

# **Assessing a Digital Medicine System in Veterans with Severe Mental Illness: A provider-randomized clinical trial**

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Submitted to: JMIR Formative Research  
on: December 09, 2021

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# Assessing a Digital Medicine System in Veterans with Severe Mental Illness: A provider-randomized clinical trial

Sarah Gonzales<sup>1</sup> BA; Olaoluwa O. Okusaga<sup>2</sup> MD; J. Corey Reuteman-Fowler<sup>3</sup> PhD; Megan M. Oakes<sup>1</sup> MS; Jamie N. Brown<sup>4</sup> PharmD; Scott Moore<sup>5</sup> MD, PhD; Allison A. Lewinski<sup>6</sup> PhD; Cristin Rodriguez<sup>2</sup> BS; Norma Moncayo<sup>2</sup> MD; Valerie A. Smith<sup>7</sup> DrPH; Shauna Malone<sup>1</sup>; Justine List<sup>2</sup> BAsC; Raymond Y. Cho<sup>2</sup> MD; Amy S. Jeffreys<sup>4</sup> MStat; Hayden B. Bosworth<sup>8</sup> PhD

<sup>1</sup>Durham Veterans Affairs Medical Center Department of Population Health Sciences, Duke University Durham US

<sup>2</sup>Michael E. DeBakey VA Medical Center Baylor College of Medicine Houston US

<sup>3</sup>Otsuka Pharmaceutical Development and Commercialization Inc. Princeton US

<sup>4</sup>Durham Veterans Affairs Medical Center Durham US

<sup>5</sup>Durham Veterans Affairs Medical Center Department of Psychiatry and Behavioral Sciences, Duke University Durham US

<sup>6</sup>School of Nursing, Duke University Durham Center of Innovation to Accelerate Discovery and Practice Transformation, Durham Veterans Affairs Medical Center Durham US

<sup>7</sup>Department of Population Health Sciences, Duke University Department of General Internal Medicine, Duke University Durham Veterans Affairs Medical Center Durham US

<sup>8</sup>Durham Center of Innovation to Accelerate Discovery and Practice Transformation, Durham Veterans Affairs Medical Center Department of Psychiatry and Behavioral Sciences, and School of Nursing, Duke University Department of Population Health Sciences, Duke University Durham US

## Corresponding Author:

Hayden B. Bosworth PhD

Durham Center of Innovation to Accelerate Discovery and Practice Transformation, Durham Veterans Affairs Medical Center  
Department of Psychiatry and Behavioral Sciences, and School of Nursing, Duke University  
Department of Population Health Sciences, Duke University  
411 W. Chapel Hill Street Suite 600  
Durham  
US

## Abstract

**Background:** Suboptimal medication adherence is a significant problem for patients with serious mental illness (SMI). Measuring medication adherence through subjective and objective measures can be challenging, time consuming and inaccurate.

**Objective:** We evaluated a digital medicine system (DMS) compared to treatment as usual (TAU) on adherence to oral aripiprazole and patient and provider perspectives on the feasibility and acceptability of a DMS.

**Methods:** This open-label, 2-site, provider-randomized trial assessed aripiprazole refill adherence in Veterans with schizophrenia, schizoaffective disorder, bipolar disorder, or major depressive disorder. We randomized 26 providers such that their patients either received TAU or DMS for a period of 90 days. Semi-structured interviews with patients and providers were used to examine feasibility and acceptability of using the DMS.

**Results:** We enrolled 46 patients across 2 Veterans Affairs (VA) sites: (21 in DMS and 25 in TAU). There was no difference in medication refill over 3 and 6 months, respectively (82% and 75% DMS vs. 86% and 82% TAU). The DMS arm had 85% days covered during the period they were engaged with the DMS (144 days on average). Interviews with patients (n=14) and providers (n=5) elicited themes salient to using the DMS. Patient themes included: pre-enrollment adherence strategies and interest in the DMS, positive impact on medication adherence, system usability challenges, support needs, and suggested design/functionality improvements. Provider themes included: concerns for patient medication adherence and interest in the DMS, concerns with the DMS, DMS dashboard usability, challenges of the DMS, and suggestions to increase provider use.

**Conclusions:** There was no observed difference in refill rates. Among those who engaged in the DMS arm, refill rates were relatively high (85%). The qualitative analyses highlighted areas for further refinement of the DMS. Clinical Trial: NCT03881449

(JMIR Preprints 09/12/2021:34893)

DOI: <https://doi.org/10.2196/preprints.34893>

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Title:

Assessing a Digital Medicine System in Veterans with Severe Mental Illness: A provider-randomized clinical trial



**Abstract:**

**BACKGROUND:** Suboptimal medication adherence is a significant problem for patients with serious mental illness (SMI). Measuring medication adherence through subjective and objective measures can be challenging, time consuming and inaccurate.

**OBJECTIVES:** We evaluated a digital medicine system (DMS) compared to treatment as usual (TAU) on adherence to oral aripiprazole and patient and provider perspectives on the feasibility and acceptability of a DMS.

**METHODS:** This open-label, 2-site, provider-randomized trial assessed aripiprazole refill adherence in Veterans with schizophrenia, schizoaffective disorder, bipolar disorder, or major depressive disorder. We randomized 26 providers such that their patients either received TAU or DMS for a period of 90 days. Semi-structured interviews with patients and providers were used to examine feasibility and acceptability of using the DMS.

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**CONCLUSION:** There was no observed difference in refill rates. Among those who engaged in the DMS arm, refill rates were relatively high (85%). The qualitative analyses highlighted areas for further refinement of the DMS.

**Trial Registration:** NCT03881449

Keywords: ABILIFY MYCITE, digital medicine, adherence, aripiprazole, Veterans, qualitative methods



## 1. Introduction

Suboptimal medication adherence is a significant problem for patients with serious mental illness (SMI), including those with schizophrenia, bipolar disorder, posttraumatic stress disorder, and major depressive disorder. Suboptimal adherence among these individuals may lead to symptom exacerbation, relapse, and hospital readmissions.<sup>1</sup> Moreover, suboptimal adherence to prescribed

psychotropic medication is associated with increased mortality.<sup>1,2</sup> However, measuring medication adherence in the clinical setting is challenging and primarily subjective (i.e. patient self-report)<sup>3</sup>. While objective methods such as pill counts and pharmacy refill data are helpful, they are time consuming to calculate and often do not provide an accurate assessment of actual medication ingestion.<sup>4</sup>

A digital medicine system (DMS), consisting of a drug-device combination, is one way to obtain objective treatment adherence data. DMS may enable patients with SMI to measure and report ingestion of atypical antipsychotic medications, most of which have broad therapeutic indications. The collection of objective, real-time data using a DMS enables providers to address nonadherence to medications, as well as facilitating interactions among patients and providers to promote and support medication adherence. We examined ABILIFY MYCITE (aripiprazole tablets with sensor) which is a Food and Drug Administration (FDA)-approved DMS, drug-device combination product comprised of four separate components that enables the monitoring of treatment adherence by a patient and the patient's provider. Adherence data obtained from a DMS may assist in understanding potential barriers to improve outcomes and more informed shared decision making regarding a patient's treatment. However, comparison of medication adherence between DMS and treatment as usual (TAU) as well as a qualitative assessment of patient and provider perspectives on the feasibility and acceptability of DMS have not been carried out in the real-world environment. As the Veterans Health Administration (VHA) is the largest healthcare provider for individuals with SMI in the US<sup>5</sup>, VHA provides a conducive setting for a clinical trial comparing DMS and TAU. Thus, the primary objective of this study was to evaluate the impact of a DMS among Veterans with SMI as compared to TAU on medication adherence. The secondary objective was to obtain patient and provider perspectives on the feasibility and acceptability of using a specific DMS.

