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Clinical Trial Strategies to Avoid the Placebo Effect in CNS Studies: The Importance of Patient Selection

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One of the most significant challenges in the clinical development of new drug candidates for central nervous system disorders is the placebo effect.

All too often, an investigational agent fails to achieve statistically significant efficacy in a clinical trial not because the drug itself didn't work, but because the placebo worked better than expected. This has been known to occur in trials across a variety of therapeutic areas, but it is particularly pervasive in the CNS arena. This may be because while trial endpoints in many diseases are objective – the tumor either shrinks or it doesn't, the patient either lives longer or dies – endpoints in CNS tend to be more subjective, involving a doctor or patient's assessment of functionality and quality of life.

The placebo effect has become so pronounced that a recent study published in *The Lancet* recommended "advances in the ethical use of placebo mechanisms."¹ The study has sparked debates in the *Boston Globe*² and the *New York Times*³ about how to deal with informed consent and other issues associated with any true attempt to harness the placebo as a treatment.

But for clinical trial sponsors, the placebo effect can mean a failed study and millions of dollars wasted. And so the issue at hand becomes: What causes the placebo effect, and how can it be avoided?

Patients Are a Virtue

Although the true cause of the placebo effect is a nebulous mix of internal and external factors that differs between studies and between patients, one underlying constant of many placebo-driven CNS trial failures is poor patient selection.

For example, in some depression trials, patients who are not truly depressed might still be able to meet the eligibility criteria for the study. Often, patients on the borderline of inclusion/exclusion criteria are enrolled. If these patients end up in the placebo group, they are not likely to show a natural worsening of their condition as you would expect in clinically depressed patients, compromising the ability to detect efficacy of the drug arm and significant separation from the placebo arm.

To understand how pervasive this problem truly is, consider the fact that today some clinical trials for schizophrenia have reported placebo response rates as high as 30 percent. Schizophrenics, particularly those under acute condition not taking medication, should experience an immediate and obvious decline, so it's difficult to explain that kind of a placebo response unless the trial has enrolled patients who are not truly schizophrenic.

Enrollment of the wrong patients into clinical trials usually occurs due to the patient not being diagnosed correctly or not being properly screened according to the trial's inclusion and exclusion criteria. One step clinical trial sponsors can take to avoid these situations is to utilize rater training programs instilled with a data assurance mechanism for baseline assessment.

Rater training is offered by a variety of vendors to ensure raters are qualified and to decrease enrollment bias. Some services review diagnostic rating scales, while others offer a centralized review system that double-checks the patient interviews conducted by investigators. For example, there are vendors that focus on ensuring the accuracy of baseline diagnoses by using an audio pen or video recording to record either mock or real investigator interviews with patients, and then having third-party experts review the interviews. This increases assurance that patients are being selected according to proper criteria, and also increases the care raters take when conducting interviews due to the oversight involved.

One other strategy that INC Research has used successfully to ensure proper patient selection is centralized review by a medical monitor. In one case, a customer came to us with concerns that an ongoing Alzheimer's disease trial was demonstrating drift in the ADAS-cog and MMSE scores. Patients who should have been getting worse were getting better or showing minimal decline, indicating that perhaps their disease was too mild for the trial's enrollment criteria. We installed a system in which every patient enrolled in the study was reviewed by our medical monitor, a board-certified psychiatrist.

While our customer was initially concerned about how investigators would react to the centralized review process and whether they would be less likely to enroll new patients, the opposite turned out to be true. Our monitor developed strong relationships with the investigators, the screen failure rate decreased, and the enrollment rate actually increased.

Strategies for Site Selection

Part of enrolling the right patients into a trial is utilizing trial sites that can tap into those patients.

One way to do this is to choose study sites in geographic locations with a high level of prospective patients. Online research can help determine locations in which a large number of patients and/or caregivers are searching for information about a given disease and experimental treatment options. This information can be combined with online patient surveys and databases in which patients opt-in to be notified about new trials.

Feasibility studies also are an important part of the site selection process. Investigators tend to "round up" when asked, for example, how many patients with Alzheimer's disease they've treated in the last year. To get a more accurate picture of a site's enrollment potential, a successful strategy is for sponsors to work with CROs to design weekly feasibility surveys, in essence a prospective feasibility that carries information forward in time and creates a more accurate picture of the patient activity at a given site. When there is a built-in requirement for investigators to report on their treatment habits week after week, for several months, their answers provide a powerful and predictive tool for understanding whether or not the site has access to the patients needed for the study.

Another important consideration is to work with a CRO that has strong relationships with CNS investigators. Even more critical than knowing which sites enroll the fastest is knowing which sites have consistently delivered high quality data.

Designing a Strong Foundation

Getting the right patients into a trial requires knowing which patients are needed – a task that is not always easy in CNS trials.

For example, if a sponsor wants patients with moderate but not mild Alzheimer's disease, what's the best way to distinguish between the two? The MMSE scale is a well-known patient assessment tool, but its ranges have cushions, and the sponsor must decide where to draw the line in the sand. One solution increasingly utilized by sponsors is to add a second scale, such as the Clinical Dementia Rating (CDR) scale, to analyze clinical dimensions, providing an extra layer of confidence in the trial's eligibility criteria.

Care must also be taken in complex trials in which there are multiple opportunities for enrollment errors. For example, some clinical trials for refractory depression require that a clinically depressed patient be enrolled into the trial and treated with an existing drug for a few months, then nonresponders are treated with the investigational agent. Such trials require attention to detail both during the baseline diagnosis and during the responder versus nonresponder analysis.

If a clinical trial succeeds in enrolling the right patients, then the experimental agent at least has a chance of success. If the drug does then fail, the sponsor is much more likely to be able to attribute that failure to the mechanism of action of the drug and avoid wasting time and money on additional trials trying to avoid the placebo effect. Enrolling the wrong patients, however, dooms a study before treatment even begins. As in any good experiment, the right ingredients are needed to have a shot at the right outcome.

INC Research is a global CRO with deep therapeutic expertise in neurology and psychiatry, including clinical trials for Alzheimer's disease, depression, schizophrenia, attention-deficit hyperactivity disorder and other conditions. We have strong relationships with the investigators, thought leaders and patient support groups that are critical to the success of CNS trials. Our team has the scientific capability to advise sponsors on which patients they need and the breadth to access and enroll those patients.

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About the Author

Tom Zoda, Ph.D., Senior Vice President of Clinical Development, Neurology & Psychiatry at INC Research completed his doctoral degree in microbiology, specializing in immunology, at the University of Texas Health Science Center at San Antonio, followed by postdoctoral work at Dartmouth Medical College. Prior to joining INC Research, Dr. Zoda worked for a large, global CRO as Executive Director for Global Strategic Development for CNS studies. He has extensive experience in the design and management of multiple Phase II and III studies focused in various neurological and psychiatric indications. His extensive experience includes oversight of US based and global CNS studies in neurological and psychiatric disorders as well as pain management. Prior to his CRO career, Dr. Zoda worked for Tanox Biosystems, Inc., overseeing the development of therapeutic antibodies and vaccines for the treatment of allergy.

¹ D. Finniss et. al., The Lancet. 20 Feb. 2010. Vol. 375, Issue 9715, pp. 686-695

² http://www.boston.com/bostonglobe/ideas/articles/2010/05/09/the_magic_cure/

³ <http://opinionator.blogs.nytimes.com/2010/05/03/enhancing-the-placebo/>