A Q&A

Protecting Sponsors Against Bias and Variability

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Placebo response is growing and contributes to the risk of trial failure.

Clinical trials succeed or fail based on the ability of the primary endpoint to differentiate study drug from control conditions. In the case of placebo-controlled studies, the levels of random error, sources of noise, variability introduced by patient or investigator factors, and placebo response rates can have a profound influence on the outcome. Design and execution teams can take several steps to reduce these risks, improve signal-to-noise ratios, and mitigate the impact of placebo response. *Applied Clinical Trials* recently spoke with Mark Opler, PhD, MPH, chief research officer of WCG, MedAvante-ProPhase, to learn how these approaches need to be incorporated into standard practice to reverse prevailing trends going forward for certain therapeutic areas and conditions.

Applied Clinical Trials: What's the difference between positive, negative, and failed trials?

Opler: A *positive trial* is what we all strive for in clinical research: the experimental treatment (e.g., the drug, the device) is clearly and unequivocally better than the control (e.g., placebo). A *negative trial* is the regrettable, but sometimes inevitable, consequence of research in which the experimental treatment is not better than the control. And, a *failed trial*—where the outcome cannot be interpreted—is probably the worst possible outcome because we've spent a lot of money and time, we've exposed patients to an experimental treatment, and we've come no closer to the answer than when we started.

Applied Clinical Trials: Is placebo response really a problem for clinical research?

Opler: Yes, definitely. The placebo response is probably the leading cause of failed trials. Placebo response and high placebo response occur when patients in a placebo-controlled study respond well to what is essentially no active treatment. The sugar pill produces the same or better outcome than the experimental treatment. It's a very serious problem in clinical research. Those of us who have been studying it for many years have realized that this problem is actually growing. The placebo response was once negative or absent in certain therapeutic areas. Now, we're seeing it routinely sometimes outstripping effect sizes from the treatments we're studying.

Applied Clinical Trials: Why does placebo response occur?

Opler: The most probable cause of placebo response is therapeutic expectation (i.e., the

expectation of improvement). We, as an industry, have not adequately addressed it in our clinical research work. The average patient that comes into a study needs to be very carefully educated about their role and about the use of placebos. We want patients to get better and they may come in expecting to get better when they enter a clinical trial, particularly if they don't fully appreciate the difference between clinical research and medical care.

Applied Clinical Trials: What should sponsors and study teams know about measurement reliability?

Opler: Another contributor to failed trials is the lack of reliability of measures. For instance, if a thermometer is used incorrectly, we get the wrong result. Measurement reliability is about ensuring that, from visit to visit, from patient to patient, and from site to site, we have reliability in our approach to evaluating the primary outcome. Whether that primary outcome is driven by a thermometer, a clinical interview, or a specific examination procedure, we can reduce the risk of failed trials and increase the likelihood of trial success by paying appropriate attention to reliability.

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Applied Clinical Trials: What role do you think technology plays in all of this?

Opler: Like anything else that we do in clinical research, technology is omnipresent. In our efforts to combat placebo response and improve measurement reliability, technology can play a very important role. Whether you are using electronic forms for clinical outcome assessments or technology to evaluate the level of noise in data over time, consider every technological aspect of the program being conducted and ask, "Is this contributing to study success? Is it improving the reliability of measurement? And is it getting me closer to my ultimate goal, a positive trial?"

Applied Clinical Trials: What are your top three recommendations to sponsors?

Opler: For sponsors in the process of planning studies, I would urge them to do three things. First, think about study design. There are aspects of study design that can contribute to lower placebo response and higher success, whether that's the number of arms in the trial or the selection of outcomes and endpoints All of these can contribute in subtle, and not so subtle ways, to a positive study.

Second, make sure that for almost every therapeutic area, sponsors and study teams have a strategy to mitigate the risk of high placebo response. This is clearly recognized in some therapeutic areas, but we have yet to build a meaningful awareness in others.

Third, the sponsor should be aware of what is being done to ensure measurement reliability, to ensure that methods and procedures are in place to make sure the most vital data—the primary endpoint—in the study is being protected from noise and from error. Those are the top three recommendations to anyone, almost regardless of disease therapeutic area or stage of development.