## 2. Methods

### 2.1 Study Design

This was an open-label, 2-site, provider randomized, prospective, 2-arm (DMS vs. TAU) clinical trial. Patients assigned to the intervention group by provider randomization were on ABILIFY MYCITE for a period of 90 days with the option to use ABILIFY MYCITE for up to 9 additional months. Participants assigned to the control arm, TAU, continued to receive care as recommended by their mental health provider, which included their continued use of aripiprazole. Study duration for both groups was up to 12 months or study closeout, whichever ever came first. At study conclusion, we used a descriptive qualitative analysis design and rapid qualitative analysis procedures to examine feasibility and acceptability of using the DMS. All study procedures were approved by both sites' respective Institutional Review Board (IRB) and Research and Development Committee (R&D). The trial is registered in ClinicalTrials.gov (NCT03881449) and the sponsor requested the study conclude prematurely.

## 2.2 Setting and Participants

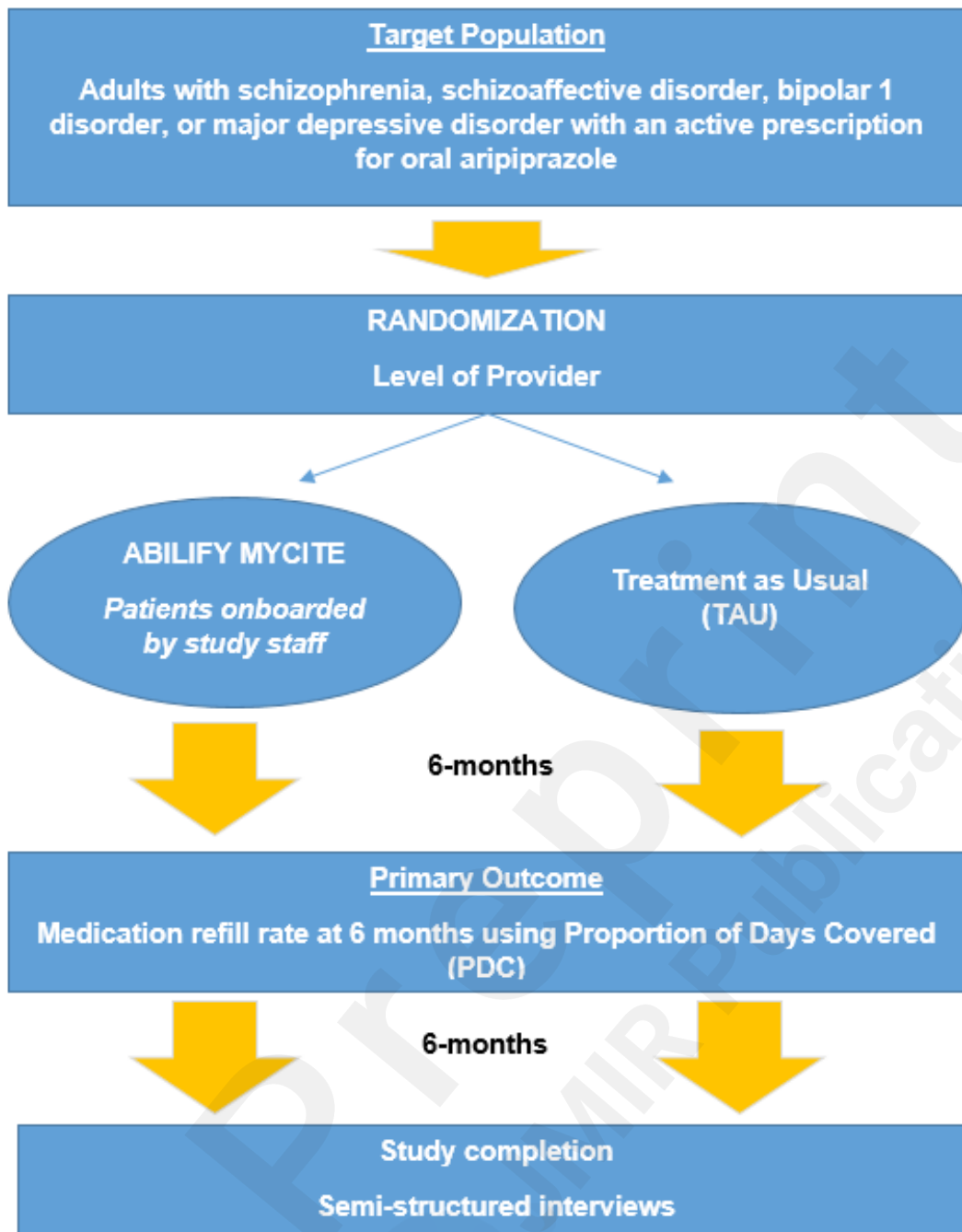
Study participants were recruited from two Veterans Affairs (VA) Medical Centers in Durham, NC and Houston, TX. Eligible Veterans were at least 18 years of age and met the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria for schizophrenia, schizoaffective disorder, bipolar 1 disorder, or major depressive disorder. Additional study eligibility included: (1) an active prescription for oral aripiprazole, and (2) approval to participate in the study by their mental health provider. Exclusion criteria included: (1) a current neurocognitive disorder that would impact the patient's ability to complete the trial (e.g. dementia); (2) the patient's mental health provider determined the patient was not fit to participate; (3) the patient was currently enrolled in an investigational drug trial or a medication management study or program or participated in an investigational drug trial 30 days prior to trial enrollment; (4) the patient was pregnant, planning on becoming pregnant during the trial, and/or breastfeeding; (5) the patient failed an initial cognitive screener; (6) the patient had a known allergy to adhesive tape or any pertinent components of the

ABILIFY MYCITE patch; (7) the patient did not have skin on the anterior chest just above the lower edge of the rib cage or has dermatologic problems such as dermatitis, open wounds, etc. in the location of where the patch would be placed or was unwilling to refrain from the use of topical products on the skin patch sites; and (8) the patient had  $\leq 20\%$  proportion of days covered (PDC) with aripiprazole in the 6 months prior to enrollment.

### 2.3 Screening and Recruitment

Potential participants were identified initially by a data pull from the electronic medical record. From this data pull, only patients of those providers who agreed to be involved in the study were screened further. Qualifying patients were sent an introductory letter in the mail describing the study and inviting them to contact the study team for more information and further eligibility screening by telephone. The study utilized an opt-out recruitment strategy that entailed contacting participants approximately 7-10 business days after a recruitment letter was sent unless participants contacted the study team to indicate they were not interested in participating. Once patients were confirmed eligible and were interested in participating, they were seen at a scheduled in-person baseline appointment. At the baseline study visit, written informed consent and HIPAA authorization was obtained, smartphone compatibility was verified and/or a study-owned smartphone was provided if needed (6 were issued), and baseline assessments and surveys were completed (*Figure 1*).

