Feasibility of a Noninterventional Decentralized Clinical Trial Model in Adults with Major Depressive Disorder

J. Corey Fowler1, Taisa Skubiak1, Kirsten Engelhardt1, Benjamin Furst2, Sophia Zhao1, Margareta Nyilas1, Debbie Profit1 and William Carson1

2 Science 37, Inc., Los Angeles, CA, US

Corresponding author: J. Corey Fowler, PhD (Corey.Fowler@otsuka-us.com)

Objective: Adding to existing challenges in conducting clinical trials, COVID-19 has indefinitely affected modern clinical research. Decentralized clinical trials, using telemedicine and digital technology, may prove critical to the future of clinical development. This type of methodology in psychiatric trials remains largely unexplored; therefore, we evaluated the feasibility and quality of data collection in a randomized, sham-interventional trial using fully decentralized methodology in subjects with major depressive disorder (MDD).

Methods: This was a four-week, noninterventional, two-cohort, decentralized, clinical trial. Eligible adults had a diagnosis of MDD and were medically stable. Subjects in cohort 1 continued stable antidepressant and antipsychotic treatment and were randomly assigned 1:1 into assisted or unassisted groups (ie, completing assessments at home aided by mobile healthcare providers or alone using study-provided materials, respectively). Subjects in cohort 2 continued stable antidepressant treatment only or with other therapy and could choose assignment to assisted or unassisted groups. Coprimary endpoints were operational effectiveness (assessed by completion rate, subject diversity, time to study start, and subject satisfaction) and data-collection integrity (assessed by subjects’ ability to collect assessments and real-time data availability). Safety analyses included incidence of adverse events and suicidality.

Results: In cohort 1, 96 subjects were screened with 31 enrolled; in cohort 2, 46 subjects were screened with 26 enrolled. Most subjects (≥81% across study groups and cohorts), and more than 80% of both cohorts, completed all assessments. No major safety concerns were encountered.

Conclusions: This study demonstrated that decentralized clinical trials can be performed in patients with stable MDD.

Clinical trial registration number: None; this was a noninterventional trial.

Keywords: Decentralized clinical trials; remote treatment; stable major depressive disorder

Introduction

Randomized controlled clinical trials are the gold-standard scientific and regulatory approach to gain health authority approval for new therapies or technologies [1]. Challenges persist with multisite clinical trials, including failure to reach accrual goals, which can prolong trial timelines and increase study costs [2, 3]. Principal investigators face barriers that contribute to these challenges, including reduced availability to balance clinical practice with research [2], increasingly complex protocol designs [4], and restrictive eligibility criteria [5]. Additional barriers for subjects include time and costs associated with completing procedures, attending appointments, and traveling or relocating to be near a trial site, which are disproportionately located near urban areas [2, 5, 6]. Subjects with mental illness such as depression may face additional barriers, including perceived stigma [7].

Access to technology may address many of these barriers in clinical trials. Notably, as of 2019, more than 80% of adults in the United States (US) owned a smartphone and 74% owned either a laptop or desktop computer [8]. Telemedicine has been introduced into clinical trials through real-time video or virtual communication, uploading data or photographs for delayed review and analysis, and remote patient monitoring including digital biomarkers [7, 9]. Studies in diabetes research suggest that use of telemedicine may remove geographical and transportation barriers, expanding access to more diverse populations [10, 11]. In a 2004 study, Ruskin et al [12] showed that major depressive disorder (MDD) psychometric assessments (e.g., Hamilton Depression Rating Scale score) had equivalent outcomes when
collected via clinical trial sites versus collection by telemedicine. Additionally, several studies have shown the utility and equivalence of telepsychiatry in clinical practice and care settings [13–15]. Collectively, the American Psychiatric Association currently rates the strength of the evidence for using telemedicine to remotely interview, assess, and perform cognitive testing as outstanding, with high levels of feasibility, validity, reliability, and subject satisfaction [16].

