental health condition(s).**

13
14 1 2 3 4
15
16 Strongly Disagree Disagree Agree Strongly Agree

17
18
19
20 **9. I know the different treatment options available for my mental health condition(s).**

21
22 1 2 3 4
23
24 Strongly Disagree Disagree Agree Strongly Agree

25
26
27
28 **10. I am able to maintain the lifestyle changes I have made for my mental health.**

29
30 1 2 3 4
31
32 Strongly Disagree Disagree Agree Strongly Agree

33
34
35 **11. I know how to prevent further mental health problems.**

36
37 1 2 3 4
38
39 Strongly Disagree Disagree Agree Strongly Agree

40
41
42
43 **12. I am confident I can figure out solutions when new situations or problems arise with my mental health.**

44
45 1 2 3 4
46
47 Strongly Disagree Disagree Agree Strongly Agree

48
49
50
51 **13. I am confident that I can maintain lifestyle changes, like diet and exercise, even during times of stress.**

52
53 1 2 3 4
54
55 Strongly Disagree Disagree Agree Strongly Agree

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3 Supplemental Material – PRECIS-2 Tool Assessment
4
5

6 Whilst the PRECIS-2 tool assessment was not completed during the design of the study, when it
7 is designed to be conducted, a post assessment use of the tool confirms the use of the term
8 pragmatic. For example, from the nine PRECIS-2 domains:
9
10

11 Eligibility: Would score 4 (out of 5) since those identified in the study would be those identified
12 in usual care. The study does exclude inpatients, which in the “real world” could in theory
13 participate but we felt the DMS intervention was of limited benefit in this setting since inpatients
14 have observed adherence
15
16

17 Recruitment: would score 4-5 since recruitment is based simply on screening patient caseloads
18 and assessment of patients who may need help with adherence measures. No advertisements
19 have been conducted.
20
21

22 Setting: Would score 4-5 since the care settings used in the study are those in usual care. We
23 have a range of participants from community and specialist mental health services
24
25

26 Organisation: Would likely score 3-4 since although the resource/expertise is largely similar to
27 usual care, the study does use NHS research staff to assist with training and screening, as is
28 commonplace with all clinical studies in the UK
29
30

31 Flexibility (delivery): Would score 3-4 since the study gives patients and HCPs the ability to
32 follow standard of care but does require specific site visit at w4 and w8 (yet one could argue this
33 would occur naturally since the w4 visit is to collect a new prescription (which would occur in
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3 the real world) and the w8 visit is the completion of the study. Patients do not experience any
4
5 other “forced” visits.
6
7

8
9 Flexibility (adherence): Would score 3 since following enrolment if patients do not utilise the
10
11 patch/app the site can contact the patient to found out why they are not engaging and try to
12
13 encourage; however, this would be the same if the DMS was indeed normal practice; this is the
14
15 intention of the tool to promote conversations between visits when individuals are not adherent.
16
17

18
19 Primary outcome: would score 3-4; whilst the outcome may not be obvious to patients, the
20
21 outcome has been supported from conversations with HCPs and payers. The good patch
22
23 coverage days are essential to provide insight into medication taking so again, if the intervention
24
25 become standard, the metric would be used since it would determine whether objective and
26
27 insightful data was being captured.
28
29
30

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33
34
35 Primary analysis: Would score 4 since all individuals will be included in the analysis with all
36
37 available data.
38
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41
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44
45 Based on the above, the average score is approx. 4 which equates to “Rather pragmatic”
46
47

48
49 The reason why the study is not the top score of 5 (Very pragmatic) is that the intervention itself
50
51 does cause changes to current care but we are not stating how individuals should respond to these
52
53 changes. They are free to decide for themselves.
54
55
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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	<u>Page 1 Line 1</u>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	<u>Page 4 Line 64</u>
	2b	All items from the World Health Organization Trial Registration Data Set	Provided on <u>ClinicalTrials.gov</u>
Protocol version	3	Date and version identifier	<u>Page 1 of protocol</u>
Funding	4	Sources and types of financial, material, and other support	<u>Page 20 Line 396</u>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	<u>Page 21 Line 408</u>
	5b	Name and contact information for the trial sponsor	<u>Page 1 Line 22</u>
	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	<u>Page 21 Line 407</u>
	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)	<u>Page 21 Line 407</u>

1 **Introduction**

2

3 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](#)

4

5

6 6b Explanation for choice of comparators [N/A](#)

7

8 Objectives 7 Specific objectives or hypotheses [Page 9 Line 163](#)

9

10 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](#)

11

12

13

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

15

16 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](#)

