CLINICAL INVESTIGATION

Data monitoring committees in clinical trials: best practice, complexities and considerations

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What is the problem all about?

Clinical trials are sometimes described as being rather 'blunt' instruments, and that often may be true: we use them to find answers to very broad questions such as 'does this drug work better than a control drug?' But they are also very important and delicate instruments: we use them to find answers to questions such as 'how much does this drug work?' 'what is the safety profile of this drug?' and so on. And in the nature of research, we do not know what the right answer is and we have to rely on the clinical trial to give us the right answer. If anything is broken in the trial, it might give us the wrong answer – but we might have no way of know whether answer is right or wrong (unless we can see a break, or maybe just a dent, in the trial).

Bias is one of the big concerns in any trial and it is why we typically use the key building blocks of blinding and randomization. It is also why we typically do not look at the data every week or two and see how one treatment is doing compared with another. We set up an experiment, we allow it to run unhindered, and then we look at the results.

The problem (of course) is what should we do if something in the trial is going in a very different direction to where we thought it was? This might be that the new treatment is far better than the control treatment – even to the extent that it is far better than we initially expected. Patients are potentially being disadvantaged by being randomized to the control arm; something needs to be done. Or it might be that our new treatment, while backed by some of the greatest investors and optimists the world has produced, actually is not working. We are wasting a lot of time, resource, patients' goodwill and, not to forget … quite a lot of money. Something surely needs to be done!

So we are in the dilemma of wanting to run a trial, without external interference, maintaining blinding and randomization, but we also want to know what the results look like. Enter the independent data monitoring committee (DMC).

Bringing control to the problem

It is impossible to know how many trials have historically been run with investigators knowing the results as they go along. It was possibly the Greenberg Report that first recognized the problem explicitly and laid out approaches to managing long-term multicenter clinical trials. It was commissioned by the National Heart Institute and completed in May 1967, although never published. Subsequently, in 1988 it was published in *Controlled Clinical Trials* [1] as a means to make it publicly available and so that it could be cited. The first implementation of the recommendations of the report was in the Coronary Drug Project trial of clofibrate and niacin for treating patients suffering from ischemic heart disease [2]. Key groups with oversight of a trial include the sponsoring agency, steering committee, data coordinating center and DMC. Although some of these terms fit more closely with the model of publicly funded trials, they are equally applicable to industry-sponsored trials and, arguably, help identify the different functions that need to exist in an otherwise 'single entity' that is running (and financing)

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a trial. Without the separation of tasks, it is easy for barriers (and blinding) to break down.

There is clear evidence of the impact of such a report (and the move in general thinking), at least in cancer trials, which might show us just the tip of the iceberg. This is how the South-Western Oncology Group implemented a new policy of not revealing interim data to investigators (or others) while trials were ongoing [3]: "Release of results: For Phase III, Phase II/III and blinded randomized Phase II trials, any (note: original emphasis) release of outcome data (either internal to South-Western Oncology Group, to NCI personnel not members of the DSMC, or external [e.g., a paper presented at professional society meetings, seminars and papers]) prior to the final approval of general dissemination of results must be reviewed and recommended for approval by the DSMC to the designated Group Chair. In general, outcome data from Phase III, Phase II/III and blinded randomized Phase II trials would not be routinely made available to individuals outside of the DSMC until accrual has ceased and all patients have concluded their randomized treatment."

> "Access to interim trial data by sponsors and data monitoring committees needs a major rethink and possibly implementation of new processes."

So why not let everyone know what is happening along the way? There are many reasons and many possible reasons. Early data (partial data) from a clinical trial will usually be unreliable. 'Trends' in efficacy, perhaps in an interesting subgroup might change the pattern of patient recruitment in favor of that subgroup and away from its counterpart. 'Trends' in incidence of particular adverse events might impact on investigators' judgments of likely causality to one or other treatment. 'Trends' of overall benefit – or lack of benefit – may sway all those involved in the study (including patients, investigators, investors) that the study should not, or need not, continue. All of these problems are based on 'trends.' The US FDA, in their Guidance to DMCs [4] put it very eloquently: 'plans or decisions based on statistically imprecise interim data may often be suboptimal.'

Hence, the idea of an independent group of people who have no vested interests in the outcome of the study and who look at the data without revealing it to wider audiences [5,6]. These experts, members of DMCs, can shout loud when necessary, but keep quiet when that is the most appropriate thing to do.

Have we, as clinical trial professionals, lost direction?

We seemed to have moved through phases. At first we had no idea there might be any problem. Ignorance was bliss. We then realized there was a problem. Some saw the light sooner than others, but eventually everyone got the message and understood the importance of keeping anyone who might know the emerging study results separate from those with day-to-day roles and responsibilities in the trial. Hard lessons were learned. And then we invented 'adaptive designs' – a catchy title that seemingly allows almost anything to be changed within a trial: treatments (well, certainly doses and dose regimens), end points, populations…the list can be endless. We can design studies that change all of these things as a study progresses and still manage to be 'statistically valid', [7] although such studies are probably of limited interpretation and use. There are more restricted adaptions which might have rather more credibility. Examples include dropping an ineffective dose, or perhaps restricting the eligible population to a subgroup of patients based on some evolving biomarker technology, or simply based on demographics or stage of disease. Other examples include judging whether sufficient evidence exists to support a regulatory submission.

DMCs might be well placed to help make these recommendations, but the decisions are often intrinsically linked to business decisions too. Does the sponsor want to restrict the indication just to a subset of the population? That might depend on the balance of benefits and risks in that subset, the balance of benefits and risks in the complementary subset and commercial aspects of market size and return on investment. These are not issues (particularly the latter) that a DMC should be getting involved with. They are for the sponsor to consider, but how can they do so without detailed insight into the data? Unless, of course, they do look at the data. And then we return to the days of pre-Greenberg Report.

DMCs have served many trials – and many patients – very well. Trial methodology is developing and we need to find ways to maintain the integrity of trials while also maximizing the benefits of new methods. Access to interim trial data by sponsors and DMCs needs a major rethink and possibly implementation of new processes.

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