

Managing the Placebo and Nocebo Perils: Applying the Placebo-Control Reminder Script in Psychosis Trials

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ABSTRACT

Introduction: At the ISCTM Annual Meeting in February 2019, data were presented on the Placebo-Control Reminder Script (PCRS), a tool specifically designed to manage placebo and nocebo responses among clinical trial subjects given by research site staff. Key factors known in the clinical trial profession to induce these effects are Placebo Response Factors (PRF) – participant expectations of benefit, lack of placebo understanding, misrepresentation of expected interactions with research site staff, and subject role uncertainty. Alpha et al., 2020, the data indicated that subjects with major depression who were read the PCRS had significantly less placebo response (p=0.038) than subjects who did not receive the PCRS (Cohen et al., 2020). In the time since that poster presentation, we initiated the same study methodology but with Schizophrenia and Schizoaffective study subjects. The current study explored if the PCRS might be similarly effective for this population. **Methods:** Across two US sites, Schizophrenia / Schizoaffective adult patients experiencing at least moderate depression, per the self-reported Beck Depression Inventory-II (BDI-II; Beck et al., 1996) primary efficacy scales, were randomized into two groups. The Intervention Group (IG) were read all or part of the three study visits (see overview, listed 2 minutes) PCRS before the BDI-II was administered, whereas the Control Group (CG) subjects were not read the PCRS. The current investigation also designed to assess the placebo effect by evaluating subjects' perceptions of improvement regarding their depressive symptoms. Depression, and not psychosis, was the dependent variable due to a combination of scale psychometric limitations (e.g., the lack of targeted self-report psychosis measures) and psychosis assessment length and duration. Adverse Events were collected to examine patient safety effects. All subjects were informed via the Informed Consent Form there was a 50% chance of receiving placebo or active drug designed to improve their depressive symptoms, but all subjects received placebo. Given this design, subjects received a Debriefing Form at the end of the study revealing the investigator's true intent and procedures. Results: An expected IG (p=0.038) and CG (p=0.024) subjects did not differ in baseline characteristics, including depression (BDI-II: IG M=20.08, SD=2.39 vs. CG M=20.48, SD=2.37, p=0.812) and diagnosis of either Schizophrenia or Schizoaffective Disorder (all p>0.05; note 76% of subjects were required to have a Schizophrenia diagnosis). As hypothesized, intergroup interaction occurred that compared to the CG, IG subjects reported significantly (p<0.001) higher BDI-II scores at the endpoint visit (IG M=22.03, SD=3.21 vs. CG M=17.17, SD=3.81), less active events (p=0.038), and perceived themselves as less improved in their address/depression (p=0.033). Conclusions: Results from the 2019 ISCTM poster and data from the current placebo sample indicate that educating subjects throughout their study participation about PRF is crucial in managing the placebo and nocebo effects. The PCRS is an easy to administer, non-time consuming, and efficient instrument that can be seamlessly implemented across various institutions as evidenced by our previous findings in MDD and current findings in Schizophrenia, which may increase effect size by minimizing variability and placebo response in clinical trials. Other PRF related tools such as research models as long as they possess similar attributes, offer methodological implications as well as study iterations will be discussed in the poster.