17

18

19 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](#)

20

21

22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered [Page 11 Line 190](#)

23

24

25 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](#)

26

27

28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) [Page 19 Line 358](#)

29

30

31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial [As listed on each drug label](#)

32

33

34

35 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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1	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)	<u>Figure 3</u>
2				
3				
4	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	<u>Page 15 Line 282</u>
5				
6				
7	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	<u>Page 13 Line 249</u>
8				

Methods: Assignment of interventions (for controlled trials)

Allocation:

13	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	<u>N/A</u>
14				
15				
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19	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	<u>N/A</u>
20				
21				
22				
23				
24	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	<u>N/A</u>
25				
26				
27	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	<u>N/A</u>
28				
29				
30		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	<u>N/A</u>
31				
32				

Methods: Data collection, management, and analysis

36	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	<u>Protocol Page 81</u>
37				
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1		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	<u>Page 14 Line 259</u>
2				
3				
4	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	<u>Protocol Page 73</u>
5				
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7				
8	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	<u>Protocol Page 73</u>
9				
10				
11		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<u>Page 15 Line 282</u>
12				
13		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)	<u>Page 15 Line 282</u>
14				
15				
16				
17	Methods: Monitoring			
18				
19	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	<u>N/A Pragmatic Trial - Safety of Interventions is Established</u>
20				
21				
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24				
25		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	<u>N/A</u>
26				
27				
28	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	<u>Protocol Page 66</u>
29				
30				
31	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	<u>Protocol Page 81</u>
32				
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35	Ethics and dissemination			
36				
37	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	<u>Page 16 Line 309</u>
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1	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
2				
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4				
5	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
6				
7				
8		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
9				
10				
11	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
12				
13				
14	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 21 Line 402
15				
16				
17				
18	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
19				
20				
21	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
22				
23				
24	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
25				
26				
27				
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29		31b	Authorship eligibility guidelines and any intended use of professional writers	Protocol page 84
30				
31		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not yet determined
32				
33	Appendices			
34				
35	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Protocol Page 107
36				
37				
38	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
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*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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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

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Complete List of Authors:	Fowler, J.; Otsuka Pharmaceutical Development & Commercialization, Inc., Cope, Nathan; Otsuka Pharmaceutical Europe Ltd. Knights, Jonathan; Otsuka Pharmaceutical Development & Commercialization, Inc. Phiri, Peter; Southern Health NHS Foundation Trust Makin, Andrew; Otsuka Europe Development and Commercialisation Ltd. Peters-Strickland, Tim; Otsuka Pharmaceutical Development & Commercialization, Inc. Rathod, Shanaya; Southern Health NHS Foundation Trust, Psychiatry
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6 2 **Trial to Assess the Acceptance and Performance of a Digital Medicine System**
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9 3 **in Adults With Schizophrenia, Schizoaffective Disorder, or First-Episode**
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36 8 Authors:

37 9 J. Corey Fowler, PhD,¹ Nathan Cope, PhD,² Jonathan Knights, PhD,¹ Peter Phiri, PhD,³ Andrew
38 10 Makin, MD,⁴ Tim Peters-Strickland, MD,¹ Shanaya Rathod, DM, MRCPsych³
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42
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44 12 Affiliations:

45 13 ¹Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, USA; ²Otsuka
46 14 Pharmaceutical Europe Ltd., Wexham, UK; ³Southern Health NHS Foundation Trust,
47 15 Southampton, UK; ⁴Otsuka Europe Development and Commercialisation Ltd., Wexham, UK
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59
60

61 17 E-mail addresses:

62 18 corey.fowler@otsuka-us.com, NCope@otsuka-europe.com, Jonathan.Knights@otsuka-us.com,
63 19 Peter.Phiri@southernhealth.nhs.uk, AMakin@otsuka-europe.com, [tim.peters-strickland@otsuka-](mailto:tim.peters-strickland@otsuka-us.com)
64 20 us.com, shanayarathod@nhs.net
65
66
67
68
69
70

71 22 Address correspondence to: J. Corey Fowler, PhD

72 23 corey.fowler@otsuka-us.com

73 24 Associate Director, Global Clinical Development

74 25 Otsuka Pharmaceutical Development & Commercialization, Inc.

