Giving Voice to Patients With Schizophrenia or Schizoaffective Disorder: Preferences for Clinical Trial Methodologies and COVID19 Mitigations

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ABSTRACT

Introduction: Clinical trials focusing on psychosis (i.e., schizophrenia and schizoaffective disorders) are beset by poor retention, averaging 50% (Levine et al., 2015). Ramifications of participant dropouts include expanded trial durations causing greater expense, less statistical study power and less validity of the results, and potential early study termination (Gul & Ali, 2010). Study design and research site staff perspectives have been examined to explain low subject accrual; however, a thorough review of the literature yielded no research specifically surveying patients with a psychotic disorder regarding their methodological and site process preferences motivating them to enter into and remain in a clinical trial, especially when such patients are familiar with studies from their previous participation. Exploring these factors is essential toward enhancing research participants' study retention (Page & Persch, 2013). In addition, since study procedures are frequently being implemented as a result of COVID19, it is crucial to explicitly survey patients on such contextual matters. **Methods:** Patients diagnosed with a psychotic disorder seeking to screen for a clinical trial completed the Research Participant Preference Survey (RPPS), a 10-point Likert 45-item paper questionnaire categorized by various study methodological, site operational, and assessment procedures that motivate participating and remaining enrolled in a trial. Study procedural preferences were also queried respective of the current COVID19 pandemic. The RPPS took approximal 5 minutes to complete before patients screened for any clinical trial and was administered at five different US research sites (three in the West coast and two in the East) from May 2020 through November 2020. Survey data was analyzed using descriptive statistics, Pearson correlations, analysis of variance and Friedman test with post hoc Wilcoxon Signed Rank tests. **Results:** A total of 195 subjects completed the RPPS, most diagnosed with schizophrenia (n=185; 95%) and having ample previous antipsychotic clinical trial participation (M=4) to provide input on study processes and site operations. Preferences that strongly motivated enrolling and continued study participation included free transportation (M=8.14), study compensation (M=8.54), access to mental health care (M=8.17), and site staff explaining the study rather than just receiving study information from the Consent Form (M=8.27). Wilcoxon pairwise comparisons indicated that study initiation and retention were motivated by shorter visits rather than longer (p<.001), more as opposed to fewer outpatient study visits (p<.001), and on-site assessments versus remote visits during COVID19 (p<.001). A Pearson analysis revealed stronger preferences for outpatient versus inpatient studies for subjects with less trial experience (r=-.21, p=.005). Surprisingly, participants had no significant differential preferences for self-report or clinician-administered assessments via paper versus tablet. Demographically, an analysis of variance indicated that racial minorities over their Caucasian counterparts significantly deemed site staff courtesy and respect as more valuable to their enrolling and continual study participation (p=.008). **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 includes infrequent study visits (e.g., once a month). 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

- The dropout rate within psychosis indication (i.e., schizophrenia and schizoaffective disorder) clinical trials is alarmingly high, ranging from 33% (Wahlbeck et al., 2001), 48% (Kemmlet et al. 2005), and even exceeding 50% (Mertin et al., 2006). Researchers have noted participant withdrawal is problematic for studies that use retention as the primary endpoint (Lieberman et al., 2005; Kahn et al., 2008) and in general for antipsychotic drug efficacy studies as it leads to missing data, costly delays in study completion (Costello, 2016; Ross et al., 1999), potential premature 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). Statistical measures aimed to fix poor subject accrual have also been noted as bias (Rabinowitz & Davidov, 2008).
- Research has explored the reasons for antipsychotic trial dropouts, including various trial design features such as study length (Wahlbeck et al., 2001), placebo versus non-placebo control studies (Kemmler et al., 2005) and flexible versus fixed dose arms (Martin et al., 2006), as well as first versus second generation medications (Rabinowitz et al., 2009). Site investigators have been surveyed on their perspective for enhancing subject retention (Kadam et al., 2016; Sullivan, 2004) and patient variables such as demographics (Driscoll et al al., 2009) have been empirically investigated. A significant missing piece in all of the above has been the lack of data directly reported by patients with schizophrenia or schizoaffective disorder regarding their preferences for entering into a clinical trial and reasons for withdrawing. Understanding subjects' preferences across various trial factors, as the current investigation explores, 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 a psychosis disorder with 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 a schizophrenia or schizoaffective disorder.

