THE SIGNAL
BLOG BY SIGNANT HEALTH

VISIT THE SIGNAL

Placebo Response in Clinical Trials: Challenges and Mitigation Strategies

Gary Sachs, MD; Juliet Brown, PhD; Marcela Roy, MA; & Alex Pavel, MD, PhD

Placebo response is a major challenge associated with failed clinical trials and significant financial loss. It is increasing in key indications and geographical areas (e.g., depression trials; U.S. trials).[1] At Signant Health, we see the complexity of this phenomenon as a call to action requiring increased knowledge and concrete, attainable mitigation strategies to improve the likelihood of study success.

Placebo vs Nocebo Effect

The terms "placebo" and "nocebo" are often misunderstood. "Placebo effect" is often used as a general term encompassing both positive and negative effects, but it actually refers to positive effects on the disease under study experienced by participants receiving an inactive substance or treatment. In contrast, "nocebo effect" involves adverse symptoms experienced by participants exposed to an inert substance or treatment. Both are real phenomena with tangible biopsychosocial impact.

Defining Placebo Response

"Placebo response" is known to be driven and moderated by multiple bio-psycho-social factors such as participant genetics, number of study sites, baseline severity, expectations, number of treatment arms and conditioning, as well as behaviors of site personnel. Placebo response is complex and varies over time. It is not solely a function of participant characteristics, site staff, study indication, and trial design, or geography. Therefore, effective mitigation strategies will be multipronged, dynamic, and provide best practice guidance.[1, 2, 3]

Getting beyond the operational definition

Operationally, the placebo response in randomized clinical trials (RCTs) is measured as the degree of improvement from baseline to endpoint in the placebo arm. To better

target mitigation strategies, the ISCTM (International Society for CNS Clinical Trials and Methodology) conceptualized two types of placebo response definitions[4]:

- **Type 1**: The "true placebo response," where clinical improvement is driven largely by expectation, resulting in improvements for both participant and scale scores.
- **Type 2**: The "pseudo-placebo response," where improvement in scale scores is not accompanied by clinical improvement, often due to measurement error or participants inflating symptoms to enter the RCT.

The Role of Bias and Expectation

In addition to these two types of placebo response, bias and expectation can also significantly influence the outcomes of clinical trials from multiple perspectives, including those of participants, research sites, and participants' families. Participants often enter trials with the hope and belief that they will receive an effective treatment, which can enhance their perception of improvement. Similarly, research sites and staff, driven by their commitment to patient care and study success, might unconsciously influence participants' responses through their enthusiasm and behavior. Families, in their support and encouragement, can also inadvertently contribute to heightened expectations and perceived benefits, further complicating the objective measurement of a treatment's efficacy.

Cultural and Site-Specific Practices

Addressing bias and expectation is challenging due to the deeply ingrained cultural and site-specific practices within clinical trial environments. We often find that some sites that enroll a primarily Latino population tend to have friendly and warm interactions with their participants. Most sites in Central Europe, for example, heavily rely on recruitment of study participants from their private practice with whom they have built a professional relationship, as opposed to US sites that rely heavily on advertising. We have found that offering a prescriptive one-size-fits-all approach to placebo response does not resonate with some sites and may even clash with local customs and practices.

Cultural aspects also may apply to the appearance and invasiveness of the investigational compound. For example, white capsules are more often associated with an analgesic effect by Caucasians, but with a stimulant effect by African Americans (Buckalew et al 1982). Also, placebo response is often reported as higher in US sites compared to European sites. This might be because of differences in health care systems or because participants in the US are more inclined to perceive clinical trials as examples of scientific progress, whereas participants from Europe may tend to be more

skeptical (Weimer et al 2015 and Kemp et al 2010).

Matching Solutions to Causes

Understanding the different types of placebo response enables us to target solutions to each problem. True placebo response, largely driven by expectation, can be offset by thoughtful study design, careful attention to communication style, and recruitment strategies. It can also be mitigated by training research staff and participants to address the variability of placebo responses throughout the lifecycle of the study.

Pseudo-placebo response can be mitigated via several customized approaches including eCOA, Computer Simulated Raters, and Central Raters. In addition, tandem ratings (comparing computer ratings to ClinRO ratings by site staff or Central Ratings), Central Quality Reviews, and Blinded Data Analytics can ensure unbiased, accurate data, and help to detect and remediate data quality issues.

Tailored Training and Cultural Sensitivity

The most effective mitigation strategies include providing sites with culturally adapted approaches to placebo response mitigation. By presenting best practices and allowing sites to tailor these to their own environments, we foster engagement and ownership of mitigation strategies.