Figure 1: Schematic of enrollment procedures



## 2.4 Randomization

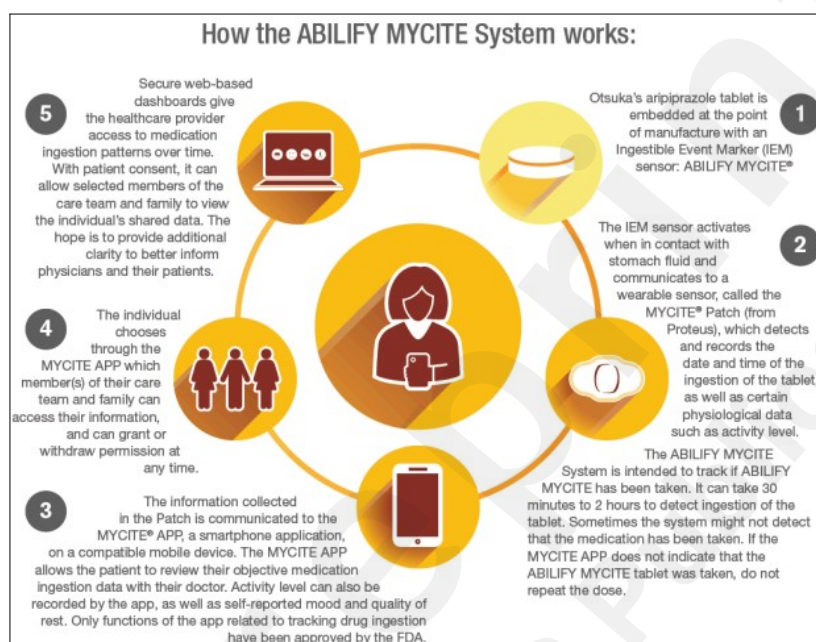
This was a provider-randomized clinical trial. Providers who agreed to have their patients approached and potentially enrolled, were randomized in a 1:1 ratio using a stratified block randomization. Provider randomization was stratified by site.

## 2.5 Treatment Arms

### 2.5.1 Digital Medicine Arm

ABILIFY MYCITE is an FDA-approved, DMS developed for patients with SMI who are taking oral aripiprazole, an atypical antipsychotic. ABILIFY MYCITE was developed to track adherence of aripiprazole and allow patients and their mental health providers the opportunity to view real-time adherence data (Figure 2).

Figure 2: Schematic of digital medicine intervention



The DMS separate

is comprised of four components (Table 1);

- (1) ABILIFY MYCITE- an aripiprazole tablet embedded with an ingestible event marker (IEM) sensor;
- (2) MYCITE patch;
- (3) MYCITE smartphone application;
- (4) MYCITE dashboard.

Table 1: Description of ABILIFY MYCITE System

Components	Description
ABILIFY MYCITE	Aripiprazole tablet embedded with an ingestible event marker (IEM) sensor
MYCITE Patch	Wearable sensor patch that detects the signal from the IEM sensor after ingestion and transmits data to a smartphone
MYCITE APP	Smartphone application used to display medication ingestion information for the patient
MYCITE Dashboard	Two separate web-based portals, one for healthcare providers and one for family/friends who care for the patient



Once a participant takes the tablet, the ingestible sensor transmits an electrical signal that is detected and then recorded by software within the patch that is worn by the participant on the left ribcage. Using Bluetooth, the patch then transmits the aripiprazole ingestion data to the participant's smartphone, which is then saved to the secure, cloud-based DMS dashboard. Participants have the ability to view this medication data each day on their smartphone, while the patient's provider, research team and selected caregivers are able to view the data on the DMS dashboard via the cloud-based server. Once participants were enrolled into the trial, they were onboarded by a trained research staff member. The onboarding process included obtaining ABILIFY MYCITE from the site's pharmacy, successfully placing the patch to the skin in the proper location, and pairing the patch with the smartphone application. The participant was then provided with additional training materials and contact information for the study team, and the product's call center. Participants were encouraged to reach out to the call center for technical assistance related to the DMS.

As part of the 12-month trial, participants in the DMS arm used ABILIFY MYCITE for 90 days. Participants then decided whether to continue use of DMS beyond the initial 90 days. If participants discontinued, they restarted their oral aripiprazole as prescribed by their provider. We continued to follow these individuals and obtained pharmacy refill data. Follow up visits for both the DMS and TAU arm occurred at 3, 6 and 12 months.

### 2.5.2 Treatment as Usual Arm

Participants randomized to the TAU arm continued to receive usual care as provided by their mental health provider. Participants assigned to the TAU arm completed all required study visits and data collection surveys.

## 2.6 Measures

### 2.6.1. Quantitative Measures

All study measures were collected by trained research staff at both sites.

### 2.6.1.1 Demographic and clinical data.

A research assistant collected demographic data (e.g., race, gender, age, comorbidities), clinical data (e.g., clinical diagnoses, medications), and data regarding use of mobile health devices. Diagnoses were obtained from medical records and the following International Classification of Diseases codes were used: F33.0 (Major Depressive Disorder), F31.0 (Bipolar 1 disorder), F25.0 (Schizoaffective disorder), F20.0 (Schizophrenia).

### 2.6.1.2 Medication Refill Adherence

The primary outcome was medication refill based upon number of days covered from baseline to 6 months. Using two approaches, we measured adherence using Proportion of Days Covered (PDC)<sup>6</sup>, a leading method used to calculate medication adherence at a population level. The first set of PDCs were calculated for 3 and 6 months independent of whether an individual was recommended to stop using the DMS (intention-to-treat). The second PDC measure was calculated as number of days covered until there was documentation that a patient was recommended to stop using DMS or until the patient reported a problem with the intervention (e.g., skin irritation) for the DMS randomized group.

## 2.6.2 Qualitative Measures

### 2.6.2.1 Semi-structured interviews

Guided by rapid qualitative analysis procedures<sup>7</sup> we completed semi-structured interviews to examine the feasibility and acceptability of the DMS system to support medication adherence. We used a convenience sampling plan to identify participants enrolled in the DMS arm up to their 12-month participation in the study or the end of study activities, whichever came first. Providers whose patients were enrolled into the DMS arm were invited to complete an interview up to the date of the end of study activities. Research assistants contacted intervention patients currently enrolled in the study and invited participants and providers to complete interviews.

Interview questions inquired about the feasibility of, and facilitators and barriers to, the DMS

system. Questions for the patients focused on medication experience (pre-enrollment), onboarding to DMS system, system usability, satisfaction with support and feedback. Questions for the providers inquired about the prescriber experience (pre-study), DMS dashboard account set up, system usability, satisfaction with support and feedback. We used probes (e.g., “please describe your experience in greater detail”, “what do you mean?”) to obtain greater detail and clarify responses. Interviews were completed by a trained research assistant and included a note-taker who recorded responses via a structured note form. After the conclusion of the interview, the research assistant and note-taker debriefed and reviewed interview responses in the context of other interviews. Interviews were conducted via the telephone, and were recorded, but not transcribed. Patient and provider interviews lasted on average for 30 minutes.

## 2.7. Analytic strategy

### 2.7.1 Quantitative Measures

Oral aripiprazole refill was measured by the number of days covered from baseline to 3 and 6 months using PDC in both intention-to-treat and DMS-engaged analyses. Due to small numbers of participants, we conducted descriptive analyses rather than a model-based approach. The intention to treat analyses utilized all data from baseline to 3 or 6 months, depending on the outcome, while the DMS-engaged analysis censored participants in the ABILITY MYCITE arm at system discontinuation.

