Attending to the Patient with Major Depression: Preferences for Clinical Trial Methodologies and COVID19 Mitigations

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ABSTRACT

Introduction: The continued significant attrition rate within antidepressant randomized clinical trials (RCTs) has long been recognized, with Khan et al. (2000) finding the mean rate to be 37%, and more recently as high as 48% within RCTs of smartphone apps among subjects with major depressive disorder (MDD; Torous et al., 2020). The consequences of such poor RCT retention are extensive, including biased study results, reduced power, lower internal validity, less generalizability, and higher study costs (Liu et al., 2018). Researchers have examined reasons for poor accrual within MDD RCTs, such as study design (Rutherford et al., 2013), but a thorough review of the literature yielded no investigation specifically surveying MDD patients regarding retention. Exploring these factors is essential toward minimizing participants' attrition (Page & Persch, 2013). In addition, given that study procedures are currently being considered and even implemented because of COVID19, it is crucial to explicitly survey these patients on such design matters to enhance their retention. **Methods:** Patients currently experiencing a major depressive episode per the DSM-5 (APA, 2013) before study entry completed the Research Participant Preference Survey (RPPS), a 10-point Likert 45-item questionnaire focusing on various methodological, site operational, and assessment procedures that motivate general participation and continued enrollment in a trial, and specifically during the current COVID19 pandemic. The RPPS was completed at five US research sites (three in the West coast and two in the East) from May 2020 through December 2020. **Results:** A total of 66 subjects completed the RPPS, with a mean of 1.47 previous MDD clinical trial participation. Preferences that strongly motivated enrolling and continued study participation included having the opportunity to discover new or improve antidepressants (M=7.68), study compensation (M=7.89), access to mental health care (M=7.52), site staff explaining the study rather than just receiving study information from the Consent Form (M=7.83), and site staff courtesy and respect (M=9.03). Wilcoxon pairwise comparisons indicated that study initiation and retention were significantly enhanced by shorter on-site study visits (p<.001), visits occurring every other week compared to multiple times a week (p=.001), and more on-site assessments versus engaging in Zoom or Skype calls while the subject is at home (p=.003) or having a lab staff member conduct such procedures at the subject's home (p=.05) during COVID19. Participants had a significant preference for clinician-administered computer/tablet assessments than paper (p=.044). An example of demographic-related findings indicated that, per an analysis of variance, racial minorities over their Caucasian counterparts significantly preferred paper assessments (p=.031). **Conclusions:** Data from the current study indicate clear preferences that motivate subjects to enroll and not drop from clinical trial participation. These findings are informative to trial developers, such as knowing retention may be significantly hindered if a trial requires subjects to participate in longer duration study visits. Also, while sponsors and CROs may develop COVID19 remote study procedural contingency plans, subjects preferred assessments be conducted on site rather than at their homes. Potential explanation for our findings as well as study limitation will be discussed in the poster.

INTRODUCTION

- Given that clinical depression is one of the most common mental disorders in the United States, effecting 17.3 million adult Americans per year (NIMH, 2017), and is the leading cause of medical disease burden worldwide (World Health Organization, 2017), the science of exploring effective treatments to this ailment is paramount. One key aspect to empirically discovering effective antidepressants is our ability to retain study participants, but the dropout rate within placebo-controlled depression trials is alarmingly high, ranging from 21% to 49% (Kahn et al., 2000; Rutherford et al., 2010; Torous et al., 2020). Patient withdrawal is problematic for studies exploring antidepression drug efficacy as it leads to missing data, costly delays in study completion (Costello, 2016; Ross et al., 1999), potential premature entire trial termination (Gul & Ali, 2010), negative research site moral (Sullivan, 2004), and questionable validity of the findings (Gul & Ali, 2010; Kadam et al., 2016; Levine et al., 2015). Moreover, statistical measures aimed to fix poor subject accrual has been noted as bias (Rabinowitz & Davidov, 2008).
- Researchers have examined the reasons for attrition in clinical trials, including participant demographics (e.g., age and gender) and study design such as increased study duration (Applebaum et al., 2012; Hui et al., 2013; McCambridge et al., 2011). However, these investigations did not focus on the indication of depression. Similarly, while Skea et al. (2010) reviewed published papers regarding participants' rationales for not completing a clinical trial, their investigation did not include subjects with major depressive disorder (the authors' one "antidepressant medication and/or cognitive behavioural therapy" citation, on closer examination, pertained to cancer patients' discontinuation of depression treatment). Notwithstanding the merit of these previous investigations as well as those examining retention among antidepressant trials (Rutherford et al., 2012), crucially absent has been the lack of data directly reported by patients with depression, particularly those with previous clinical trial experience, regarding their preferences for entering into an antidepressant trial and reasons for withdrawing. Understanding subjects' penchants across various trial factors is a fundamental step toward enhancing their retention (Costello, 2016; Gul & Ali, 2010; Northrup et al., 2017; Page & Persch, 2013; Sullivan, 2004).
- No empirical work could be found on trial methodology propensities of patients with major depressive disorder (MDD) in respect to the current COVID19 pandemic, although the challenges posed by COVID19 at the site level have been routinely solicited by sponsors and CROs and discussed during several industry meetings. As such, the current study evaluated COVID19 related design scenario preferences from patients with MDD.