INTRODUCTION

- Clinical trials focusing on psychotic disorders, namely Schizophrenia and Schizoaffective, continue to be significantly impacted by an increasing placebo effect (Cohen et al., 2010; Kemp et al., 2010). The placebo response has implications toward heightened drug development costs, more inconclusive and failed trials, as well as delay and even abandonment of researching new antipsychotic medications (Alpha et al., 2020; Rutherford et al., 2024).
- To rectify the preponderance of placebo response within such trials, various methodological approaches have been implemented or recommended (e.g., central data ratings, remote real-time monitoring, data surveillance before subject is randomized, subject duration of current illness exacerbation, and different lead-in phase procedures); however, the authors of this poster know of only one subject-targeted intervention, the Placebo-Control Reminder Script (PCRS), which has been empirically validated to reduce this phenomenon (Cohen et al., 2018). The paucity of scientifically substantiated participant-focused procedures is surprising given the obvious, direct role study subjects have in producing the placebo effect.
- It was at ISCTM 2019 where Cohen and his colleagues reported that the PCRS was found to significantly control for the placebo effect on subjects experiencing a major depressive episode (MDE), as compared to subjects who were not administered this intervention. As was described in the ISCTM 2019 poster, the PCRS is a methodological straightforward tool (a script) read to all subjects at all study visits which reminds, and subsequently educates, study participants about the commonly cited subject-producing causes of the high placebo rate within our clinical trial industry (e.g., Alpha et al., 2012; Weber et al., 2005) or what we term Placebo Response Factors (PRF):
 - Lack of subject understanding of the placebo
 - Subject expectations of benefit
 - Subject misconception of expected interactions with research site staff
 - Subject uncertainty of his/her role in the trial
- The current investigation replicated the Cohen et al., methodology to explore if the PCRS had a similar impact in managing the placebo effect on subjects with Schizophrenia and Schizoaffective Disorder. It also assessed if the PCRS might help reduce the **nocebo effect**. This is crucial for the industry as approximately 25% of clinical trial subjects, including those in Phase I studies, experience a nocebo effect which leads to subject early withdrawal and perhaps unnecessarily halting a compound's research program (Barley et al., 2002; Cohen, 2012; Faase & Petrie, 2013; Preston et al., 2000; Webster et al., 2013; Wells, 2012).

METHODS

- This IRB approved study implemented a US multicenter (one site in the East and the other in the West Coast), randomized, single-blind, all placebo design to mirror the methodology typically used in psychiatry indication clinical trials, such as implementing conventional inclusion and exclusion criteria (see Inclusion and Exclusion Table), multiple study visits, and the inclusion of Adverse Events (AE) and Serious Adverse Events (SAE).
- Also similar to other trials, subjects were informed via the Informed Consent Form that they have a 50% chance of receiving active medication or a placebo. However, as part of the purpose of methodology of the current study, all participants received placebo:
 - Deception was necessary to assess for the placebo and nocebo effects and all subjects received a Debriefing Form at the end of their participation which revealed the true intent and procedures of the study.
- The placebo was used in the Investigational Product (IP) because it allowed the study to measure the extent to which the PCRS (the independent variable; see Figure 1) could maintain depressive symptoms (the dependent variable). If there was a decrease in depression, this would indicate a placebo effect occurred, whereas the relative maintenance of depression (or worse) would demonstrate that the PCRS helped control for the placebo effect. The PCRS takes about 2 minutes to read and answer subject questions.

METHODS (CONTINUED)

- The Beck Depression Inventory-II (BDI-II; Beck et al., 1996) was used as the primary efficacy scale to assess depressive symptoms. Using the self-report scale was necessary given the single-blind design of the current study. Depression, as opposed to psychosis symptoms, was selected as the dependent variable because only two widely used self-report scales assess psychosis (the Brief Symptom Inventory and Symptom Checklist 90-Revised), but only do so validly and reliably by evaluating other general mental health factors (e.g., hostility, obsessive-compulsiveness, phobic anxiety, and somatization) not relevant to the purposes of the current study with the potential to confound our primary study objective. Moreover, using either of the scales would add significant duration and possible bias on behalf of the subjects when completing the primary efficacy scale.
- Subjects diagnosed the 12 clinical tests within indicated placebo capsules at the Screening Visit and Visit 2 at the site rather than at home each day of the week in order to minimize the risk that many clinical trial experiences regarding study drug adherence at home (Miyoshi et al., 2016) to help with the capsules' reputation by subjects of taking medication at home each day, subjects were informed the use of help with capsules were developed to sufficiently limit medication exposures.