### 2.7.2. Qualitative Measures

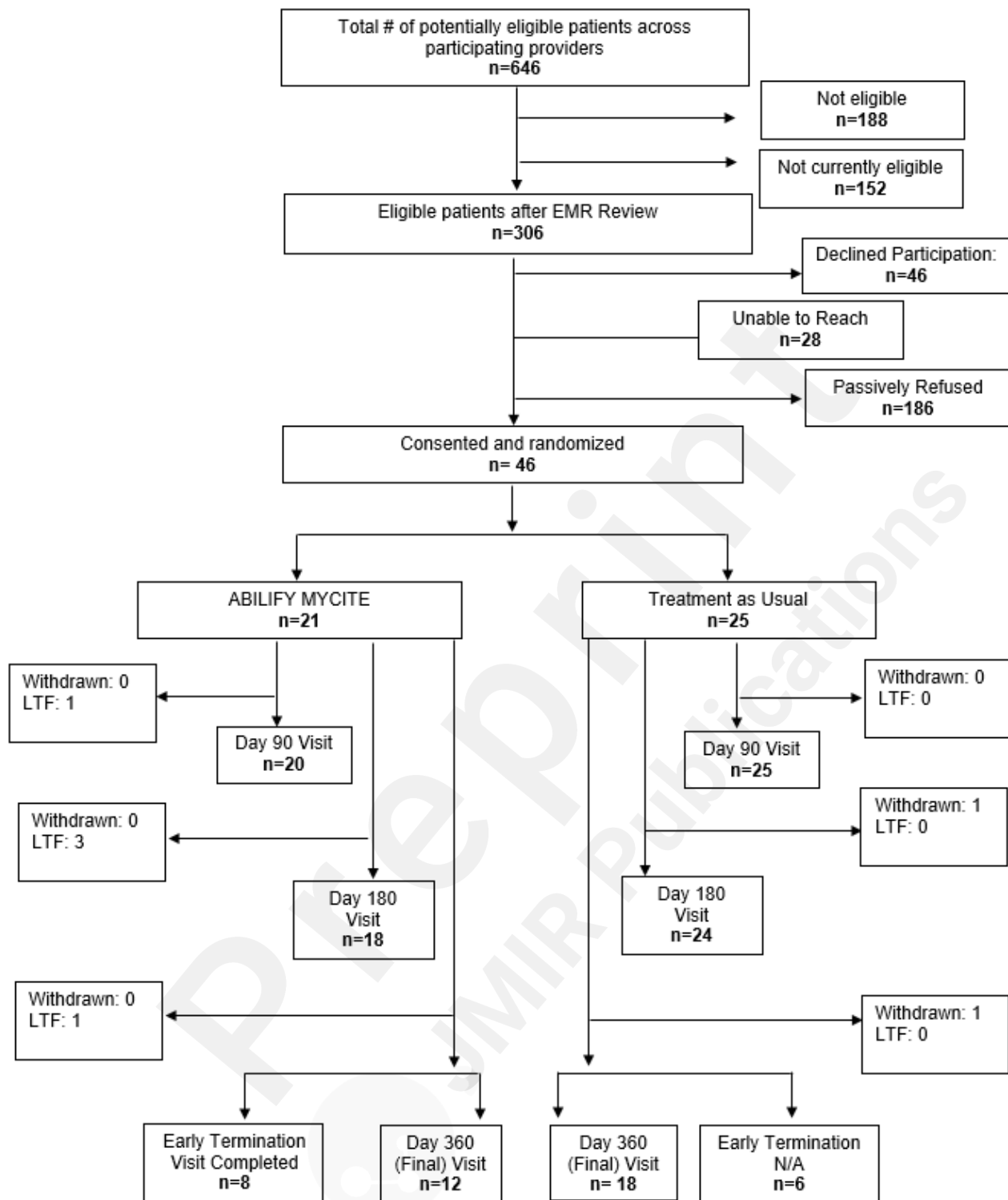
We followed rapid analysis procedures for data analysis and MS Excel (version 2002) to support coding and analysis. Two authors (AAL and SG) reviewed all notes and debrief notes taken during interviews with patients and providers. These authors used thematic analysis<sup>8</sup> and the matrix method<sup>9</sup> to analyze and identify salient themes across all interviews. We established rigor and validity by independently coding and summarizing all data, discussing emerging codes and thematic groupings during meetings, and reviewing findings with the larger research team.

### 3.0 Results

#### 3.1. Sample

A total of 26 providers were randomized for this trial (Durham: n=22; Houston: n=4). Of the eligible patients from participating providers, a total of 46 patients were consented and enrolled into the trial (Durham: n= 28; Houston: n=18), with 21 participating in the DMS group and 25 participating in the TAU group (*Figure 3*).

Figure 3: Enrollment



The sample was on average 53.0 (SD=13.3) years of age, majority male (72%), 52% self-reported as Black, and 15.2% had a high school education or less. The clinical diagnoses breakdown for enrolled patients included 54.3% with major depressive disorder, 6.5% with schizophrenia, 10.9% with schizoaffective disorder, and 28.3% with bipolar 1 disorder. Prior to study enrollment,

half of enrolled patients had downloaded a health app onto their cell phone and approximately a third of participants had used a wearable tech device such as a fitness tracker or smartwatch (*Table 2*).

Table 2: Participant Demographics

	DMS (n = 21)	TAU (n = 25)
Age in years, mean (SD)	54.67 (12.73)	51.64 (13.40)
Males, n (%)	17 (81.0)	16 (64.0)
Females, n (%)	4 (19.0)	9 (36.0)
Race, n (%)		
Black	12 (57.1)	12 (48.0)
White	8 (38.1)	13 (52.0)
Asian	1 (4.8)	0 (0.0)
Education, n (%)		
High school or less	5 (23.8)	2 (8.0)
Any college	14(66.67)	21 (84.0)
Grad school	2 (9.5)	2 (8.0)
Clinical Diagnosis, n (%)		
Major Depressive Disorder	14 (66.7)	11 (44.0)
Bipolar 1 Disorder	3 (14.3)	10 (40.0)
Schizoaffective Disorder	2 (9.5)	3 (12.0)
Schizophrenia	2 (9.5%)	1 (4.0)
Pre-Study Mobile Device Use, n (%)		
Health application	9 (42.9)	14 (56.0)
Wearable tech	8 (38.1)	6 (24.0)
DMS = digital medicine system; TAU = treatment as usual		

### 3.2. Quantitative Outcomes

In the intention to treat analyses, percent days covered over 3 and 6 months was 82% and 75% in the DMS group and 86% and 82% in the usual care arm. In the DMS-engaged analysis, the DMS arm had 85% days covered over the period (*Table 3*).

Table 3

Percent Days Covered by Aripiprazole – Mean (SD)

PDC	DMC (N=21)	TAU (N=25)
3 Months	0.82 (0.24)	0.86 (0.19)
6 Months	0.75 (0.26)	0.82 (0.21)
DMS Engaged	0.85 (0.20)	N/A

The DMS group stayed engaged with the MYCITE system for 144 days on average (median = 147; range 0 to 376 days). Among those in the DMS arm, 5 stopped using the system by 3 months because of skin irritation adverse events from use of the MYCITE patch.

### 3.3. Qualitative outcomes

Qualitative interviews were completed with 14 Veterans and 4 providers, with half of each group coming from each of the two sites. Veteran respondents were mostly male (n=12, 86%) while 64% (n=9) were Black, 29% (n=4) White, and 7% (n=1) Asian. Eighty-six percent (n=12) of Veteran respondents used the DMS for 90 days or more; 43% (n=6) used the DMS system for 180 days or more. Of the providers, 2 (50%) identified as male, 3 were providers, and 1 was a prescribing pharmacist.

We identified 5 themes when analyzing the patient data and 5 themes for the providers' data that described the feasibility and acceptability of using the DMS. Patient themes included: pre-enrollment adherence strategies and interest in the DMS, positive impact on medication adherence, system usability challenges, support needs, and suggested improvements to system design/functionality. Provider themes included pre-study concerns for patient medication adherence and interest in the DMS, concerns with the DMS (pre-study), DMS dashboard usability issues/support, challenges in impact of the DMS, suggestions to increase provider use.