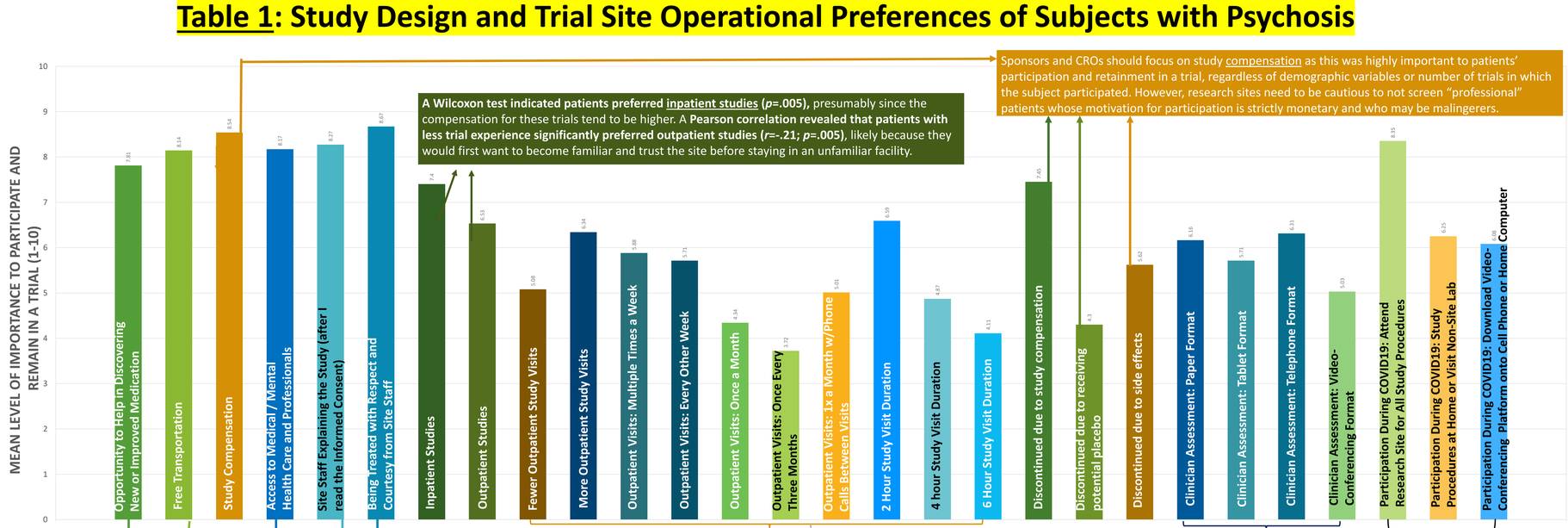
METHODS

- This study was conducted from May-September, 2020 at two East and three West coast US research sites.
- Through the site's database and advertisements, patients with schizophrenia or schizoaffective disorder came to the research sites expressing interest in participating in a trial for their respective diagnosis.
- The diagnosis 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 195 patients who completed the RPPS, their demographics were:
  - 149 males (76%)
  - 46 females (24%)
  - Mean age was 44 (range from 21-65)
  - 20 White (10%)
  - 122 African-American (63%)
  - 33 Latino (17%)
  - 9 Asian (05%)
  - 185 (95%) diagnosed with schizophrenia and 10 with schizoaffective disorder (5%). The former group was too low in sample size to analyze intergroup differences between the studied variables.
- Patients were informed completing the RPPS was voluntary but no patient refused to complete the questionnaire.
- The mean number of participated clinician trials was 3.88 (range 0-15), 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.
- The psychiatric stability / psychotic symptoms of the patients in this study were 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 Subjects with Psychosis



This finding suggests that when patients with psychosis struggle to stay in a trial, it may be beneficial to remind subjects they are participating in a study to discover new treatments and help their peers.

Sites should provide free transportation as this factor seems to be deemed highly motivating by patients with

Patients reported having access to mental health care professionals is essential to their enrolling and remaining in a trial. **An ANOVA indicated this was particularly endorsed for females (p=.02).** Sites can enhance their retention by reminding subjects about after study care services given this finding.

Although a majority of the patients ranked staff courtesy and respect as the highest motivation for their trial participation, an **ANOVA revealed that this was significantly championed by the racial minority patients compared to the Caucasian patients (p=.008).** This may be because of the long mistrust minorities have with clinical trials (e.g., the Tuskegee experiments) and the medical field (Armstrong et al., 2007).

Wilcoxon ranked tests showed patients preferred to enroll and are motivated to stay in trials with more study visits, that are more frequent (e.g., multiple times a week rather than every other week), and shorter duration onsite (p<.001 for each of these three findings). This latter finding may be driven by our Pearson correlation finding that younger patients over older patients preferred shorter visits (r=-.18; p<.000).

- These findings reveal that if onsite study procedures cannot occur weekly, it would benefit antipsychotic study designers to insert weekly check-in phone calls where such factors as AEs and suicidality can be assessed as well as protocol rules be reminded (e.g., med compliance, contraception and alcohol consumption).
- This finding highlights the 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.

Patients did not seem to have a strong preference for being assessed via paper vs computer/tablet, regardless if the evaluation was administered by a clinician or themselves.

This was surprising given subjects often wait to be assessed in the rater's office because of tablet malfunctioning.

A Wilcoxon test indicated that **study responders preferred to come into the research site (p<.001)** to conduct study visit assessments during the COVID19 pandemic as opposed to having study procedures done at home, a non-site location (e.g., lab draws), or downloading a video-conferencing platform.

These data are important because since COVID19 escalated in the US, sponsors and CROs have asked sites to engage in the latter evaluation locations.

Patients believed it was "extremely important" having a staff member explain the study as opposed to solely reading the Consent Form, regardless of the number of trials the patient had participated in.

- Sites should not assume the patients would not want the study explained just because he/she was in multiple other trials.
- **An ANOVA revealed that more females than males significantly believed this variable as essential (p=.025) to their participation.** Research states that: (a) in general females ask less questions in environments where there is a perception/fear they will be judged for their inquiries (Carter et al., 2018; Hinsley et al., 2017) and (b) women tend to have enhanced learning through collaborative discussion as compared to men (Bear & Woolley, 2013; Pauls et al., 2013).

STUDY LIMITATIONS

- (1) The current study had 68% more males than females and thus our findings should be considered within this context. (2) Our current investigation had a large proportion (63%) of African-American subjects, and while no study could be found indicating whether this typically occurs in antipsychotic clinical trials, anecdotally we believe this is representative of such trials. (3) Given the low schizoaffective disorder sample size, generalizability of this diagnosis should be questioned and further research is recommended. (4) The data in the current study was retrospective (regarding past self-reported reasons for trial withdrawal) and thus participants' memory may be a confounding variable.

References provided upon request to ecohen@hritrials.com

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