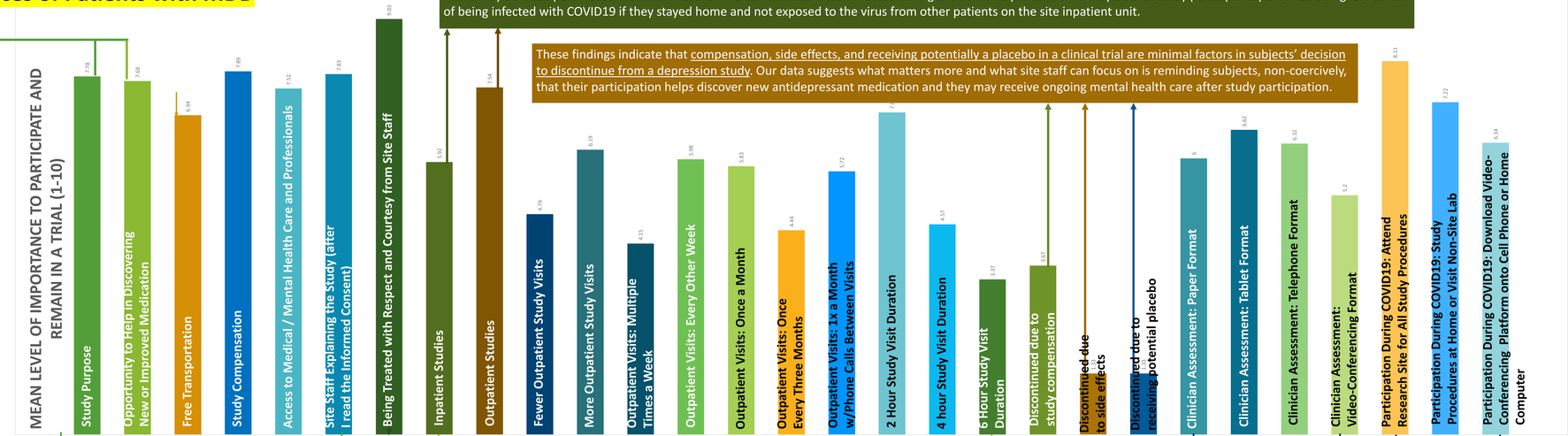
METHODS

- This study was conducted from May-December, 2020 at two East and three West coast US research sites.
- Through the site's database and advertisements, patients with MDD came to the research sites expressing interest in participating in a trial for their respective diagnosis.
- The diagnosis of the patient currently experiencing a major depressive episode (MDE) was confirmed by a qualified site clinician via the DSM-5 (APA, 2013).
- Before signing consent for any clinical trial while waiting in the site waiting room, the diagnosed patients completed a seven-page, 10-point Likert scale, 45-item, 5-minute Research Participant Preferences Survey (RPPS) which queried study methodological, site operational, and assessment procedures that motivate participating and remaining enrolled in a trial. Open ended questions were also queried.
- Age, gender, and race were collected per patient.

RESULTS

- Out of the 66 patients who completed the RPPS, their demographics were:
  - 25 males (38%)
  - 41 females (62%)
  - Mean age was 45 (range from 18-70)
  - 21 White (32%)
  - 37 African-American (56%)
  - 5 Latino (8%)
  - 2 Asian (3%)
  - Other: 1 (1.5%)
- Patients were informed completing the RPPS was voluntary but no patient refused to complete the questionnaire.
- The mean number of participated clinician trials was 1.47 (range 0-11), with 43 (65%) subjects having been in at least 1 previous major depression study, indicating that responders had enough trial experience to provide input on issues queried by the RPPS and data may be generalizable to other subjects with a psychosis disorder in respective indication trials.
- Severity levels of the MDE was not collected.
- Descriptive results of patient preferences on study design and site operational matters are shown in **Table 1** with further **DISCUSSION** points in the colored boxes.
- Correlations and differences across variables are noted in **bold print**.