#### 3.3.1 Semi-structured interviews – patient responses.

*Pre-enrollment strategies and interest in the DMS system.* Patients described the following

pre-enrollment medication adherence strategies: maintaining a routine and setting up reminders through environmental cues (e.g., seeing pills on their counter, reminder from spouse or from reminders on their phone/calendar). Regarding their pre-enrollment medication adherence strategy, one patient stated the “hardest part for me is sometimes I can't remember if I took my meds that day, so that's why I try to take them first thing in the morning when I wake up....” Patients were interested in using the DMS because they felt that the DMS would help them with their medication adherence. One patient shared, "...I have issues with taking medication on time, not remembering to take it, skipping doses, so the way that the [DMS] would remind you...that would be helpful to someone.” Many patients expressed interest in the technology used in the DMS system, including one patient who stated, “I was interested because of the new technology...having the [DMS] app so you can see what your daily activities are.”

*Positive impact on medication adherence.* Patients reported the DMS system made them more mindful of taking their medication. For example, one patient shared, “[the DMS] made me more cognizant of what time my dosages were and definitely to make sure that I took [my medications] daily ...when I opened my phone I would see the app and remember, oh, I have to take my medicine in the morning.” The visual reminder of seeing their patch and the DMS app on their phone acted as a prompt to take their medication while the DMS app medication reminders to log missed doses reinforced the habit of taking their medication consistently. One patient stated, “the application itself, it asks you a series of questions why you forgot to take it and so when you're going through that it just feels like it's telling you to not forget it again. I definitely thought it was helpful...it reinforced that good habit of remembering to take your medication every day. ”

*System usability challenges.* Many patients shared that they experienced problems with patch connectivity and skin irritation. One patient described the challenges they experienced, "if the patch wasn't paired and I wasn't paying attention to the app, I would take my medication and it wouldn't register and that was very frustrating...I [also] had problems with the patch adhering and when it

wouldn't adhere, it would unpair [with the DMS app]." A patient who experienced skin irritation from the patch stated that "it seemed the more that I changed the patch, the more irritated my skin got with the patch...no matter where I put it." Patients also expressed the patch was uncomfortable to wear as the patch caught on things when working in tight spaces and fell off when the patient sweated due to weather or physical activity.

Patients experienced challenges with the DMS app during pill registration (e.g., app would freeze and/or need to be rebooted; technical assistance needed; unable to log missed doses). A patient stated, "I had a lot of issues with the app also, the app was freezing up on me and I would have to call [DMS support] and we would have to walk through it, we'd have to uninstall it and reinstall it to get the app to not be frozen anymore so that it would download the patch and pair the patch." Overall, despite assistance from study staff, patients felt the DMS system was complicated to learn because of the numerous steps needed to complete each process and many patients shared that they discontinued use due to recurring challenges.

*Support needs.* Patients expressed that their onboarding to the DMS system was helpful because of the in-person, one-on-one training with their local study staff members. Patients that called DMS support felt that while DMS support was professional and knowledgeable in describing step-by-step solutions, that they were not always able to resolve the issue and provide them with a long-term fix for their challenges with using the DMS system. One patient described, "I continued to have the same issue and that's why I discontinued using the DMS ...[DMS support]'s recommendation to change the patch and re-pair it wasn't a long-term fix." Patients preferred in-person support for resolving issues with the DMS system because study staff members could see their telephone and app in real-time. When asked about support for the DMS system, a patient stated, "since the research team was local, I was more inclined to call them if I needed help with something...just being there and having them explain to me face-to-face and answer my questions right away, it was helpful...and also that they were able to see my app and see what was going on."

*Suggested improvements to system design/functionality.* Patient feedback for the DMS system included two main suggestions 1) developing a smaller patch and/or an alternative way to track ingestion that did not involve wearing a patch and 2) improving the usability and functionality of the DMS app, as well as the reliability and accuracy of the DMS system as a whole.

Regarding patch improvement suggestions, a female patient shared that "if I could have placed the patch somewhere else on my body, I might have continued...if it could be worn somewhere discreetly on the body that would be ideal...where it had to be at the top of my torso, that was problematic for me...I don't think it would be problematic for a man or someone with a smaller chest." Several patients described how the patch was cumbersome to wear, wearing the patch for long periods of time led to skin irritation, or that they experienced issues with the patch sticking to their skin. Another patient shared " I did not like the patch...it gave me a rash...if we could figure out some other way of doing it without the patch involved that would be wonderful." A patient who experienced patch adherence issues stated "I think having to have it on your torso is a problem...how active I am, it just couldn't stay on me. Maybe if it was moved to an extremity...even if it was a fitness tracker, that would have made that part of the whole process much easier."

Regarding suggested improvements to the DMS app usability and functionality, one patient said, "when you log into the app, it logs you off rather quickly...the login information wasn't saved, so it was time consuming to access the app." Additionally, another patient suggested, "if your old patch doesn't upload information [to the DMS app]...having a mechanism to bypass that and record it and send it to support, so you can continue going through the pairing process with the new patch [would be helpful]."

Lastly, some patients suggested that technical support be more proactive (e.g., calling patients periodically to check in rather than patients needing to call DMS support to obtain technical assistance). One patient stated, "for people like us that's not as savvy with technology as others are...if [DMS support] have called me and checked, maybe [using the DMS] would have been easier

and simpler too..." Additionally, patients described an interest in receiving further training and material on strategies for addressing potential challenges to the DMS system, including technical issues with the DMS app, the DMS system, patch connectivity, and patch contact. One patient expressed they would have liked to receive written material as this patient wanted to refer back to information during the study.

### 3.32 Semi-structured interviews – provider responses.

*Pre-study concerns for patient medication adherence and interest in the DMS.* Providers shared a common concern for Veteran compliance with medication and acknowledged several challenges to medication adherence (e.g., disease-specific, healthcare system related, side effects of medications). One provider explained, "it's hard to know, by patient report, how consistently they've been taking the medication..." One provider described challenges Veterans have in refilling medications, "it's very daunting to get the refills and if the refills are done, they often times...get them late or they forget to order it...it's not like they don't want to intentionally not take their medicine." Overall, providers were interested in the DMS system as this system could provide an objective measure of adherence instead of self-report. One provider verbalized, "I'm always looking for ways to help my patients...take ownership of their own care and to improve quality of care. Those are the two things that drew me to the DMS [system]." Providers also shared that a common issue can be reconciling what a patient says compared to medication data in the electronic health record. The provider said, "I was drawn to something like use of technology that would help both on the provider/clinician's end and the patient's end to overcome that kind of barrier."

*Concerns with the DMS (pre-study).* Providers expressed concerns with the implementation of DMS in their patient populations, specifically those who experience paranoia and would be apprehensive of using the DMS system to track medication adherence. The provider said, "my initial reaction was paranoid, psychotic patients might be a bit concerned that they're taking a pill that has a

sensor...I was thinking that they might not be willing to take such a medication where one would know [provider or family member] whether they are taking it or not.” An additional concern was around the use of the DMS patch, due to the provider’s experience with skin sensitivity to adhesives.

*DMS dashboard usability.* Providers experienced frustration with the multi-step process to log into the DMS dashboard via the notification email. This frustration led them to not check notification emails or log into the dashboard. Improvement suggestions included streamlining the log-in process for the dashboard (e.g., ability to save password and not needing to re-enter it each time) and including additional details (e.g., missed dose, multiple doses taken at one time) in the notification email to encourage them to log into the dashboard more frequently. Of note, none of the providers interviewed called DMS support for assistance with the dashboard rather these providers called the study team due to their accessibility.