Among other medical conditions, decentralized clinical trials have proven comparable to on-site or in-person studies. Pfizer’s REMOTE study, considered the first fully decentralized clinical trial, used virtual methodology to repeat a previous on-site trial evaluating tolterodine extended-release (then under review as an Investigational New Drug) in subjects with overactive bladder [17]. Some fields of study, such as dermatology, have also successfully embraced decentralized clinical trials [18]. However, decentralized trials in psychiatry are less common. Virtual photovoice-based technology was used in the “Recover 4 US” study that assessed loneliness in research subjects [19]. The BRIGHTEN study used a web-based research portal to prescreen subjects based on mobile device ownership, obtain consent, and randomly assign those with depression to one of three mobile mental health applications. The subjects then remotely completed mental health assessments every four weeks for 12 weeks [20]. It should be noted, however, that the BRIGHTEN study had minimal contact with subjects, did not conduct medical screening, and only 37%–56% of subjects completed the four-weekly assessments [20]. To our knowledge, no prior clinical trial in psychiatry has mimicked a randomized interventional trial in a decentralized setting, including robust medical screening.

The novel coronavirus disease 2019 (COVID-19) pandemic has made apparent the need to reevaluate how investigators collectively conduct clinical trials [21]. Personal protective equipment, laboratory equipment, and nonessential personnel access to hospitals and healthcare facilities are all limited by the pandemic [22]. In the US, new subject enrollment in clinical trials for March 2020 was reduced by 67% compared with March 2019 [23], and over 400 clinical trials have been suspended because of COVID-19 [24]. The US Food and Drug Administration (FDA) issued guidance for remote monitoring to collect patient-generated outcome assessments and clinician-reported outcome assessments, including guidance on protocol deviations that require amendments prior to implementation [25]. For trials involving investigational products, protocol amendments to enable home delivery of study drugs to participants were permitted [25]. The Centers for Medicaid and Medicare Services advised implementing decentralized healthcare options instead of on-site visits whenever possible [26]. Decentralized clinical trials may address some of these disruptions by consolidating multiple physical trial sites into one or more remote sites at varied geographic locations [18]. Investigators licensed in multiple states can recruit diverse subjects to complete assessments from home. Therefore, decentralized trials may play an important role in the future of the clinical development process. In our current noninterventional study, we evaluated the feasibility and quality of data collection in a decentralized clinical trial of subjects with MDD.

**Methods**

**Subjects and study design**

This was a four-week, noninterventional, two-cohort, decentralized, clinical trial. The study was performed remotely at subjects’ residences in California, Florida, Illinois, and New York. Subjects were recruited using a multiplatform approach through social media and web-based search engines (see Supplemental Methods, Recruitment for additional details). All subjects completed screening and trial visits (at baseline and weeks one to four) from home using a Zoom Videoconferencing Inc (San Jose, CA) interface that was Health Insurance Portability and Accountability Act compliant, with study data captured through the Network Oriented Research Assistant (NORA) telemedicine platform (Science 37, Los Angeles, CA, USA). The trial was conducted by Science 37 investigators, coordinators, raters, and nurses, in accordance with local laws and the International Council for Harmonization Good Clinical Practice guidelines. The protocol was approved by the relevant Institutional Review Boards. Subject identification codes were used to protect subject privacy; information generated by the trial was considered highly confidential and was available for remote monitoring with view-only access to authorized personnel. After receiving a complete trial description, all subjects provided written informed consent using a handwritten signature digitally executed on a computer or tablet.

Eligible subjects were aged 18 to 65 years, had MDD confirmed via virtual Mini-International Neuropsychiatric Interview (MINI) performed by study staff trained in the assessment, and were considered medically stable per investigator judgment. Subjects were ineligible if they had received electroconvulsive therapy for their most recent episode or were receiving adjunct oral aripiprazole with an ingestible electronic marker (Abilify MyCite®, Otsuka Pharmaceutical, Tokyo, Japan). Subjects who had been involuntarily committed or hospitalized within 90 days prior to screening or who had experienced psychotic symptoms or active suicidal ideation within six months of screening were also ineligible for the study. Subjects with substance use disorder, who screened positive for illicit drugs (except marijuana), or who were pregnant, were excluded.