Table 1: Study Design and Trial Site Operational Preferences of Patients with MDD



A t-test indicated that female subjects, compared to their male counterparts, were more motivated to enroll into a depression clinical trial because of its purpose (p=.009). Although not statistically significant, female subjects rated the opportunity to discover new antidepressant medication as having a greater influence to their participating in a depression trial than did male patients.

- It may benefit recruitment and retention to speak with female study subjects about the study's rationale.

A Wilcoxon test indicated patients preferred outpatient studies than inpatient (p=.05). This finding may be confounded given our ANOVA finding that more females than males preferred outpatient visits (p<.01). The main finding of inpatient studies being less preferred was surprising as we often hear at sites that subjects favor inpatient trials. There may be a temporal reason for these results. The current data were collected during the COVID19 pandemic – it may be that study participants perceived being less at risk of being infected with COVID19 if they stayed home and not exposed to the virus from other patients on the site inpatient unit.

These findings indicate that compensation, side effects, and receiving potentially a placebo in a clinical trial are minimal factors in subjects' decision to discontinue from a depression study. Our data suggests what matters more and what site staff can focus on is reminding subjects, non-coercively, that their participation helps discover new antidepressant medication and they may receive ongoing mental health care after study participation.

Subjects placed equal importance to trial purpose, the opportunity to discover new medications, being provided free transportation, study compensation, access to receiving mental health care, and site staff explaining the study to them.

- All of these factors should be used when considering subject recruitment and retention, while being mindful to not be coercive in such conversations. For example, it may be beneficial to remind subjects they are participating in a study to discover new treatments and help their peers who are also suffering from depression or that the site will continue to provide mental health treatment.

A Wilcoxon ranked test indicated that subjects rated being treated with courtesy and respect by site staff as most important for enrolling and remaining in a depression clinical trial (p<.0001).

- Treatment by site staff to study subjects can never be underappreciated by site staff. CROs and sponsors should also query sites about how they ensure such rapport is maintained at the site.

Wilcoxon ranked tests showed patients preferred to enroll and motivated to stay in trials with more outpatient study visits (p<.05) and shorter duration onsite (p<.001).

- The data suggests retention would be enhanced by having at least weekly check-in phone calls where, for example, AEs and suicidality can be assessed as well as protocol rule reminders be given (e.g., med compliance, contraception and alcohol consumption).
- The finding that patients with depression preferred shorter onsite duration visits is good news for efforts to reduce the placebo effect, as research and experts (Alphs et al., 2012; Taiminen et al., 1996) alike have asserted there is a strong chance of enhanced placebo response with longer onsite visits.
- The current study participants' preference for more outpatient visits conflicts with research on the placebo effect. Tuttle et al. (2015) found that more visits yield higher placebo response, but other investigations reported that shorter trial durations are higher predictors of this phenomenon (Agid et al., 2013; Fenton et al., 2001; Rutherford et al., 2014; Welge & Keck, 2003). Study designers should consider the impact trial duration has on the placebo effect.

A Wilcoxon ranked test indicated that depressed patients had a stronger preference for being assessed by a clinician using a computer/tablet than paper (p<.05), and this held true for patient-reported outcome measures (p<.01).

- These results were surprising given subjects often wait to be assessed in the rater's office because of tablet malfunctioning. As long as the sponsor / CRO appropriately vet the tablet being used for the study, our data indicate patients have limited concern using a tablet over paper evaluations.

A Wilcoxon analysis indicated patients least preferred video-conferencing (p<.01). These findings should be noted by sponsors / CROs who recommend or offer the use of video-conferencing evaluations during COVID19.

A Wilcoxon test indicated patients preferred during the COVID19 pandemic coming into the research site to complete study procedures versus having them done at their home or performed at a non-site location (p<.05) or via their downloading a video-conferencing platform to be assessed (p<.01). These data are important because since COVID19 escalated in the US, sponsors and CROs have asked sites to engage in the latter evaluation locations.

STUDY LIMITATIONS

- The temporal relationship between when the data was obtained (during the COVID19 pandemic) and our results should be considered. It may be that depressed patients surveyed reported certain preferences (e.g., outpatient vs inpatient studies) because of their fear of the virus and our results would be different if it were not for the pandemic.
- Study Demographics: the current study had 39% more females than males and thus our findings should be appreciated within this context. The current investigation had a large proportion (56%) of African-American subjects, and while no study could be found indicating whether this typically occurs in antidepressant clinical trials, anecdotally we believe this is representative of such trials.
- The current study used retrospective data regarding past self-reported reasons for trial withdrawal and thus participants' memory may be a confounding variable to our findings.

References provided upon request to ecohen@hritrials.com

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