KEY INCLUSION CRITERIA	KEY EXCLUSION CRITERIA
Male or female 18-65 years old	History DSM-5 criteria for such disorders as Bipolar Schizophrenia, Dissociative Disorder, Intermittent Explosive Disorder, Post-Traumatic Stress Disorder, Anxiety Disorder, Compulsive Disorder, and Personality Disorder (criteria for another DSM-5 psychiatric disorder may be met as long as the disorder is unrelated to the MDE)
Currently experiencing a MDE per the DSM-5	Current or past 6 months of ongoing moderate to severe substance use disorder
Have a current primary diagnosis of Schizophrenia or Schizoaffective Disorder (Depressive Type) Disorder	No present or active suicidal thoughts within 6 months of screening and no attempt within one year of screening. No BDI-II score of 10 (Suicidal Thoughts of Patients) 1-5 screening (a score of 1-5 have thought of killing myself, but I did not carry them out)
Be on at least one antipsychotic medication at the same dose > 30 days from screening (eligible to continue this case medication) and able throughout study visit to tolerate	Initiated, terminated, or done change of any psychiatric medication within 30 days of screening (subjects permitted to stay on such drugs until the day of screening only, no change during study participation)
BDI-II Item 10 score of > 1 (I feel sad most of the time); MAD total score > 30 (reporting at least a moderate-to-severe MDE) AND Item 10 (sadness) (or Item 10) score equal to 5 (no suicidal thoughts)	Initiated, terminated, or changed professional interventions within 6 weeks of screening (subjects permitted to maintain this intervention as long as no change occurs during study participation)
The subject is not currently on any medications for managing of any mental health symptoms within 6 months of the screening visit	Females: Inconceivable, lactating, or pregnant
Able to consent to study participation and able to comply with study protocol requirements	



The PCRS was placed here in the actual poster at the ISCTM Annual Scientific Meeting.

The PCRS is a proprietary, licensed document.

If the reader would like a copy or discuss use of the PCRS in any research or clinical trial, they should contact:

Dr. Eitan Cohen at ecohen@vivtrials.com

Figure 1: Placebo-Control Reminder Script (PCRS) which reviews PRF and read to IG subjects at all study visits before the primary efficacy scale was administered.

RESULTS

- Only two completed subjects were included in the analysis, with 20 participants not-randomly assigned to the IG and CG (Table 1). Six of the subjects' demographic by group.
- The IG and CG subjects did not differ in any of the baseline characteristics, including BDI-II scores (IG M=20.08, SD=2.39 vs. CG M=20.48, SD=2.36, p=0.812) and diagnosis of either Schizophrenia or Schizoaffective Disorder (all p>0.05 - see Table 1).
- The above results were consistent across the two research site locations as well as the Schizophrenia and Schizoaffective Disorders.
- As hypothesized:
 - Figure 3 illustrates the results from a repeated measures two-way analysis of variance (ANOVA) whereby there was a significant time by group interaction (p=0.001) of the IG subjects showing significantly higher BDI-II scores at Visit 3 compared to IG (M=22.03, SD=3.21, p=0.001) and CG (M=17.17, SD=3.81, p=0.001). This mean increase of approximately 5 points may be statistically meaningful for randomized placebo-controlled studies because achieving a high depression from placebo can be a matter of only a few points difference, such as readily 10 in the primary efficacy scale (Rutherford et al., 2024; Himmelfarb et al., 2020; Himmelfarb et al., 2024).
 - Figure 4: A Mann-Whitney analysis indicated 4 subjects (20%) reported adverse events, all were in the CG group (p=0.04). No group reported SAE.

RESULTS (CONTINUED)

- Figure 5: A Chi-square test revealed that perceived improvement in address/depression was significantly more common in IG subjects (N=17/46 vs. CG=12/26, p=0.03) and the opposite among the IG.
- Figure 6: A Chi-square test indicated no difference in belief about receiving real medication (IG 10/26 vs. CG 17/26, p=0.27), but data revealed lower hypothesis, and perhaps the greater sample size will yield for expected results.
- The above results were consistent across the two research site locations as well as the Schizophrenia and Schizoaffective Disorders.

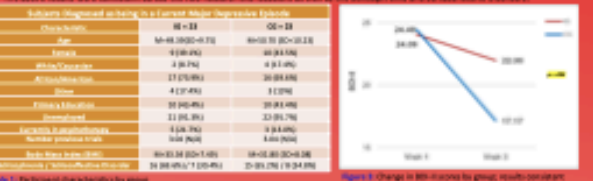


Table 1: The subject demographics by group.

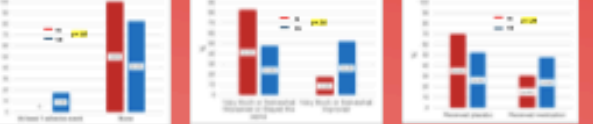


Figure 3: Subject self-report of BDI-II scores.