75 26 508 Carnegie Center Blvd, Suite 300

76 27 Princeton, NJ 08540, USA

77 28 +1 919 475 4823

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36 ABSTRACT

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

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

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

64
65 ClinicalTrials.gov: NCT03568500; EudraCT 2017-004602-17

66 **Keywords**

67 Coproduction, digital medicine, schizoaffective disorder, schizophrenia

68 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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

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3 80 • Possible limitations of this study are the small sample size (N=60), limited
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6 81 generalizability to the broader pool of UK mental health patients and providers, and the
7
8 82 relatively short 12-week timeframe.
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10 83 • The DMS was not developed for all mental health patients, but for a subset of patients
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12 84 who realize they have difficulty with adherence and want to improve their status by self-
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14 85 monitoring with potential for their HCP's to make better clinical decisions based on
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17 86 objective data from the DMS.
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87 INTRODUCTION

88 Schizophrenia has an enormous social and economic burden worldwide, accounting for 1.1% of
89 total disability-adjusted life-years and 2.7% of years lived with disability [1, 2]. In Europe, the
90 economic impact of schizophrenia and other psychotic disorders and syndromes in 2010 was
91 estimated at €93.9 billion [3]. Because schizophrenia is a chronic disease, maintenance treatment
92 is often necessary to prevent relapse and preserve quality of life over the long term [4, 5].

93 Although antipsychotic medications are effective [6-8], poor insight into schizophrenia can
94 increase risk of medication nonadherence [9, 10]. In patients with schizophrenia, the rate of
95 nonadherence to prescribed antipsychotics has been reported to be as high as 74% [11]. Not only
96 is medication nonadherence burdensome to patients and their families, it also increases the
97 likelihood of rehospitalization and relapse [12] and contributes substantially to healthcare costs
98 [13]. In 2005/2006, mean annual psychiatric inpatient and medication costs for patients with
99 schizophrenia in England were estimated to be approximately £3,000 and £2,000 per patient,
100 respectively [14].

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

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

111 The use of modern technology such as personal digital assistants [19], digital wristwatches [20],
112 handheld computers [21], and mobile phones [22] to help people with schizophrenia dealing with
113 their disease has shown success. A digital medicine system (DMS) has been developed as a drug-
114 device combination to objectively assess and report ingestion of prescription antipsychotics [23].

115 The DMS has 4 main components: an ingestible sensor embedded within an inert tablet, a
116 nonmedicated wearable sensor (patch) worn by the patient, a mobile application (app), and a
117 Web-based dashboard [23]. Upon interaction with stomach fluids, the ingestible sensor is
118 activated and communicates with the wearable sensor, which sends a signal to a Bluetooth-paired
119 mobile device where it can be viewed by patients or be subsequently viewed by HCPs and
120 caregivers using secure mobile- and cloud-based software [23]. The DMS also enables patients
121 to share data on their activity and rest levels as well as subjective data on mood and rest quality,
122 which can be generated while the patient is engaged with the system. The intention of the DMS
123 is to encourage greater patient self-management and behavior change while enabling caregivers
124 and HCPs to provide better care and support both within and outside of office visits, further
125 engaging patients in their ongoing disease management. The data is communicated to the
126 psychiatrist that is connected to the patient on the MyCite platform. Additionally, should the
127 patient choose to share their data, they are able to invite additional healthcare providers,
128 caregivers and/or family or friends. Recipients of the data, through a web-based password
129 protected platform, are able to view this data and assist the patient with their treatment plan,
130 however HCPs can only access the portal for a specific patient once he/she has consented to give
131 them access to their information in the system. It is envisioned that HCPs will be able to use this

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

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

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

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

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3 155 Previous studies performed using the DMS were conducted in relatively stable individuals with
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5 156 schizophrenia. For this study, we have broadened the inclusion criteria and will be assessing the
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7 157 technology in a range of clinical groups from different care settings, such as those individuals
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9 158 managed in the community or on specialized services such as Early Intervention in Psychosis
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11 159 services to determine the performance in these different environments.
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15 160 The study is not intended to measure and report or make any claims of adherence, but instead, to
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17 161 report the observed ingestions recorded by the DMS. Our goal is to look at the impact of
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19 162 patients' improvements as a result of participation (e.g. reduced need for follow-up care,
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21 163 knowledge of adherence to medication to help physicians decide whether patients are medication
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23 164 compliant or require a long acting injectable or other follow-up care) with the hypothesis that
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25 165 DMS will reduce overall healthcare utilization burden by optimizing treatment decisions.
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31 166 **METHODS AND ANALYSIS**