*Challenges in impact of the DMS.* Providers stated that the objective medication adherence data for each patient in the DMS system was helpful. However, due to numerous usability challenges (e.g., data inaccuracy, multi-step log-in process), these providers did not use the DMS dashboard, rather they relied on the study team for information on their patient’s medication data.

*Suggestions to increase provider use.* Provider feedback for DMS centered around 1) improving accessibility to the DMS dashboard and 2) change in DMS data management to improve workflow. Providers suggested a streamlined process for receiving notifications such as including additional information in the notification email, and embedding the DMS login into the EHR (e.g. a link taking them to the DMS dashboard) to make it easier to integrate into their regular workflow. One provider stated, "if there was some way we could incorporate [ingestion data] in our templated notes...while we are writing, documenting the notes, we could click the link to the dashboard...that might work." Finally, many providers recommended that the DMS dashboard and data should instead be managed by an individual in the clinic (e.g., nurse or clinical coordinator) as this individual can summarize patient data for the provider. One provider said, "... if the DMS system could be created

in a way that there will be a go-between, an intermediary between the provider and the patient on the DMS system, who would be monitoring, more closely, the ingestion data...[and summarize] this is number of days of adherence, number of days of not adhering...so that the prescriber has that information right in front of them, even before seeing the patient."

#### 4. Discussion

This open-label, 2-site, 12-month, provider-randomized trial assessed aripiprazole refill adherence in Veterans with SMI and examined patient and provider perspectives on the feasibility and acceptability of DMS for this population in the VA Healthcare System. Our study showed that there was no notable difference in the refill rates between the DMS group and TAU group in intention-to treat analyses. Among users of the DMS, the refill rates were 85% for those patients when engaged in the DMS. Our qualitative analysis summary showed challenges for both patients and providers in the impact of the DMS system on their medication adherence, many due to technical issues and contact issues with the DMS patch, including skin irritation and adherence on the skin. These issues impacted the length of user participation as well as overall confidence and interest in using the system as a reliable and accurate method of tracking medication ingestion. Further improvements to the DMS system are recommended to improve the patient-provider experience and increase satisfaction and confidence in its use for SMI patients, particularly with patients that may not have extensive experience with smartphones, Bluetooth technology and health app use.

In another trial using the same DMS system<sup>10</sup>, adherence was measured by the proportion of days with good patch coverage (ingestible event marker registration), however, in the current study, medication adherence was assessed by the proportion of days covered (PDC) on aripiprazole using pharmacy record data. Due to the prevalence of patient reported technical difficulties with pill registration for the DMS and provider concern for data accuracy that were described during the qualitative interviews, PDC was a preferred measure of medication adherence in the current study. Compared to a medication adherence rate of 80% or greater reported over an 8-week period (when

good patch coverage was reported) in the previous study<sup>10</sup>, our study saw 82% adherence in our intention to treat analysis over a 3-month (~12 week) period, which was comparable. However, this rate changed to 75% at 6 months in our study, which reveals an area of further study into the potential cause of lower adherence rates after 90 days.

Our study's qualitative findings highlighted a similar concern regarding patch use and contact issues (skin irritation and adherence to skin). In a recent qualitative analysis study that evaluated patient responses to using a comparable digital medicine program (DMP) with an ingestible sensor co-encapsulated with antiretroviral therapy medication, patients reported similar issues seen in our qualitative findings, including issues with patch adherence to skin and overall frustration with using the DMP patch.<sup>11</sup> As detailed above and in our qualitative summary findings, these issues impacted the length of user participation; consideration should be given for making improvements to the usability of the patch, particularly long-term use, to improve the patient experience and adherence to the DMS.

*Limitations.* Several considerations should be acknowledged. First, enrollment and data collection for the study ended early. Additionally, many patients in the DMS group experienced system connectivity issues and/or issues with skin irritation from use of the DMS patch. In many cases, patients opted to discontinue use of the DMS system due to these issues. A limitation for consideration with regard to adherence is the potential of the Hawthorne effect related to the observation of both participant groups (DMS and TAU) in a trial. This may have impacted adherence rates as measured by PDC. The small sample size with provider randomization could lead to residual imbalance in baseline characteristics of the two groups.

In addition, while qualitative interviews were conducted with 14 VA patients who used the DMS system during their study participation, only 4 providers were interviewed. Overall, provider engagement with the DMS dashboard was limited – some providers were unable to share feedback on their experience with the DMS dashboard and the impact that use of the DMS system had for their

patient and for patient/provider communication. Providers that consented to participate in the qualitative interviews shared their level of interaction with the DMS dashboard and interview questions were designed to capture potential barriers to use and to gather feedback on how to increase provider use. Individuals enrolled had a relatively high rate of refill at baseline, future studies using DMS may want to focus on individuals who are having greater challenges with refill adherence. Finally, regarding VA patient qualitative interviews, some participants were interviewed about their DMS onboarding and DMS system use experience several months or sometimes up to 1 year after enrollment, which could have impacted how well patients remembered specific details about their experience.

*Strengths.* Despite the aforementioned limitations, we collected data on the impact of a DMS system use in a Veteran population, while also gathering detailed feedback on patient and provider experiences, suggested improvements and considerations for improvements by primary users. Evaluation of this novel digital medicine system in the VA Healthcare system provided insight into real-world use for increased utilization in community-based, private practice and public healthcare settings. Another important distinction present in this study was overall extended patient use of the DMS. Patients were asked to use the DMS for 90 days, at which time they, along with their provider, could decide whether to continue using the DMS beyond 90 days and up to the full 12 months of study participation. Compared to previous studies using a DMS with an ingestible sensor pill for a period of 8<sup>10</sup> or 12<sup>12</sup> weeks, use of the DMS lasted up to 12 months, which provided insight into DMS use that was 90 days or longer (n= 12), with 6 respondents opting to use the DMS for 180 days or more.

*Conclusion.* DMS is feasible in individuals with SMI in the real world but both Veterans and providers raised issues that need to be further addressed to achieve the desired outcomes in terms of long-term monitoring. The qualitative analyses highlighted areas for further refinement, including DMS system improvements to increase usability and impact for patients and providers as well as

consideration of alternative methods to DMS system integration in provider and clinic workflows.

**Acknowledgments:** The research reported in this publication was supported by Otsuka Pharmaceutical Development and Commercialization, Inc. The content is solely the responsibility of the authors and does not reflect the position or policy of Duke University, the US Department of Veterans Affairs, the US government or Otsuka Pharmaceutical Development and Commercialization, Inc.

**Conflicts of Interest:** Dr. Bosworth reports receiving research funds from Sanofi, Otsuka, Improved Patient Outcomes, Novo Nordisk, PhRMA Foundation, Boehringer Ingelheim as well as consulting funds from Sanofi, Otsuka, Abbott, and Novartis. Dr. Lewinski reports receiving funds from PhRMA Foundation and Otsuka. Drs. Smith and Moore report receiving funds from Otsuka. Dr. Fowler is an employee of Otsuka. The remaining authors have no competing interests to declare.