Eligible subjects in cohort 1 had been taking a stable dose of an antidepressant plus a second-generation antipsychotic for at least four weeks prior to study start. Eligible subjects in cohort 2 had been taking a stable dose of an antidepressant alone or with other therapy for at least four weeks prior to study start. All subjects continued their treatment regimen for the study duration and commercially obtained their prescribed medications. Prior to study start, all participants were shipped a trial-specific iPhone preloaded with NORA and the KardiaMobile application (AliveCor, Inc, Mountain View, CA), the one-lead electrocardiogram (ECG) device (KardiaMobile, AliveCor, Inc, Mountain View, CA), and medication proxy with instructions for use (see Supplemental Methods). Subjects in the unassisted group were also shipped a blood microsampling kit (Neoteryx Mitra Microsampler, Neoteryx, Torrance, CA), Ideal Life trial devices (scale,
blood pressure cuff, thermometer), and their iPhones were preloaded with the Ideal Life application (Raziel Health, Winter Park, FL). Delivery of smartphones and trial materials were confirmed by trial staff.

**Group assignments and procedures**

This trial had two study groups in each cohort: assisted and unassisted. In the assisted group, subjects used telemedicine in combination with in-person visits from a mobile healthcare provider (mHCP), such as mobile nurses, who assisted subjects in collection of trial assessments (*Figure 1*). In the unassisted group, subjects used telemedicine and calibrated mobile instruments to complete assessments on their own. Subjects in cohort 1 were initially randomly assigned 1:1

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**Figure 1**: Decentralized clinical trial design.

*a* Screening assessments included subject demographics and medical history, and MINI. Subjects in cohort 1 were randomly assigned 1:1 at screening, and again at baseline, to study groups.

*b* Physical data included: height, weight, and vital signs; ECGs, urine pregnancy test, and drug screen; clinical laboratory tests; and blood collection for plasma concentration sampling and blood microsampling. All physical data except vital signs were collected only at screening. Vital signs were collected weekly.

*c* ePROs included medication proxy use via daily electronic diary, subject satisfaction survey, and QIDS-SR<sub>16</sub>. Medication proxy use and QIDS-SR<sub>16</sub> were reported at each visit except at screening. Subjects completed the satisfaction survey at the week four/end of study visit.

*d* Safety assessments included collection of AE information by mHCPs for the assisted group, or by the decentralized study team in the unassisted group.

*e* ClinROs included C-SSRS, MADRS, CGI-I, and CGI-S, and for subjects taking antipsychotics, AIMS, and BARS. C-SSRS assessments were performed at all visits. MADRS assessments were completed at baseline and week four. CGI-S, AIMS, and BARS assessments were completed at every visit except screening. CGI-I assessments were completed at every visit except screening and baseline visits.

*f* Subjects in the unassisted group had their height measured at a national patient services center or a local laboratory facility at the screening visit. Physical examinations were performed by the subject’s primary care provider or at an urgent-care facility at the investigator’s request.

*g* Study materials were shipped directly to subjects’ homes in the unassisted group and confirmed by trial staff.

AE, adverse event; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; CGI-I, Clinical Global Impression–Improvement; CGI-S, Clinical Global Impression–Severity of Illness; ClinROs, clinician-reported outcomes; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; ePROs, electronic patient-reported outcomes; I/E, inclusion/exclusion; MADRS, Montgomery-Åsberg Depression Rating Scale; MINI, Mini International Neuropsychiatry Interview; mHCP, mobile healthcare provider; Phys Data, physical data; QIDS-SR<sub>16</sub>, Quick Inventory of Depressive Symptomology, Self-Report, 16 questions.
into assisted or unassisted groups immediately after signing consent (first randomization). Screening assessments were performed according to protocols from the group assigned by the first randomization. Following eligibility verification, subjects in cohort 1 were randomly assigned 1:1 again into assisted or unassisted groups (second randomization), so half the subjects remained with their original group assignment and half switched to the other group (Figure 1). The trial was designed with an interim pause to allow for protocol adjustments in cohort 2 based on cohort 1. In cohort 2, immediately after signing consent, subjects chose between assisted or unassisted groups as they preferred (Figure 1). The assessments used for screening were equivalent between groups, but methodology of procedures differed based on whether subjects were aided by an mHCP (Figure 1; Supplemental Methods).

