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Ethical issues of placebo-controlled clinical trials in multiple sclerosis

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Jeffrey A Cohen speaks to Ruth Williamson, Assistant Commissioning Editor.

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Q The balance between study subject burden and risk, scientific rationale and interpretability of trial outcomes is a difficult one to achieve. Within the field of multiple sclerosis (MS), are placebo-controlled trials the best way to achieve this?

The gold standard for therapeutic trials is the randomized controlled design, when possible with blinding. Also, the most straightforward design to interpret is where the test agent is compared with a no-treatment group, specifically a placebo, where the attempt is to simulate the test drug in all aspects except for the active ingredient. Therefore, yes, in general, placebo-controlled clinical trials are the best way to test a new therapy. However, as a therapeutic area evolves over time and as therapies become available, using placebo-comparison groups becomes increasingly difficult. This is the situation that we have now encountered in MS.

Q Is it ethical to use placebo controls in MS when effective treatments are known to exist?

I think that there is no doubt that one can now challenge the use of placebos in the field of MS; however, it is a very complicated discussion, for a number of reasons.

Firstly, even though we now have established effective therapies in MS, the first one being approved nearly 20 years ago, all of the therapies available now, including the ones approved more recently, have shortcomings. These include either incomplete efficacy, side effects, inconvenience or potential risks. Therefore, even though we have established effective therapies, there is clearly a need for additional therapies.

Secondly, a field does not go from having no therapies to having perfect therapies instantaneously, there is always an intermediate period where you have some

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therapies but they have shortcomings. This is the situation we are in now for MS. Therefore, the question is not whether there are issues with using placebo controls, but whether placebo controls are necessary and, therefore, what one can do to protect participants in the studies.

Thirdly, one has to distinguish the appropriateness of individual studies. During the overall development of a potential new therapy, it goes through stages of testing; the appropriateness of a placebo control is going to be different at different stages. Likewise, the utility of a placebo control is going to be different at different stages. What one really needs to do is develop an overall set of data regarding an agent, and different types of studies are going to serve different purposes in that overall plan.

I think that if an ethics review committee is going to take a strictly hard-line approach that, due to established effective therapies, placebos are not appropriate, then the field of MS will stop developing new therapies. We need to be aware of the issues and to evaluate every trial in its own right.

Q With placebo controls, as the physician is proposing to withhold an effective treatment, are there challenges in ensuring that rigorous informed consent is obtained?

Some patients freely elect to go into a trial where they may potentially be assigned to placebo, the appropriateness of that decision hinges on the feasibility of informed consent. Whether or not they are capable of making an informed decision can be very difficult, because it is hard to impart the complete understanding of all the implications. Potential participants have varying levels of education and understanding of all the aspects of trials and a varying understanding of the MS disease process, and sometimes they have their own misperceptions and their own unrealistic hopes. I have had a lot of experience in clinical trials and it has become very clear to me that the informed-consent process is not always as successful as we would like to think it is. So yes, ensuring that rigorous informed consent is obtained can be a challenge.

Q In order to avoid such issues, is it ethical to turn to countries where patients do not have access to established effective therapies?

This issue is specifically related to trials where one group is going to receive a placebo as their only disease treatment for their MS, and not other approaches such as add-on studies. As established effective therapies have become increasingly available, particularly in North America and western Europe, MS trials have turned to eastern Europe, Asia and South America, where established effective therapies are less available. I think that, in general, it is ethical to do that; however, there are certainly a number of caveats.

Firstly, the study still has to be scientifically valid; the biology of the disease has to be comparable in these regions so that you are, in effect, studying the same disease and the results can be generalized. Secondly, the clinicians may not have as much experience in clinical research; therefore, one has to be careful that the data obtained are valid and that the results can be interpreted. Finally, for any study to be ethically valid, there has to be an appropriate trade-off between potential benefit and risk. In terms of risk, it is important that patients in these trials have the same level of protection and that they are not exposed to unacceptable risk of irrecoverable harm; once again, informed consent becomes critical. In terms of benefit, one of these should be that society will benefit from the results of the trial. Therefore, in order to ensure benefit is gained, one of the stipulations for trials being completed in these so-called disadvantaged areas would be that, if the drug looks promising, it will potentially be available to the participants in the study. This is where extension studies come in; once the trial is over, if the drug looks promising, it is offered in an open-label fashion to people who participated in the trial. In addition, there has to be a realistic chance that the drug will be submitted for regulatory approval in that country so that the region would benefit from the trial. This means that trials are not merely conducted in one area in order to benefit people in another area of the world.

Q As effective treatment becomes more widely available in developed countries, will ethical concerns increase?

I think that the issue is going to become more prominent because many treatments are being developed and at least some will become available. Therefore, it is becoming increasingly difficult for both practical and ethical reasons to do large trials in western countries; every trial that I get involved with seems to involve more and more sites in new areas. I think that if the requirements that I outlined previously are met then studies can be done in developing countries ethically. The clinical trial effort is becoming increasingly global and in some ways that is a good thing, as it offers opportunities in these regions to be involved in the development of new therapies, which means they will hopefully get access to new therapies as they develop.

Q Should guidance be further tightened for those MS trials conducted in resource-restricted environments?