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## Abbreviations:

DSM-V: Diagnostic and Statistical Manual of Mental Disorders

DMS: Digital medicine system

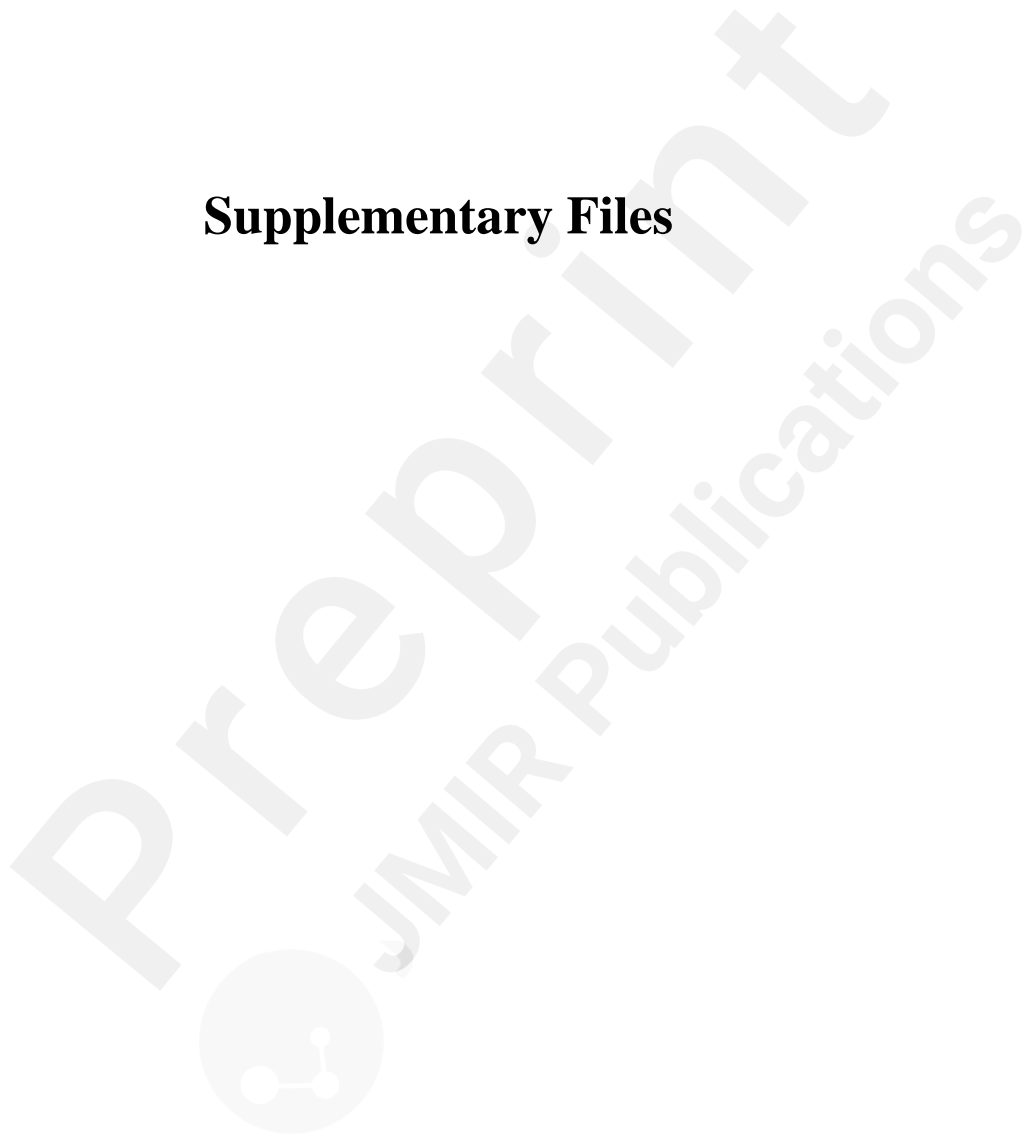
FDA: Food and Drug Administration

IRB: Institutional Review Board

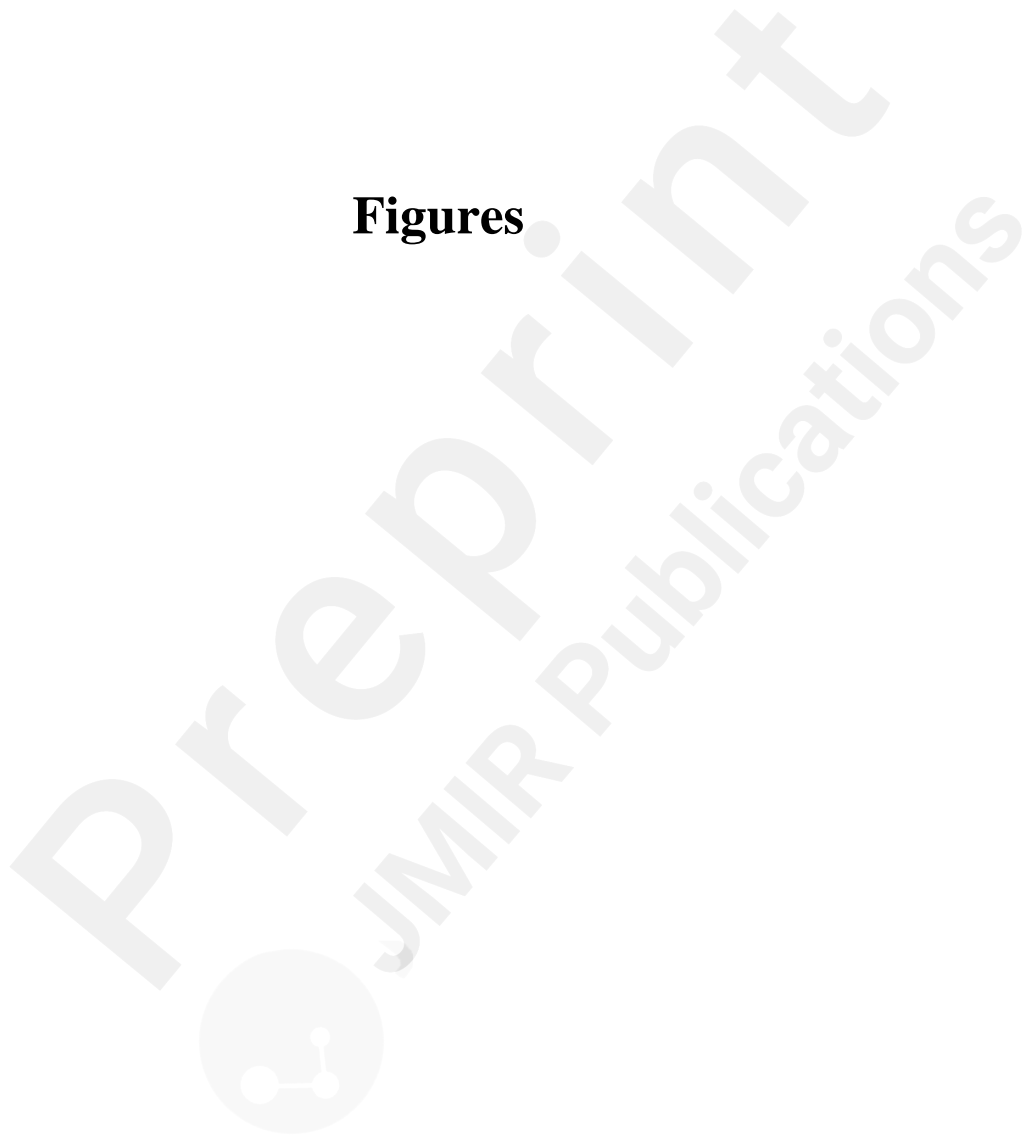
PDC: Proportion of days covered  
R&D: Research and Development Committee  
SMI: Serious mental illness  
TAU: Treatment as usual  
VHA: Veterans Health Administration