Outcomes
Assessments in this trial mimicked those of a traditional trial but were completed outside of a centralized trial site. The coprimary endpoints were operational effectiveness and data collection integrity. Operational effectiveness was measured by subject completion rate of all trial visits, demographic and geographic diversity of subjects, mean time from providing informed consent to study start (baseline visit), and subject satisfaction, assessed at week four by survey. Data collection integrity was measured by subjects’ ability to collect protocol measures at screening and at week 4 (defined as yes or no responses according to the schedule of assessments) and real-time availability of data, defined as within 24 hours. Protocol measures included the Montgomery-Åsberg Depression Rating Scale (MADRS), Clinical Global Impression of Severity of Illness (CGI-S), Clinical Global Impression of Improvement (CGI-I), Quick Inventory of Depressive Symptomatology Self Report, 16 questions (QIDS-SR_16), Columbia Suicide Severity Rating Scale (C-SSRS), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and vital signs.

The secondary endpoint was reliability of data collection, measured by the mean change from baseline to week 4. MADRS, CGI-S, CGI-I, AIMS, and BARS assessments were performed by video interview; study staff were trained to perform MADRS, AIMS, and BARS assessments by the central rater company. QIDS-SR_16 was self-reported. As trial eligibility criteria required subjects to maintain stable doses of medications for the treatment of MDD, the decentralized trial mimicked medication administration using a drug proxy taken in addition to each subject’s daily medications (see Supplemental Methods).

As this was a noninterventional trial, safety assessments were performed to test the methodology by which safety could be monitored in a remote setting. The incidences of adverse events (AEs) and serious adverse events (SAEs), and C-SSRS scores were evaluated. All AEs were classified using preferred terms of the standardized Medical Dictionary for Regulatory Activities version 22.0 and were documented virtually using video interviews.

Statistical analyses
As this was a feasibility study, sample size was not based on statistical power considerations. Descriptive statistics were used for all endpoints. Continuous variables were summarized by means, medians, ranges, quartiles, and standard deviations (SD). Categorical variables were tabulated by frequency distributions.

Results
Operational effectiveness (coprimary endpoint)
Using a multiplatform approach to recruitment beginning in August 2018, 30,397 subjects initially signed up using the trial’s online landing page (Figure 2). Completion of an online survey resulted in prequalification of 2511 subjects, and subsequent telephone prescreening identified 142 eligible subjects who consented to participate. For cohort 1, between September 2018 and March 2019, 96 subjects completed screening assessments and 31 were randomly assigned to assisted (n = 15) or unassisted (n = 16) groups (Figure 2a). In cohort 1, 100% (15/15) of the assisted group and 81% (13/16) of the unassisted group completed the trial (Figure 2a). For cohort 2, between June 19, 2019 and September 11, 2019, 46 subjects completed screening assessments and 26 were enrolled and selected assignment to the assisted (n = 11) or unassisted (n = 15) groups (Figure 2b). In cohort 2, 100% (11/11) of the assisted group and 93% (14/15) of the unassisted group completed the study (Figure 2b). Across both cohorts, n = 26 subjects were enrolled in the assisted group while n = 31 subjects were enrolled in the unassisted group.

Subjects were predominantly white (90%; 51/57), female (82%; 47/57) and had a mean age of 47.4 years (Table 1). Subjects were from California, Florida, Illinois and New York, and all subjects lived in separate zip codes (Table 1). In cohort 1, all subjects were taking antidepressants plus an antipsychotic. In cohort 2, 14 subjects were taking antidepressants alone and 12 subjects were taking antidepressants plus antipsychotic (assisted, n = 5; unassisted, n = 7).

The mean time from providing informed consent to study start was 29 days (SD: six days) in the total assisted group and 28 days (SD: nine days) in the total unassisted group (hazard ratio, 0.925 [95% CI: 0.545–1.571]; P = 0.7565; Figure S1). For cohort 1, the mean time to study start for the assisted group was 30 days and 32 days for the unassisted group. In cohort 2, the mean time to study start for the assisted group was 26 days and 25 days for the unassisted group. Time to full enrollment in cohort 1, defined as the time between first and last subjects enrolling, was 25 days for the assisted group and 48 days for the unassisted group. For cohort 2, time to full enrollment was 14 days for the assisted group and 22 days for the unassisted group.
Responses to the subject satisfaction and experience survey showed that subjects in both study groups were reasonably satisfied with the core elements of decentralized trials (Table S1). Completing daily study activities from home was reported as easy in 96% (24/25) of subjects in the assisted group and 77% (23/30) of subjects in the unassisted group. Over 90% of subjects in both groups were satisfied by interactions with study coordinators and doctors and felt safe and cared for during the study. Most subjects in cohorts 1 and 2 were reasonably satisfied with their data collection method, regardless of receiving assistance (Table S2). For subjects in the assisted groups, most were satisfied with having study personnel enter their home (cohort 1: 93% [13/14]; cohort 2: 100% [11/11]). A preference for completing study visits on their own was reported by 64% (nine of 14) of subjects in the assisted group and 40% (six of 15) of subjects in the unassisted group in cohort 1. In cohort 2, 73% (eight of 11) of subjects in the assisted group reported being unlikely to prefer completing assessments on their own. For the cohort 2 unassisted group, 33% (five of 15) of subjects reported they were unlikely to prefer to complete studies with an mHCP. For cohort 2, survey responses indicated 27% (three of 11) of subjects in the assisted group and 33% (five of 15) of the unassisted group had prior clinical trial experience. All subjects in both study groups rated the decentralized trial experience as either favorable or neutral in comparison to previous clinical trial experiences (Table S3).