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35 167 **Study design**

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37 168 This is a multicenter, 8-week, single-arm, open-label trial to evaluate the acceptance and
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39 169 performance of the DMS in adult patients with schizophrenia, schizoaffective disorder, or first-
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41 170 episode psychosis on an oral atypical antipsychotic medication (aripiprazole, olanzapine,
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43 171 quetiapine, or risperidone) and in HCPs. Recruitment began the same day that we submitted to
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45 172 CT.gov, 25/MAY. However, we didn't consent our first patient until 11/JUN and dosing
46
47 173 occurred on 18/JUN. The study will take place at 5 institutions in the United Kingdom:
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49 174 Northumberland, Tyne and Wear National Health Service (NHS) Foundation Trust, Surrey and
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51 175 Borders Partnership NHS Foundation Trust, Oxford Health NHS Foundation Trust, South
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53 176 London and Maudsley NHS Foundation Trust, and Southern Health NHS Foundation Trust. The
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177 first patient's first visit occurred in May 2018. Patient recruitment will be targeted to last
178 approximately 4 months.

179 **Patient selection**

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

186 **Table 1. Inclusion and Exclusion Criteria**

Inclusion criteria
<ul style="list-style-type: none"> • Willing and able to give written informed consent and adhere to trial procedures • Able to read and understand English • Age 18–65 years at the time of informed consent • 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.) • Cooperative, able to ingest oral medication, willing to complete aspects of the trial, and capable of reporting adverse events (AEs) • 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 • Prescription for aripiprazole, olanzapine, quetiapine, or risperidone • Fulfills ≥ 1 of the following: <ul style="list-style-type: none"> ○ Discharge from a hospital admission (within 7 days of discharge) to an acute intervention team ○ Referral to an acute intervention team before hospital admission ○ Referral from an acute intervention team to a community team ○ Managed by community services ○ Inclusion within early intervention caseload (<3 years from initial symptoms) ○ Healthcare professional (HCP) determines the patient would benefit • General medical condition does not pose additional risk

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- 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
- Likely to be incapable of using DMS technology, even with assistance
- History or evidence of a medical condition that would expose patient to undue risk of an AE
- Known allergy to adhesive tape or any component of the patch or co-encapsulation product
- Current incarceration in prison system
- Hospitalization at the time of screening due to mental or physical illness
- HCP recommendation to not participate
- Aversion to taking gelatin capsules
- Women who are breastfeeding, pregnant, or plan to become pregnant

187

Intervention

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

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

202

203 **Patient and Public Involvement Statement**

204 **Coproduction**

205 This study was designed using coproduction methodology involving NHS staff and patients (**Figure 2**).

206 Coproduction in this protocol is the involvement of people with lived experience of mental illness

207 (diagnosed or otherwise) as equal partners alongside other healthcare stakeholders, in the design and

208 contribution to the protocol. The lead site, Southern Health NHS Foundation Trust, held 5 coproduction

209 workshops, and a subset of these workshops was repeated at other study sites to elicit feedback on the

210 study design. At least 2 of these workshops involved patients. The discussions from the workshops

211 addressed pharmacy items for the CoE product; HCP recruitment strategies; and protocols for

212 identification, recruitment, and interactions with suitable patients and their general practitioners.

213 Throughout the various workshops at the different sites, participants included clinicians, pharmacists,

214 researchers, IG personnel (refers to the way in which the NHS handles, stores and processes information,

215 in particular personal and sensitive information relating to patients and employees; it was vital to ensure

216 that IG individuals were happy with the privacy and storage features of the digital medicine system),

217 psychiatrists, care coordinators, nurses, information technology personnel, CCGs (clinically led groups

218 within the NHS that are responsible for the planning and commissioning of healthcare services for their

219 local area), and patients (**Figure 2**).

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221 **Patient Involvement**

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

229

230 **Procedures**

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

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

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

260 **Outcomes**

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

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266 The following exploratory endpoints will also be included:

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

283 **Statistical analysis**

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

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

294 **Data protection**

295 Before initiating participation, informed consent will be obtained from all patients and
296 caregivers. Health information will be de-identified to the fullest possible extent. However, some
297 identifiers or sensitive health information cannot be stripped (eg, psychiatric medical history,
298 participation in a care program approach, presence of a community treatment order, employment
299 status, disabilities, housing arrangements, or armed forces history). Health information will be
300 used to develop and improve the DMS application and user experience. The DMS and associated
301 third-party vendors are compliant with the General Data Protection Regulation (GDPR), and all
302 accessed health information will be maintained in the strictest confidence and in compliance with
303 the GDPR. Data from the DMS are encrypted in activity and rest and will be accessed only by
304 role-specific individuals for discrete time periods and functions (eg, technical troubleshooting).
305 All data will be completely anonymized for graphical, statistical, and publication purposes.
306 Research staff from NHS sites will store consent documents, demographic forms, and receipts
307 for reimbursement of travel in locked filing cabinets to which only research staff will have
308 access. Accessing of health data will be compliant with IG policies of each participating NHS
309 trust.