CONCLUSIONS

- PLACEBO EFFECT:**
- The results of the current investigation indicate that subjects with a primary psychotic disorder experiencing a MDE had significantly less improvement in depressive symptoms after receiving an inert substance if they were read the PCRS as compared to subjects being given the same inert substance but who were not administered the PCRS. While it appears the PCRS probably helped control for the placebo effect, the authors are not over-interpreting its role. Rather, we want the reader to understand the current study's intended methodological contribution.
 - Also as expected, subjects who received education about the PRF (i.e., were read the PCRS) were significantly more likely to self-report (perceive) either staying the same regarding their depressive symptoms or that their symptoms worsened, as opposed to subjects who were not educated about these factors. These data findings are not surprising given that the subjects who were not read the PCRS had a significantly higher placebo response (i.e., they reported less depressive symptoms) (progressing) after receiving the inert substance at each study visit.
 - The accumulation of the above study findings, as well as those from Cohen et al.'s (2018) investigation of the PCRS among subjects experiencing a MDE, illustrates a positive trend toward suggesting that the placebo effect may be optimally managed when study subjects are systematically informed (i.e., educated) throughout their participation in the PRF. The current study's results become more applicable to psychosis clinical trials considering that the PCRS is quite manageable to implement within the methodology of such clinical trials – it has a short administration time (approximately 2-3 minutes total), is easy to understand for subjects of various races, education, and diagnosis background, and is administered procedurally. Moreover, the BDI-II findings indicate that the effect size of studies using this tool may be enhanced given the PCRS' potential to decrease variability and placebo as well as nocebo responses.
- NOCEBO EFFECT:**
- Indeed the PCRS has been seamlessly implemented in place for used in clinical trials and with positive results. Haven Pharmaceuticals conducted a Phase 1, 6-week, oral, single-blind, randomized, placebo-controlled, parallel, daily significant separation of their RP-3073 (lanicovene) from placebo, resulting in FDA approval. Haven tentatively shared the unblinded data post study completion with Hassman Research Institute (HRI), which administered the PCRS to their post-trial subjects. HRI used the highest US study enrollee and 6th highest globally, while HRI's data could not be analyzed for significance given the low N, the site's 25.3 average post-difference (see Figure 7) between RP-3073 and placebo at week six suggests that the PCRS may be a contributing factor to the site's data and that the active medication group was not negatively impacted by the PCRS (see below Study Limitations section). To confirm this in placebo-controlled trials, it would be ideal for future studies to include a POS and non-POS group or have an accumulation of such trials using the POS or similar script with a strong separation between the study compared and placebo.

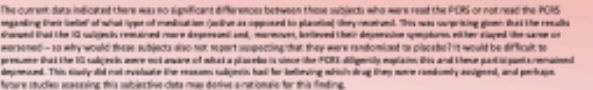


Figure 7: Line data on an acute inpatient Schizophrenia placebo-controlled investigation. Haven Pharmaceuticals administered the PCRS to all study site subjects immediately after all MAD administration.

- The current data indicated there was no significant difference between those subjects who were read the PCRS or not read the PCRS when their belief of what type of medication (real or placebo) they received. This was surprising given that the results showed that the IG subjects remained more depressed and, moreover, believed their depressive symptoms either stayed the same or worsened – so why would these subjects also not report suspecting that they were randomized to placebo? It would be difficult to presume that the IG subjects were not aware of what a placebo is since the PCRS allegedly explains this and these post-trial respondents dependent. This study did not evaluate the reasons subjects were not suspecting they drug they were randomly assigned, and perhaps future studies assessing this subjective data may derive additional for this finding.
- STUDY LIMITATIONS:**
- Although the goal was to duplicate typical clinical trials, the current investigation was not identical to such studies insofar as (a) the IP was provided to subjects once a week as opposed to three times weekly, (b) there were three total visits rather than the more common 6-8 study visits, (c) the study comparison was 50% vs 50% and not the more typical 1:2 and, subsequently, it is unclear if subjects would have reported depressive symptoms differently with higher comparison, (d) it is unclear if the results of the dependent variable (depressive symptoms) transfer to psychotic symptoms, and (e) while the above findings data begin to address this matter, there was no active drug arm in the current investigation which was aimed to reduce MAD symptoms, etc. Moreover, it is unknown how the PCRS would have impacted those assigned subjects' reporting of depressive symptoms (i.e., would the PCRS influence active medication subjects' reporting of depressive symptoms?). These factors may have impacted the current study results and should be addressed in future studies, in which replication would serve to increase confidence in its findings.