**Data collection integrity (coprimary endpoint)**

All protocol measures were reliably collected from 100% (57/57) of subjects at screening and over 80% of subjects at week four in both cohorts regardless of group assignments. At week four, 100% (57/57) of subjects from both cohorts and group assignments completed assessments for MADRS, CGI-I, CGI-S, QIDS-SR, and C-SSRS. Collection of vital signs appeared most susceptible to attrition, with 8% (two of 26) of assisted subjects and 7% (two of 30) of unassisted subjects failing to complete these assessments at week four. All data were available to the sponsor in near real-time (within 24 hours).

**Psychological and physiological assessments**

The mean change from baseline to week four in psychological and physiological parameters were minimal, and the magnitude of change between assisted and unassisted groups were similar (Table 2). Improvements in total MADRS scores of more than 50% from baseline to week four were observed in 21% (12/56) of the total study population (assisted: 23% [6/26]; unassisted: 20% [6/30]).

**Safety**

As this was a noninterventional trial, safety assessments were performed to confirm that safety could be successfully monitored in a decentralized trial setting. All AEs were consistent with previously reported AEs for this population with the prescribed medications. For both cohorts, 50% (13/26) of subjects in the assisted group and 77% (24/31) of
subjects in the unassisted group reported AEs. In the total study population, 65% (37/57) subjects reported AEs. Six AEs of orthostatic hypotension were reported. No SAEs, discontinuations due to AEs, or deaths were reported during this study.

Discussion
In this noninterventional decentralized clinical trial, subjects with MDD from four US states completed enrollment within 29 days of consent. Most subjects completed the study (≥81% across study groups), regardless of being randomly assigned to (cohort 1), or choosing between (cohort 2), the assisted or unassisted groups. All subjects completed assessments at baseline and over 80% completed assessments after four weeks on study. Subjects in both groups reported a high level of satisfaction with study procedures. Data appeared reliable, with minimal changes in assessments from baseline to week four; results from most assessments were available to investigators within 24 hours. Safety was successfully monitored remotely in this trial, and no major safety concerns were raised.

Previous analyses of decentralized options versus conventional on-site psychiatric care have reported comparable outcomes [7, 27]. Although this trial did not have an on-site arm, insights can be gained from previously completed trials for brexipiprazole (Figure 3) [28–31]. As subjects in this trial each lived in a different zip code, across four US states, decentralized clinical trials may have wider geographic reach than conventional trials. Decentralized trials may reach a

