

RESEARCH/CLINICAL UPDATE

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The Ethics of Placebo Controls in MS Clinical Trials: International Meeting Convened by National MS Society

An international panel met in Washington, DC, recently under the auspices of the National MS Society's International Advisory Committee on Clinical Trials in MS to discuss the ethics of conducting placebo-controlled trials in multiple sclerosis. This has become of increasing concern now that there are multiple partially effective agents available to treat relapsing forms of MS, and because placebo-controlled trials require that a proportion of patients receive "dummy" medication to contrast their outcomes with those treated with the experimental therapy.

The international gathering of MS physicians, ethicists, drug regulatory authorities, statisticians, industry representatives and clinical trial experts who study other diseases facing similar issues debated complex pros and cons of placebo controls in the context of approved therapies. The meeting was chaired by Chris H. Polman, MD, PhD (Free University Medical Center, Amsterdam).

The last time the Society convened a summit on this topic, it resulted in publication of an influential report that has helped to guide the design of MS clinical trials since 2001 (Lublin FD, Reingold SC, [Annals of Neurology 2001;49:677-681](#)). The 2001 guidelines laid out specific circumstances in which it has been considered ethical to conduct placebo-controlled trials in relapsing MS, such as when participants refuse to take or have not responded well to existing therapies. The new panel met to revisit those guidelines in light of today's clinical landscape.

Background: Using placebo as a control has been the historic "gold standard" for clinical trials in MS, and permits potential benefits – or safety issues – of an experimental treatment to emerge in high relief against a control group that receives the same amount of physician care except for inactive therapy.

There is little controversy about the need for and ethics of conducting well-designed placebo-controlled trials in forms of MS for which there is no approved therapy, such as primary-progressive MS, because doing so would not prevent patients from receiving any recognized, effective therapy for that form of disease. The ethical concerns are greater when there are approved [disease-modifying therapies](#), such as in relapsing forms of MS.

Design Issues: For trials in relapsing forms of MS, comparing a new drug to inactive placebo allows a study to proceed with a relatively small number of subjects, which can ease recruitment and reduce costs, yet leaves those on placebo possibly vulnerable to the immune attacks and relapses that currently available therapies can partially prevent.

In MS and other diseases for which there are multiple treatments available, there are many trial design options that can avoid the use of control groups given only inactive placebo. One potential solution is to conduct “add-on” trials (where participants take a standard treatment plus either a new therapy or placebo version of the experimental therapy). Alternatively, “superiority” trials (where participants receive either a standard therapy or the new therapy) can be considered.

In a relatively infrequent disease like MS, recruiting the large numbers of participants needed for such trials is difficult. In addition, safety concerns can arise because of the unknown impact on adverse events of adding therapies together in add-on trials and of the unknown safety profile of a new agent to which a large number of people will be exposed in a superiority trial.

Whether a trial is placebo-controlled or not, above all, a clinical trial’s results must be interpretable – meaning that the trial must be designed and conducted properly so that it is absolutely clear in the end whether the experimental therapy worked or not – or else it would be unethical because it exposed participants to potential harm without contributing to the greater good.

Patient Choice and Protection: In any clinical trial, whether or not it involves placebo controls, it is essential that people considering enrollment in a clinical trial are given ample information to ensure that they can give truly “informed consent” to enroll. Some individuals may want to participate in clinical trials of new drugs and are willing to accept the odds that they will end up on inactive placebo. This is especially the case when people, for any of several reasons, do not have access to standard therapies. Potential conflicts of interest may arise when the patient’s treating physician, whose sole focus should be on the individual’s optimal care and protection, is also a clinical researcher actively involved in recruiting participants for clinical trials.

There is also some evidence that a proportion of patients enrolled in placebo trials do not understand that they may not receive the active experimental treatment. This underscores the need for better methods of informed consent.

Next Steps: These and other important topics were discussed at length during the two-day meeting. A report of the outcomes is being developed by the International Advisory Committee on Clinical Trials and will be widely disseminated when published. It is expected that a new set of recommendations regarding the ethics of placebo controlled clinical trials and their alternatives will help to guide the evolution of MS clinical trials into the future.

-- Research and Clinical Programs Department