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310 **Ethical considerations**

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

318 **Dissemination of study results**

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

325 **DISCUSSION**

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

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

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

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3 355 developed to leverage the advantages of digital technology to positively influence adherence in
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5 356 patients with schizophrenia.
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8 357 The DMS is a multimodal, user-friendly system that provides medication reminders and
9
10 358 measures patient ingestion of prescribed antipsychotic medications. The CoE product, in
11
12 359 particular, advances the ability to confirm medication ingestion and to assess adherence on a
13
14 360 continuous basis, which can inform whether uncontrolled symptoms may be explained by
15
16 361 nonadherence. Information from the DMS is made readily available to patients, caregivers (with
17
18 362 the patient's consent), and physicians for supported decision making, proactive intervention, and
19
20 363 individualized care. DMS also provides adherence feedback electronically to the patient, HCP,
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22 364 and/or caregiver. The DMS provides this feedback discreetly, through user-owned and operated
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24 365 applications and a patch that is not readily visible as it is worn on the torso underneath clothing,
25
26 366 reducing any potential stigmatization if it (the patch) was visible. The DMS also provides
27
28 367 feedback on activity and rest levels, which is important given that maintenance of a healthy
29
30 368 lifestyle can help address the problems of weight gain and obesity that are related to both
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32 369 medication side effects and sedentary lifestyles [31]. Furthermore, shifts in activity levels may be
33
34 370 indicative of altered patient disposition.
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36
37 371 This ongoing study was designed using coproduction methodology to incorporate input from
38
39 372 patients, caregivers, psychiatrists, pharmacists, nurses, and researchers. For all 5 study sites, a
40
41 373 minimum of 2 engagement/setup meetings were conducted and 2 specific patient focus groups
42
43 374 were held to guide protocol development and app design. Although a PRECIS-2 assessment tool
44
45 375 was not used during the design of the study the authors feel that based on a retrospective
46
47 376 PRECIS-2 analysis (refer to supplemental materials for this analysis) this study does meet the
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49 377 criteria for a pragmatic study. The exploratory data collected in this study, although limited to a
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378 small number of patients, will help provide a better understanding of the ease of use for patients,
379 HCPs, and caregivers to inform the development of future software or hardware iterations.
380 Given the level of unfamiliarity with digital medicine systems, conducting clinical trials in this
381 space requires a higher level of stakeholder management and alignment, especially when the trial
382 is being held in a new environment. Whether it's a new country, a new healthcare system, or a
383 new set of investigators, formal buy-in and input is critical to participation. The protocol outlines
384 one way of managing and aligning stakeholders in such an environment - the UK mental health
385 system. Additionally, and increasingly important within mental health services and interventions
386 in the UK, is the involvement of end-users, so called service users who have lived experience of
387 mental health. The methods paper describes a robust engagement strategy using such individuals
388 in mental health research.

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

392 **CONCLUSION**

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

398

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27

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29
30
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32
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34
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4 521 **Figure Legends**

5 522 **Figure 1.** Digital medicine system: co-encapsulated antipsychotic medication with miniature
6
7 523 ingestible event marker in tablet (MIT) and compatible medical device. DM=digital medicine;
8
9 524 HCP=healthcare professional. Image reprinted from article in npg Digital Medicine [In Press].

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13 525 **Figure 2.** Description of coproduction workshops with Southern Health NHS Foundation Trust.

14
15 526 DMS=digital medicine system; EIP=Early Intervention in Psychosis; IG=information
16
17 527 governance; MoSCoW=must have, should have, could have, won't have; NHS=National Health
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19 528 Service; PANSS=Positive and Negative Syndrome Scale; PPI=Patient and Public Involvement
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22 529 program.