**Table 1:** Subject demographics and baseline characteristics combined for cohorts 1 and 2.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Assisted (n = 26)</th>
<th>Unassisted (n = 31)</th>
<th>Total (n = 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>46.5 ± 10.9</td>
<td>48.0 ± 11.0</td>
<td>47.4 ± 10.9</td>
</tr>
<tr>
<td>Sex, n</td>
<td>Mean %</td>
<td>Mean %</td>
<td>Mean %</td>
</tr>
<tr>
<td>Female</td>
<td>22 %</td>
<td>25 %</td>
<td>47.2 %</td>
</tr>
<tr>
<td>Male</td>
<td>3 %</td>
<td>6 %</td>
<td>9 %</td>
</tr>
<tr>
<td>Not specified</td>
<td>1 %</td>
<td>0 %</td>
<td>1 %</td>
</tr>
<tr>
<td>Race/ethnicity, n</td>
<td>Mean %</td>
<td>Mean %</td>
<td>Mean %</td>
</tr>
<tr>
<td>White</td>
<td>26 %</td>
<td>25 %</td>
<td>51 %</td>
</tr>
<tr>
<td>Black or African American</td>
<td>0 %</td>
<td>3 %</td>
<td>3 %</td>
</tr>
<tr>
<td>Asian</td>
<td>0 %</td>
<td>1 %</td>
<td>1 %</td>
</tr>
<tr>
<td>Other</td>
<td>0 %</td>
<td>2 %</td>
<td>2 %</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>California</td>
<td>13 ± 50</td>
<td>14 ± 45</td>
<td>27 ± 47</td>
</tr>
<tr>
<td>Florida</td>
<td>5 ± 19</td>
<td>3 ± 10</td>
<td>8 ± 14</td>
</tr>
<tr>
<td>Illinois</td>
<td>3 ± 12</td>
<td>5 ± 16</td>
<td>8 ± 14</td>
</tr>
<tr>
<td>New York</td>
<td>5 ± 19</td>
<td>9 ± 29</td>
<td>14 ± 25</td>
</tr>
<tr>
<td>Psychological assessments, total score</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>MADRS</td>
<td>21.8 ± 10.2</td>
<td>18.7 ± 10.3</td>
<td>20.1 ± 10.3</td>
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<tr>
<td>CGI-I</td>
<td>4.0 ± 0.5</td>
<td>3.8 ± 0.6</td>
<td>3.9 ± 0.6</td>
</tr>
<tr>
<td>CGI-S</td>
<td>3.5 ± 1.2</td>
<td>3.0 ± 1.3</td>
<td>3.2 ± 1.3</td>
</tr>
<tr>
<td>QIDS-SR16</td>
<td>9.7 ± 5.1</td>
<td>8.1 ± 3.9</td>
<td>8.8 ± 4.5</td>
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<tr>
<td>Physiological assessments, total score</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>AIMS*</td>
<td>2.7 ± 3.0</td>
<td>2.1 ± 2.2</td>
<td>2.4 ± 2.6</td>
</tr>
<tr>
<td>BARS*</td>
<td>0.7 ± 1.2</td>
<td>0.7 ± 1.0</td>
<td>0.7 ± 1.1</td>
</tr>
</tbody>
</table>

*AIMS and BARS were evaluated in subjects taking antipsychotics, which was not a requirement for cohort 2. Numbers of subjects evaluated were n = 20 for the assisted group and n = 22 for the unassisted group.

AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; BMI, body mass index; CGI-I, Clinical Global Impression–Improvement; CGI-S, Clinical Global Impression–Severity of Illness; MADRS, Montgomery-Åsberg Depression Rating Scale; QIDS-SR16, Quick Inventory of Depressive Symptomology Self Report, 16 questions; SD, standard deviation.
Table 2: Change from baseline to week 4 of secondary endpoints.

<table>
<thead>
<tr>
<th></th>
<th>Assisted (n = 26)</th>
<th>Unassisted (n = 31)</th>
<th>Total (n = 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychological assessments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MADRS score</td>
<td>–3.7 (9.4)</td>
<td>–1.4 (8.7)</td>
<td>–2.5 (9.2)</td>
</tr>
<tr>
<td>CGI-S score</td>
<td>–0.5 (1.1)</td>
<td>–0.2 (0.7)</td>
<td>–0.3 (0.9)</td>
</tr>
<tr>
<td>CGI-I score</td>
<td>3.5 (1.1)</td>
<td>3.8 (0.7)</td>
<td>3.7 (0.9)</td>
</tr>
<tr>
<td>QIDS-SRscore</td>
<td>–2.5 (3.3)</td>
<td>–2.2 (3.4)</td>
<td>–2.4 (3.3)</td>
</tr>
<tr>
<td><strong>Physiological assessments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIMS</td>
<td>0.2 (2.2)</td>
<td>0.3 (2.2)</td>
<td>0.3 (2.2)</td>
</tr>
<tr>
<td>BARS</td>
<td>0.1 (0.9)</td>
<td>–0.0 (0.7)</td>
<td>0.0 (0.8)</td>
</tr>
</tbody>
</table>

*Psychological assessments were evaluated in the efficacy sample; one subject was excluded because they failed to complete their baseline visit.

b CGI-I scores reflect change over time from baseline.