The status, both of therapy for a disease and of doing clinical trials for a disease, evolves over time. All the issues that we are encountering now in North America and western Europe will start to become issues in central and eastern Europe, as they will go through the same evolution that we have gone through; therefore, they can use the previous guidance.

I think the same thing will happen as trials are increasingly done in more so-called disadvantaged areas. For example, I am now seeing trials being conducted in India, in areas where MS trials have not traditionally been done. I think we will see an increase in the amount of trials done in such countries and I think they will go through the discussions that we have had in the USA, and part of that is that increasingly restrictions are placed on what one can do and how one does it.

Q What is your opinion to those who argue that active-comparator-controlled studies are valuable to clinicians and should be used instead of placebo-controlled trials?

Active-comparator-controlled studies are an important component of an overall drug-development plan, because ultimately once one has reasonable therapies for a disease, one wants to compare new therapies to the previous therapies to see what their relative utility is. Therefore, ethical issues aside, the best development program would include both placebo-controlled trials and some active-comparator-controlled trials, so you have both sorts of data. However, active-comparator-controlled trials alone do have some issues.

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One is that, because every trial is different, even when the eligibility criteria and the trial design look very similar to previous trials, they always seem to enroll a different population. Therefore, an active-comparator-controlled trial alone does not give a very good measure of the absolute safety and efficacy of a new medication.

The bigger issue is that active-comparator-controlled studies may not be practical for all end points. The end points that we are becoming increasingly interested in within MS are 'clinical meaningful' end points. Thus, one needs to show benefit not only on MRI, but also on relapses and, even more importantly, on accrual of impairment and disability. These clinical meaningful end points are less sensitive and require more patients to show a difference. It is hard enough to show advantages of a new therapy over an active comparative for MRI, but to show advantages on relapses becomes even more difficult, and to show advantages on disability becomes extremely difficult.

One also has the issue of how to analyze those data. Do you try to show superiority? It is always a more straightforward interpretation, if one can demonstrate superiority of a drug versus something else. But one can imagine situations where the intent is not to show the new drug is superior, just to show that it is comparably effective but has some other advantages, such as it is a pill as opposed to an injection. This situation is where study designs using equivalence or non-inferiority get mentioned, but there are many issues with that kind of comparison. Regulatory agencies do not tend to favor that kind of design. It is important to remember that equivalence is not the same as failing to show superiority – it is a completely different statistical approach and requires, in general, even more patients to convincingly show equivalence. It is appropriate in certain settings but it has its own issues.

Q What is the status on new and alternative trial designs for MS being developed?

I think the field will definitely have to develop new approaches, more efficient designs and better outcomes; however, there is always going to be a potential trade-off between using outcomes that are more responsive and sensitive to change, and their clinical interpretability and meaningfulness. This is something where investigators and regulators need to work together, because it serves no purpose for investigators to develop outcomes that are not acceptable to regulators. Conversely, regulators should convey what it is they are looking for, because ultimately the goal is to develop new therapies, and a prerequisite for that is going to be to do studies that are both feasible and acceptable to regulatory agencies.

Q Are 'virtual placebo groups' the best option for MS trials?

To a great extent I think of virtual placebo groups as very similar to historical controls – using computer modeling. In essence it is a historic control and I think in the MS field this will not be very useful in the near future. There have actually been several large undertakings to

develop datasets that can be used in that way and they have not been successful, in part because of the issue that every trial seems to enroll a different population and our ability to predict behavior of patients based on demographic or clinical attributes is very imprecise. As a result, efforts have not been very successful and I do not think that it will obviate the problem of placebo controls.

Q Do you think that with advancing technology it could become a realistic option?

I think if we get a better handle on what aspects of the disease are measurable, for example aspects that do determine clinical behavior such as better MRI metrics or other biomarkers, it is feasible. But we are not there yet.

Q What are your future perspectives on placebo-controlled trials in MS?

I think we will continue to see some trials that utilize placebo controls, specifically in Phase II studies of anti-inflammatory strategies. The 3–6-month MRI-based studies to show proof-of-concept are a very well worked out trial design. I think we will see fewer and fewer large placebo-controlled Phase III pivotal trials, and I think when most of the drugs that are being developed now get to that stage, active-comparator controlled studies will be included as part of a development plan.

My biggest concern is that we are going to have a very difficult time showing benefit on disability if we only do active-comparator controlled studies and there is a big need to demonstrate protection of tissue. Therefore, either we are going to have to do trials that are very large and very long to show benefit on clinical disability, or we are going to have to validate measures as surrogates for disability, such as brain atrophy.

Q Overall, are you of the opinion that placebo-controlled MS trials are the best option?

In a trial, particularly in trials that use a placebo control, one needs to build in several layers of protection at the level of the protocol. Three layers in particular should be involved: 'safety nets', which should be there so that if an individual participant exhibits certain disease activities that put them at risk of harm, some strategy can be pursued to offer other therapies; informed consent, investigators need to remember that informed consent is not merely signing a document, it is a process, and it is an ongoing process over the course of a trial, which includes keeping the patient informed of their own status; independent review of the studies, oversight by funding agencies, regulatory agencies, human subject committees, independent committees and data-safety-monitoring committees that assess the ethics of the trial and also any ongoing safety issues in the trial.

There is no way to build a perfect trial; therefore, you have to build several layers of protection, and with these layers of protection some placebo-controlled trials in MS can be ethical.

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