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25 530 **Figure 3.** Study design.
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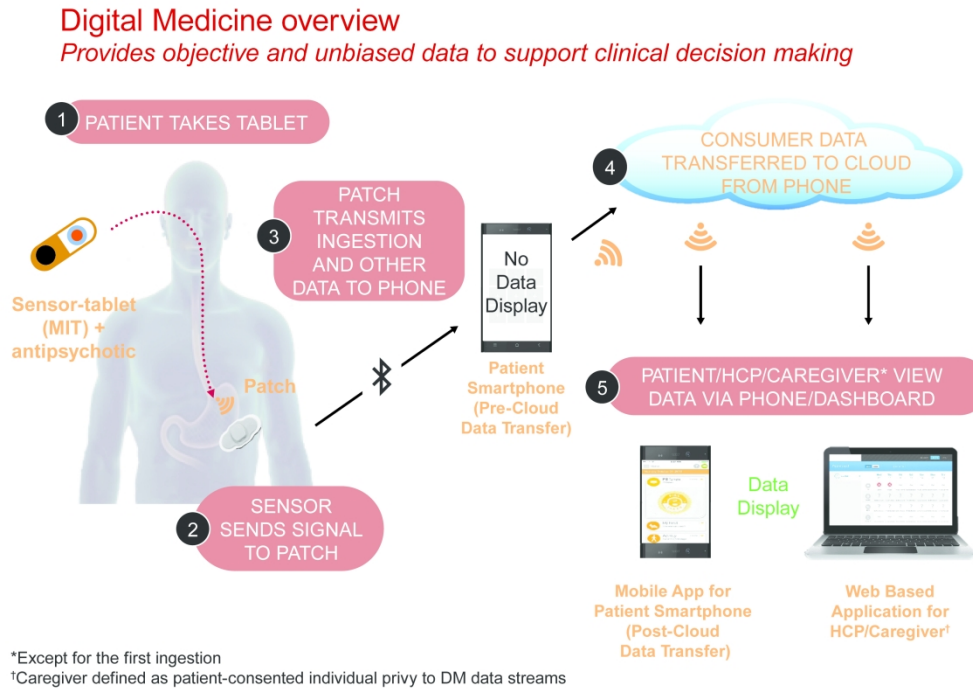


Figure 1. Digital medicine system: co-encapsulated antipsychotic medication with miniature ingestible event marker in tablet (MIT) and compatible medical device. DM=digital medicine; HCP=healthcare professional.

254x177mm (300 x 300 DPI)

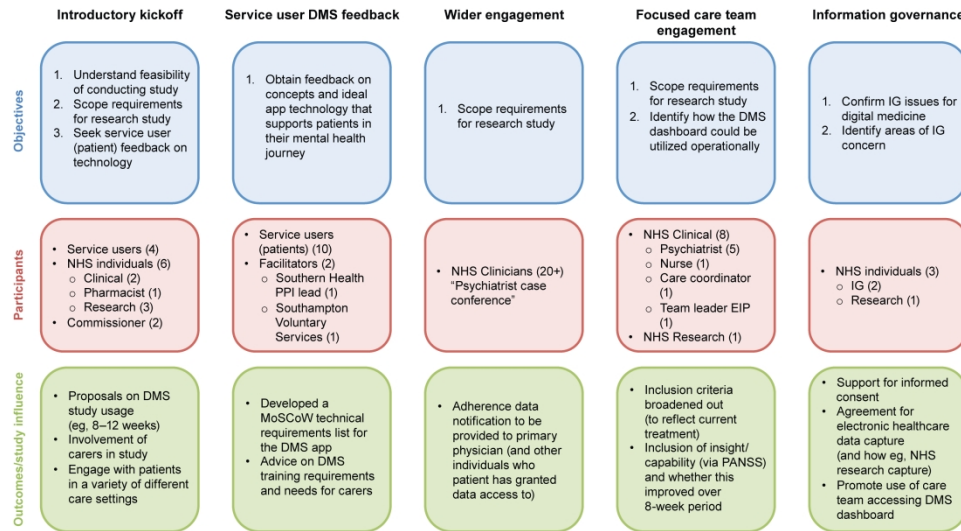
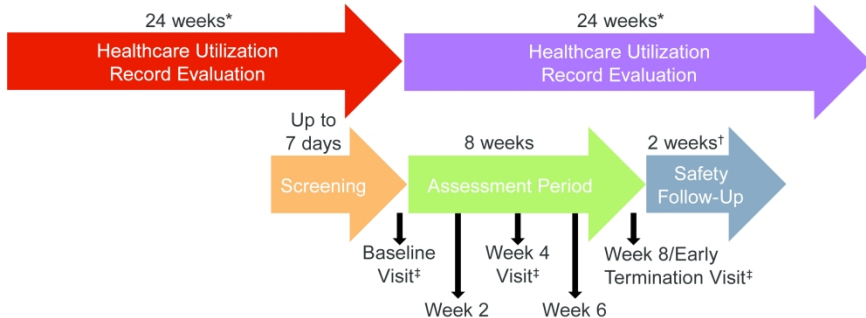


Figure 2. Description of coproduction workshops with Southern Health NHS Foundation Trust. DMS=digital medicine system; EIP=Early Intervention in Psychosis; IG=information governance; MoSCoW=must have, should have, could have, won't have; NHS=National Health Service; PANSS=Positive and Negative Syndrome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

317x184mm (300 x 300 DPI)

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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?