Physiological assessments were evaluated in all enrolled subjects taking antipsychotics who underwent at least one trial procedure and assessment were included.

AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; CGI-I, Clinical Global Impression–Improvement; CGI-S, Clinical Global Impression–Severity of Illness; MADRS, Montgomery-Åsberg Depression Rating Scale; QIDS-SR16, Quick Inventory of Depressive Symptomology Self-Report, 16 questions; SD, standard deviation.

Figure 3: Features of the decentralized clinical trial model versus select completed on-site brexpiprazole trials.

- **Polaris trial** (NCT01360632) [28].
- **Pyxis trial** (NCT01360645) [29].
- **Delphinus trial** (NCT01727726) [31].
- **Sirius trial** (NCT02196506) [30].
- **Fogel DB** [5].

- Fraction of subjects who, after initially signing up on the trial’s online landing page, were eventually enrolled.
- Fraction of subjects who, after prequalification via survey and telephone screening, were eventually enrolled.
- For the current study, different methodological considerations between assisted and unassisted groups (e.g., scheduling nurse visits, shipping supplies) necessitated reporting time from consent to study start.
- Time from first to last subject enrolled.
- Time range to full enrollment for assisted and unassisted groups across both cohorts.
- Completion rate for assisted and unassisted groups across both cohorts.

HCP, healthcare provider.
broader and more diverse population by recruiting through social media, compared with relying on HCP referral and clinics linked to physical trial sites. In the decentralized trial, 39% of screened subjects were enrolled versus 67%–74% of screened subjects in completed on-site brexpiprazole trials [28–31]. Even more striking was the 0.2% conversion rate from those recruited to those ultimately enrolled in the current study: of the total sign-ups on the trial’s online landing page, 91.7% (27,880 of 30,397) failed to meet study criteria. This trend is consistent with a recent meta-analysis, which found that the conversion rate was consistently higher in trials that used offline recruitment strategies vs trials which used online recruitment [32]. This phenomenon may be explained by the virtual patient recruitment process, which relies on patient self-selection rather than known patients or HCP referral. Therefore, the recruitment net is cast very widely, and the initial group of interested individuals must be significantly narrowed to identify eligible patients. In addition to the patients excluded by eligibility criteria, a further 7.6% of patients (2301 of 30,397) did not complete the next step in the qualification process, lost interest, and/or did not respond to contact attempts. These latter factors are likely not unique to decentralized clinical trials and impact conventional on-site trials as well. Further efforts are needed to identify methods of improving conversion rates in decentralized trials.

The mean duration of time elapsed between consent and study start in the decentralized study was 29 days and was similar across both groups and cohorts. This metric, rather than time to complete enrollment, was reported for the decentralized trial because of methodological differences between assisted and unassisted groups (e.g., scheduling mHCP visits, shipping supplies). For on-site brexpiprazole trials, the mean time from consent to enrollment was 20 days (Figure 3). Decentralized trials may enable more rapid subject accrual compared with on-site trials [33], as the time to reach full enrollment in the decentralized trial was 14–48 days versus 24–381 days for the four completed brexpiprazole trials (Figure 3). In the decentralized trial, 100% of subjects in the assisted group completed the trial, while four subjects in the unassisted group across both cohorts failed to complete the trial. However, overall completion rates for the two groups in this decentralized trial were similar (81%–100%) compared with previously completed brexpiprazole trials (90%–93%) (Figure 3). Decentralized trials may, therefore, alleviate many challenges of conventional on-site trials, including real-time data checks, enhanced data verification and processing, improved workflow, and increased protocol compliance [34]. Together, these results support the feasibility of conducting randomized interventional trials with decentralized designs.

