

Use of Placebos for Drug Research in Rehabilitation:
Factors to Consider in Pilot Studies and Clinical Trials
John Whyte, MD, PhD

The use of placebo groups in drug research is controversial throughout medicine. The knowledge that one might only receive placebo treatment is often a deterrent to participant enrollment, e.g., [1] and the ethics of placebo use when effective treatments are available are strongly debated. [2-4] On the other hand, placebos provide the starkest contrast (and therefore, the greatest statistical power to detect a difference) with the active agent under study. Acceptance of study designs involving a placebo group is enhanced if no treatment for the condition of interest has been proven effective, when the illness or condition is mild, and when the only available access to a promising treatment is through a placebo controlled study.

In rehabilitation research, these same issues with placebos exist, but there are some additional facets that are of heightened importance. First, many pharmacologic treatments have been developed with other patient populations in mind and have been adopted for “off label” use in various rehabilitation populations. In some cases (e.g., cognitive and behavioral problems in TBI rehabilitation), off-label use of psychoactive drugs has virtually become the standard of care in some regions. In other cases, psychoactive drugs have known efficacy in uninjured individuals and are used routinely in rehabilitation environments, despite never having been rigorously tested in neurologically involved populations (e.g., SRRI for treatment of depression after TBI). Thus, a desire for access to the treatment does not serve as an incentive to participant enrollment, and concern about depriving patients of “needed treatment” undermines support from clinicians as well as patients.

Because of these difficulties, it is appropriate to implement placebo controlled designs only where clearly scientifically necessary, and then to make clear to referring clinicians as well as potential participants, the reasons that such a design is essential. For definitive clinical trials where no existing treatment is of proven value, a placebo controlled design is generally mandatory. For preliminary research leading up to a definitive clinical trial, the requirement is less uniform, and there may be more flexibility in the type of placebo controlled design that will suffice.

One way of increasing the acceptance of placebo use is through a crossover design, where each subject can be sure to receive the treatment of interest, but the timing of the active treatment is randomized. However, crossover designs suffer from a number of design weaknesses unless very specific circumstances are met. These are addressed individually below:

Is this pilot research intended as a “proof of principle” or as a definitive clinical trial?

In pilot research one needs to establish that there is a reasonable likelihood of a treatment effect, that the proposed tools for measuring that effect work properly, and to get an estimate of the size of the treatment effect and variance in order to plan the definitive

trial. In many situations these factors can be determined, at least with moderate confidence, using crossover designs, pre-post designs, or multiple baseline designs, that would not be considered definitive for a clinical trial. However, where the treatment of interest is intended to alter the course of recovery in the acute and rapidly changing period, even pilot studies to demonstrate a plausible treatment effect may require a parallel group design.

Is the treatment thought to increase performance reversibly (only while the patient receives it), or to alter the pace of performance improvement (recovery) in an irreversible way?

Treatments that improve performance but where performance reverts to baseline levels after the treatment is stopped can often be successfully studied in crossover or multiple crossover designs. The duration of each phase of the crossover will be constrained by the pharmacokinetics of the drug, in terms of reaching the required therapeutic level and then clearance of the drug and its effects, and this can limit the practical feasibility of crossover trials.

Even where performance effects are fully reversible, using crossover designs in the acute recovery period is often very challenging, because the slope of recovery is constantly changing, such that the expected improvement under the null hypothesis is not the same for the first and second phases. This problem can be reduced by using multiple crossovers which allows one to estimate the recovery curve separately from the drug's effects at different points in that curve.

Crossover designs of reversible treatments can provide clinically useful data for individual patients as well. If they and/or their clinicians and caregivers provide ratings of relevant treatment targets during each phase and express global preferences, such blinded comparisons may be very helpful in gauging the individualized value of treatment.

Treatments intended to permanently alter the course of recovery require a parallel group design, since this is one of the types of "carryover effects" that invalidate crossover designs.[5, 6] One can sometimes increase the acceptance of such trials by using a hybrid design. That is, the main study is designed as a placebo controlled parallel group structure and the primary outcome measures are taken at the end of phase I of the study. However, patients are then either uniformly or optionally crossed over into the other condition, though the data gathered in that phase are not included in the main analysis. Depending on the specifics of the treatment and the design, some additional evidence may result from this second phase, particularly if the individuals who received placebo initially show a relatively large improvement in Phase II.

In summary, studies to establish a likely benefit of a drug treatment and to validate the measurement of treatment effects may or may not require the use of placebos and, if they do, may allow for a within-subject (crossover) design that is more acceptable and often clinically informative. Parallel group designs involving a placebo group are more likely to be required in definitive clinical trials. Placebo controlled parallel group designs are

particularly critical during periods of rapid spontaneous change, irreversible treatment effects, and high variability.

1. Roberts, L.W., et al., *Patient and psychiatrist ratings of hypothetical schizophrenia research protocols: assessment of harm potential and factors influencing participation decisions*. American Journal of Psychiatry, 2002. **159**(4): p. 573-584.
2. Baldwin, D., et al., *Placebo-controlled studies in depression: necessary, ethical and feasible*. European Archives of Psychiatry & Clinical Neuroscience, 2003. **253**(1): p. 22-8.
3. Puzynski, S., *Placebo in the investigation of psychotropic drugs, especially antidepressants*. Science & Engineering Ethics, 2004. **10**(1): p. 135-42.
4. Saunders, J. and P. Wainwright, *Risk, Helsinki 2000 and the use of placebo in medical research*. Clinical Medicine, 2003. **3**(5): p. 435-9.
5. John, J.A., K.G. Russell, and D. Whitaker, *CrossOver: an algorithm for the construction of efficient cross-over designs.[see comment]*. Statistics in Medicine, 2004. **23**(17): p. 2645-58.
6. Putt, M.E., *Power to detect clinically relevant carry-over in a series of cross-over studies*. Statistics in Medicine, 2006. **25**(15): p. 2567-86.