	Extremel y 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)?

	Extremel y 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?

	Extremel y 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)?

	Extremel y 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)?

	Extremel y Difficult	Difficult	Somewhat Difficult	Neutral	Somewhat Easy	Easy	Extremel y 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

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4 **11. How helpful or unhelpful was the Digital Medicine System in improving your conversations with**
5 **your patient about their treatment plan and progress?**
6

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

13 **12. How helpful or unhelpful was the Digital Medicine System in the identification of**
14 **potential lifestyle changes for your patient (eg sleep and exercise)?**
15

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

22 **13. Other than during the patient visit(s), did you look at the HCP dashboard at other**
23 **times? Please select all that apply**
24

	Place a \checkmark (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: <i>Please Specify:</i> _____	

32 **14. What features did you find helpful? Please select all that apply**
33

	Place a \checkmark (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: <i>Please Specify:</i> _____		

1
2
3 **15. Did you set up alerts to be notified of missed doses? Yes/no**

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

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

13
14 15a. If you received a missed dose alert what action did you take, if any? (If none,
15 please write N/A) _____

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

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

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

26
27 16a. If you received a multiple dose alert what action did you take, if any? (If none, please write
28 N/A) _____

29
30 **17. How well do you agree with the following statement?**

31 **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

38
39 **18. Based on your overall experience with this patient, how would you rate your satisfaction with the**
40 **Digital Medicine System?**

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

1
2
3 **Supplemental Figure 3. Caregiver/Support Person Involvement Scale (Ver 2.0)**
4
5

6 **DMS Caregiver/Support Person Involvement Scale**
7

- 8
9
10 **1. Are you aware that the study participant/patient is currently participating in the Digital**
11 **Medicine study (check one)?**
12

Yes	No*

13
14
15
16
17
18 ***If no, stop here and do not answer the rest of the questions on this form.**
19

- 20
21 **2. Indicate your relationship to the study participant/patient by placing a √ (check).**
22

Friend	Hired Caregiver	Relative*	Other**

23
24
25
26
27
28 ***If you are a relative, please specify relationship to the study participant/patient, e.g.,**
29 **wife, father:**
30

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

4 = Moderately ill

1 = Normal, not at all ill

5 = Markedly ill

2 = Borderline mentally ill

6 = Severely ill

3 = Mildly 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
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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	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. Personal and social relationships	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Self-care	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. Disturbing and aggressive behaviors	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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

1
2
3
4
5 **7. I am confident that I can follow through on mental health treatments I need to do at home.**

6
7 1 2 3 4
8
9 Strongly Disagree Disagree Agree Strongly Agree

10
11
12 **8. I understand the nature and causes of my mental health condition(s).**

13
14 1 2 3 4
15
16 Strongly Disagree Disagree Agree Strongly Agree

17
18
19
20 **9. I know the different treatment options available for my mental health condition(s).**

21
22 1 2 3 4
23
24 Strongly Disagree Disagree Agree Strongly Agree

25
26
27
28 **10. I am able to maintain the lifestyle changes I have made for my mental health.**

29
30 1 2 3 4
31
32 Strongly Disagree Disagree Agree Strongly Agree

33
34
35 **11. I know how to prevent further mental health problems.**

36
37 1 2 3 4
38
39 Strongly Disagree Disagree Agree Strongly Agree

40
41
42
43 **12. I am confident I can figure out solutions when new situations or problems arise with my mental health.**

44
45 1 2 3 4
46
47 Strongly Disagree Disagree Agree Strongly Agree

48
49
50
51 **13. I am confident that I can maintain lifestyle changes, like diet and exercise, even during times of stress.**

52
53 1 2 3 4
54
55 Strongly Disagree Disagree Agree Strongly Agree

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3 Supplemental Material – PRECIS-2 Tool Assessment
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5

6 Whilst the PRECIS-2 tool assessment was not completed during the design of the study, when it
7 is designed to be conducted, a post assessment use of the tool confirms the use of the term
8 pragmatic. For example, from the nine PRECIS-2 domains:
9
10

11 Eligibility: Would score 4 (out of 5) since those identified in the study would be those identified
12 in usual care. The study does exclude inpatients, which in the “real world” could in theory
13 participate but we felt the DMS intervention was of limited benefit in this setting since inpatients
14 have observed adherence
15
16

17 Recruitment: would score 4-5 since recruitment is based simply on screening patient caseloads
18 and assessment of patients who may need help with adherence measures. No advertisements
19 have been conducted.
20
21