Among the total study population, 77% rated completing study activities from home as easy and most were satisfied by interactions with, and quality of care received from, the study staff. All subjects with previous clinical trials experience considered the decentralized trial as favorable or neutral in comparison to conventional trials. These data indicate that subjects adapted well to decentralized trial methodologies and found the experience of participating in a decentralized trial acceptable, independent of study group or method of assignment. Data collected remotely were of high integrity and high quality, as most subjects completed psychological and physiological assessments with minimal changes from baseline to week four. MADRS scoring via video interview was relatively similar between groups (mHCP-assisted or unassisted). Of note, six subjects each in assisted and unassisted groups had improvements in total MADRS scores of more than 50% from baseline to week four. A previous study showed that different personnel rated the same subjects’ MADRS assessments similarly over video and face-to-face interviews [35]. “Touch time” and in-person contact, such as experienced with mHCPs, is thought to have physiological and psychological benefits [36]; this phenomenon is not dissimilar from the well-documented placebo effect [37]. In the current study, however, MADRS scores and other assessments were similar between assisted and unassisted groups. This reliability of data, coupled with the largely successful collection of assessments, support that data collection integrity can be maintained in decentralized clinical trials.

Future studies would benefit from considering the necessity of the double randomization method (used in cohort 1), which could prolong the time between subjects signing consent and study start. Like most decentralized trials, this trial benefited from wider geographic recruitment compared with trials limited by physical study sites. However, many states require providers using telehealth technology for patients in different states to be licensed in the patient’s home state [38], which may impair recruitment in some areas. Notably, the COVID-19 pandemic has resulted in 43 states and three territories relaxing telemedicine licensure requirements [39]; long-term effects of these changes remain uncertain. As a general limitation of decentralized clinical trials, subjects may find it difficult to establish a therapeutic relationship with staff when interacting through entirely virtual means [7]. However, a previous analysis of 11 studies using decentralized methods to care for subjects with mental health disorders found that most subjects did not miss face-to-face contact and found that their relationship with the provider was pleasant and grew over time [40]. Finally, as the current trial was non-interventional, future interventional studies in MDD using decentralized methodology may benefit from including an on-site arm to ensure similar intervention efficacy for patients.

The framework for regulatory approval of decentralized clinical trials and the acceptance of decentralized methodology in submissions to regulatory agencies remains largely unknown [7], though some signals are emerging. The FDA created a docket for public feedback on the use of decentralized healthcare technologies to improve clinical trial efficiency and identify barriers to implementation [41] and the Clinical Trials Transformative Initiative released a guidance document of legal, regulatory, and practical considerations for digital health trials [33]. Moreover, the COVID-19 pandemic prompted several regulatory agencies to issue guidance on decentralized management of clinical trials, including the US, Europe, the United Kingdom, and Singapore [21]. As COVID-19 is expected to remain a global concern well into 2021 [42], decentralized clinical trials remain a key option to maintain progress in clinical research.
Conclusions

This pilot study is the first to evaluate the feasibility of conducting a decentralized, randomized, sham-interventional, psychiatry trial, including assessments that would be completed in a traditional trial, such as medical screening. Overall, this study demonstrated that decentralized clinical trials can be performed in subjects with stable MDD. Study assessments can be collected through assisted or unassisted methods while maintaining data collection integrity, without appreciably impacting the subject or the ability to collect clinical endpoints. Finally, the conduct of decentralized clinical trials may not require an all-or-nothing approach. Hybridizing elements of decentralized trials with conventional on-site methodology may improve trial efficiency and expand patient access, while maintaining the benefits of on-site equipment and staff procedural expertise [33, 34].

Additional File

The additional file for this article can be found as follows:

- Supplementary file 1: Table of baseline demographics and table showing change from baseline to week 4 of secondary endpoints. DOI: https://doi.org/10.29024/jsim.84.s1

Ethics and Consent

The trial was conducted by Science 37 investigators, coordinators, raters, and nurses, in accordance with local laws and the International Council for Harmonization Good Clinical Practice guidelines. The protocol was approved by the relevant Institutional Review Boards. Subject identification codes were used to protect subject privacy; information generated by the trial was considered highly confidential and was available for remote monitoring with view-only access to authorized personnel. After receiving a complete trial description, all subjects provided written informed consent using a handwritten signature digitally executed on a computer or tablet.

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Competing Interests

J Corey Fowler, Taisa Skubiak, Kirsten Engelhardt, Sophia Zhao, Margaretta Nyilas, Debbie Profit, and William Carson are employees of Otsuka Pharmaceutical Development & Commercialization, Inc. Benjamin Furst is an employee of Science 37.

Author Contributions

All authors contributed to the study conception and design, analysis, and interpretation of data. All authors contributed to drafting and critical revision of the manuscript and approved the final version for submission.

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