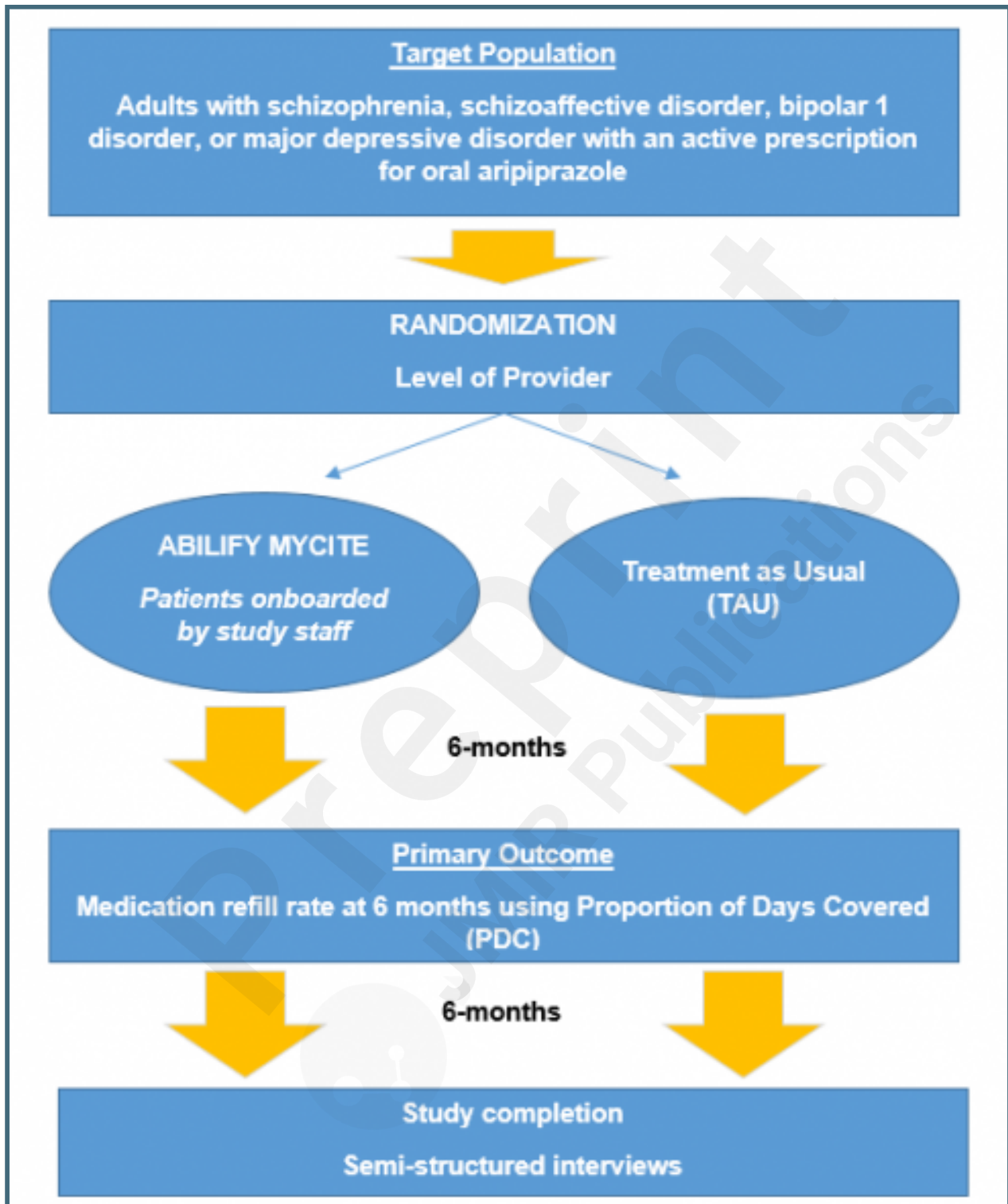
## Supplementary Files



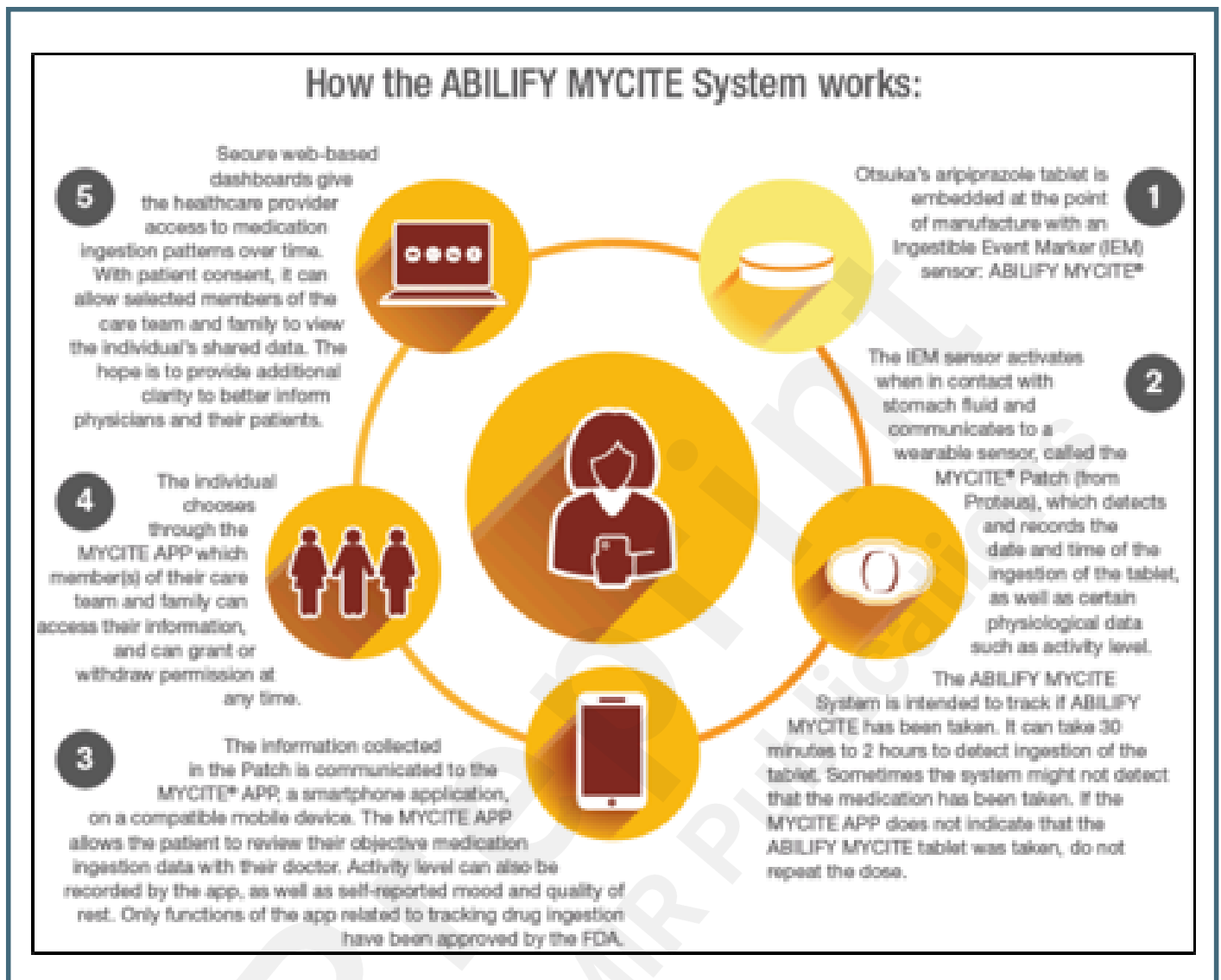
## Figures



Schematic of enrollment procedures.



Schematic of digital medicine intervention.



Enrollment.