22 Setting: Would score 4-5 since the care settings used in the study are those in usual care. We
23 have a range of participants from community and specialist mental health services
24
25

26 Organisation: Would likely score 3-4 since although the resource/expertise is largely similar to
27 usual care, the study does use NHS research staff to assist with training and screening, as is
28 commonplace with all clinical studies in the UK
29
30

31 Flexibility (delivery): Would score 3-4 since the study gives patients and HCPs the ability to
32 follow standard of care but does require specific site visit at w4 and w8 (yet one could argue this
33 would occur naturally since the w4 visit is to collect a new prescription (which would occur in
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3 the real world) and the w8 visit is the completion of the study. Patients do not experience any
4
5 other “forced” visits.
6
7

8
9 Flexibility (adherence): Would score 3 since following enrolment if patients do not utilise the
10
11 patch/app the site can contact the patient to found out why they are not engaging and try to
12
13 encourage; however, this would be the same if the DMS was indeed normal practice; this is the
14
15 intention of the tool to promote conversations between visits when individuals are not adherent.
16
17

18
19 Primary outcome: would score 3-4; whilst the outcome may not be obvious to patients, the
20
21 outcome has been supported from conversations with HCPs and payers. The good patch
22
23 coverage days are essential to provide insight into medication taking so again, if the intervention
24
25 become standard, the metric would be used since it would determine whether objective and
26
27 insightful data was being captured.
28
29
30

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34
35 Primary analysis: Would score 4 since all individuals will be included in the analysis with all
36
37 available data.
38
39
40
41
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43
44

45 Based on the above, the average score is approx. 4 which equates to “Rather pragmatic”
46
47

48 The reason why the study is not the top score of 5 (Very pragmatic) is that the intervention itself
49
50 does cause changes to current care but we are not stating how individuals should respond to these
51
52 changes. They are free to decide for themselves.
53
54
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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	<u>Page 1 Line 1</u>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	<u>Page 4 Line 64</u>
	2b	All items from the World Health Organization Trial Registration Data Set	Provided on <u>ClinicalTrials.gov</u>
Protocol version	3	Date and version identifier	<u>Page 1 of protocol</u>
Funding	4	Sources and types of financial, material, and other support	<u>Page 20 Line 396</u>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	<u>Page 21 Line 408</u>
	5b	Name and contact information for the trial sponsor	<u>Page 1 Line 22</u>
	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	<u>Page 21 Line 407</u>
	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)	<u>Page 21 Line 407</u>

1 **Introduction**

2

3 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

4

5

6 6b Explanation for choice of comparators N/A

7

8 Objectives 7 Specific objectives or hypotheses Page 9 Line 163

9

10 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

11

12

13

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

15

16 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

17

18

19 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

20

21

22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered Page 11 Line 190

23

24

25 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

26

27

28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) Page 19 Line 358

29

30

31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial As listed on each drug label

32

33

34

35 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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1	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)	<u>Figure 3</u>
2				
3				
4	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	<u>Page 15 Line 282</u>
5				
6				
7	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	<u>Page 13 Line 249</u>
8				

Methods: Assignment of interventions (for controlled trials)

Allocation:

13	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	<u>N/A</u>
14				
15				
16				
17				
18				
19	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	<u>N/A</u>
20				
21				
22				
23				
24	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	<u>N/A</u>
25				
26				
27	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	<u>N/A</u>
28				
29				
30		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	<u>N/A</u>
31				
32				

Methods: Data collection, management, and analysis

36	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	<u>Protocol Page 81</u>
37				
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1		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	<u>Page 14 Line 259</u>
2				
3				
4	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	<u>Protocol Page 73</u>
5				
6				
7				
8	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	<u>Protocol Page 73</u>
9				
10				
11		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<u>Page 15 Line 282</u>
12				
13		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)	<u>Page 15 Line 282</u>
14				
15				
16				
17	Methods: Monitoring			
18				
19	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	<u>N/A Pragmatic Trial - Safety of Interventions is Established</u>
20				
21				
22				
23				
24				
25		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	<u>N/A</u>
26				
27				
28	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	<u>Protocol Page 66</u>
29				
30				
31	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	<u>Protocol Page 81</u>
32				
33				
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35	Ethics and dissemination			
36				
37	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	<u>Page 16 Line 309</u>
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1	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
5	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
8		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
11	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
15	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 21 Line 402
18	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
21	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
24	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
29		31b	Authorship eligibility guidelines and any intended use of professional writers	Protocol page 84
31		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not yet determined
33	Appendices			
35	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Protocol Page 107
38	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

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*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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