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 its review of key factors known in the clinical trial profession to induce these effects or Placebo Response Factors (PRFs) – participant expectations of benefit, lack of placebo understanding, misconception of expected interactions with research site staff, and subject role uncertainty; Alphs et al., 2012). The data indicated that subjects with major depression who were read the PCRS had significantly less placebo response than subjects who did not receive the PCRS (Cohen et al., 2019). 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 scale, were randomized into two groups. The Intervention Group (IG) were read at each of the three study visits the one-page, brief (2 minute) PCRS before the BDI-II was administered, whereas the Control Group (CG) subjects were not read the PCRS. The current investigation also deepened its assessment of 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 potential nocebo 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 deception, subjects received a Debriefing Form at the end of the study revealing the investigation's true intent and procedures. **Results:** As expected, IG (n=23) and CG (n=23) subjects did not differ in baseline characteristics, including depression [illegible] **Conclusions:** [illegible] findings in MDD and current findings in Schizophrenia, which may increase effect size by minimizing variability and placebo response in clinical trials. Other PRF educational tools can be recommended as long as they possess similar attributes. Other methodological implications as well as study limitations 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 (Chen 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 (Alphs et al., 2012; Rutherford et al., 2014).
- To rectify the preponderance of placebo response within such trials, various methodological approaches have been implemented or recommended (e.g., centralized ratings, remote rater 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 among 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 methodologically 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., Alphs et al., 2012; Weber et al., 2005) or what we term Placebo Response Factors (PRFs):
  - **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 (Barsky et al., 2002; Cohen, 2012; Faase & Petrie, 2013; Preston et al., 2000; Webster et al., 2017; 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 aimed to mirror the methodologies typically used in psychosis indication clinical trials, [illegible]
- [illegible]
  - [illegible]
- [illegible]

METHODS (CONTINUED)

- [illegible]
- [illegible]

KEY INCLUSION CRITERIA	KEY EXCLUSION CRITERIA
Male or female 18-65 years old	[illegible]
Currently experiencing a MDE per the DSM-5	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	

The PCRS was placed here in the actual poster presented 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. Elan Cohen at ecohen@hritrials.com

Figure 1: [illegible]

Figure 2: [illegible]

RESULTS

- [illegible]
- [illegible]
- [illegible]
- As hypothesized:
  1. Figure 3: [illegible]
  2. Figure 4: [illegible]

RESULTS (CONTINUED)

3. Figure 5: A Chi-Squared test revealed that perceived improvement in sadness/depression [illegible]

- Figure 6: A Chi-Squared test indicated no difference in belief about receiving real medication [illegible] toward the hypothesis and perhaps the greater sample size will yield the expected results.
- The above results were consistent across the two research site locations as well as the Schizophrenia and Schizoaffective Disorders.

Subjects Diagnosed as being in a Current Major Depressive Episode		
Characteristic	IG = 23	CG = 23
Age	[illegible]	[illegible]
Female	[illegible]	[illegible]
White/Caucasian	[illegible]	[illegible]
African/American	[illegible]	[illegible]
Other	[illegible]	[illegible]
Primary Education	[illegible]	[illegible]
Unemployed	[illegible]	[illegible]
Currently in psychotherapy	[illegible]	[illegible]
Number previous trials	[illegible]	[illegible]
Body Mass Index (BMI)	[illegible]	[illegible]
Schizophrenia / Schizoaffective Disorder	[illegible]	[illegible]

Table 1: Participant characteristics by group

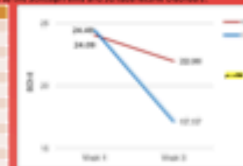

Figure 3: [illegible]

Figure 4: Subject report of AEs by group

Figure 5: Subjects' reported perceptions of improvement level by group

Figure 6: Subjects' reported perceptions of which medication they were randomly assigned by group

CONCLUSIONS

PLACEBO EFFECT:

- [illegible]
- [illegible]
- [illegible]
- [illegible]

Figure 7: [illegible]

- [illegible]

NOCEBO EFFECT:

- [illegible]

STUDY LIMITATIONS:

- [illegible]

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References provided on reverse side of poster handout.