“Self- scripting” is an appealing approach to reaching this goal. By scripting their own communication that will be used to mitigate placebo response, sites use the language that they can adhere to and are comfortable using. This approach not only respects cultural differences but also empowers sites to implement practices that are more likely to succeed within their specific contexts. Training sessions should emphasize the importance of maintaining blinding integrity and managing participant expectations while being adaptable to local customs and norms.

No single intervention is likely to sustain behavior changes recommended for placebo response mitigation. Empowering site staff to act as placebo response mitigation ambassadors can help ensure that best practices are followed and enforced.

Your Partner for Accurate and Reliable Study Outcomes

Placebo response mitigation is a nuanced and critical component of successful clinical trials. At Signant Health, we understand the complexity of these challenges and offer tailored solutions that respect and adapt to the cultural contexts of research sites. These include:

- Robust, culturally sensitive training
- Best practice guidance for sites and study participants
- Central Ratings
- Computer simulated rating
- eCOA
- Tandem ratings services
- Visit-level Data Quality Monitoring
- Data Analytics

These approaches have helped mitigate the risk of increased placebo response, ensuring more accurate and reliable trial outcomes and increasing the likelihood of study success.

Contact us to learn how we can support your study.

Authors

Gary Sachs, Therapeutic Area Leader in bipolar disease and mood disorders at Signant Health, is a recognized expert in clinical trial methodologies. He founded the Bipolar Clinic at Massachusetts General Hospital and is an Associate Professor of Psychiatry at Harvard Medical School. With over 200 publications, Dr. Sachs also serves on the Scientific Advisory Boards of the National Alliance on Mental Illness and the Depression and Bipolar Support Alliance.

Juliet Brown, Director of Endpoint Reliability and a Clinical Thought Leader at Signant Health, has over 25 years of clinical and research experience, specializing in MDD, Bipolar Disorder, Anxiety Disorders, Psychotic Spectrum Disorders, Substance Use Disorders, and Cognitive Behavioral Psychotherapy. She holds a PhD and Master's Degrees in Clinical Psychology from Drexel University. Before joining Signant Health 8 years ago, Dr. Brown provided psychotherapy to individuals with Severe Mental Illness and treated Substance Use Disorders. At Signant, she oversees phase 1-3 global trials, offers clinical guidance, and serves as a Blinded Data Analytics Scientist and Subject Matter Expert.

Marcela Roy is a Senior Clinical Director in Signant's Digital Health Science department. She has been with Signant for over 15 years and has over 20 years of clinical and research experience. Her focus is Mood Disorders and Endpoint Reliability quality monitoring. She provides strategic direction in the organization, as well as team leadership and business development support.

Alexandru Pavel is a Clinical Scientist at Signant Health where he specializes in Schizophrenia, Mood, and Cognitive Disorders. He holds a PhD in psychiatry from the University of Medicine and Pharmacy "Carol Davila" in Bucharest, where he also taught clinical psychiatry. Alexandru provides clinical oversight for numerous trials and continues to practice as an adult psychiatry specialist. He is an award-winning researcher and has authored multiple papers and book chapters on psychiatric topics.

References:

1. Ozdemir, V., & Endrenyi, L. (2021). Rethinking clinical trials and personalized medicine with placebo genomics and placebo dose. A Journal of Integrative Biology, 25:1, 1-12.
2. Colloca, L., & Miller F.G. (2011). How placebo responses are formed: a learning perspective. Philos Trans R Soc Lond B Biol Sci., 366(1572):1859-69.
3. Hafliðadóttir, S.H., Juhl, C.B., Nielsen, S.M., Henriksen, M., Harris, I. A., Bliddal, H., & Christensen, R. (2021). Placebo response and effect in randomized clinical trials: meta-research with focus on contextual effects. Trials. 26;22(1):493.
4. Horan, W.P., Sachs, G., Velligan, D.I., Davis, M., Keefe, R.S.E., Khin, N.A., Butlen-Ducuing, F., & Harvey, P.D.. (2024). Current and emerging technologies to address the placebo response challenge in CNS clinical trials: Promise, pitfalls, and pathways forward. Innov Clin Neurosci. 21(1-3):19-30.

WHO IS SIGNANT HEALTH?

SIGNANT HEALTH
THE EVIDENCE GENERATION COMPANY™

Signant Health is the evidence generation company. We are focused on leveraging software, deep therapeutic and scientific knowledge, and operational expertise to consistently capture, aggregate, and reveal quality evidence for clinical studies across traditional, virtual, and hybrid trial models. For more than 25 years, over 600 sponsors and CROs of all sizes – including all Top 20 pharma – have trusted Signant solutions for remote and site-based eCOA, EDC, eConsent, RTSM, supply chain management, and data quality analytics. Learn more at **www.signanthealth.com**.