# Placebo Response Mitigation

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All of us in research have a love-hate relationship with the powerful placebo. We know placebo controlled studies are absolutely needed to conduct good, valid studies but we also worry about exposing patients to placebo.

When the study is completed and the data is examined very carefully, if subjects on the study drug show significant improvement in their symptoms as compared to subjects on placebo, who either stay the same or sometimes get worse, the study is called a POSITIVE study. This shows that the Investigational product is better than placebo for the indication under study.

When subjects on the study drug show little or no improvement, just like the subjects on placebo, we have a NEGATIVE study. The conclusion is that the drug is ineffective, but that is not all bad, as something definite has been learned.

However, when subjects on study drug show significant improvement and subjects on placebo show close to the same or more improvement, we have a FAILED study. This is a sponsor's nightmare because they cannot conclusively show that their drug is effective or ineffective as it did not separate from placebo. The expense of failed studies is staggering and negatively affect the sponsor, the site and the patient.
There are many factors that can cause a placebo response and the literature is rich with articles and scholarly explanations. We will not address all these factors in this writing but will focus on things at the site level that may be contributing to the placebo response. We will look at some behaviors and changes that have a high potential to mitigate a placebo response.

Patient Expectations: We have all heard patients say, "I hope I get the real thing" or " I will know if I get the dummy pill". We also know patients are curious about clinicians and want to know and share personal details and often do not want to disappoint us. A recent phenomenon has been the "professional patient" who exaggerates his/her symptoms to get into a study for monetary gain and does not even take the investigational product.

Investigator (Site Staff) Expectations: As clinicians, we are trained to take care of patients and see them get well. We have a therapeutic relationship with patients and tend to answer all questions they ask and be "nice" to them and want them to like us because we have helped them. We also guess at who may be on drug and who may be on placebo. We want to meet our recruitment goals and sometimes may miss cues and let questionable subjects in the study who contribute to a high placebo response.

So, if patient and staff expectations do contribute to placebo response, what can we do to change that? Most of the reminders below, are very simple and common sense, but we should have them at the forefront to guide our research practice.

- Remember that research is NOT treatment.
- Accept that some patients may get worse during the study.
- Be pleasant but consistently maintain a neutral attitude.
- Re-direct subjects when they try to ask personal questions.
- Refrain from telling patients "you look so much better" or "I know you are not doing well" or "you must be on the real medication because you are having side effects".
- Remind subjects that they are in a study and neither they, nor we know what they are getting.
- Make patients comfortable to tell us exactly what symptoms they are experiencing and how those symptoms are affecting them. This is VERY important during assessments and ratings.
- We should, to the best of our ability, enroll subjects who meet all inclusion/exclusion criteria, (that is a given), but also understand the purpose of the study, know that research participation is different from regular medical care and understand their role in a placebo controlled study.