Data and Safety Monitoring Boards

The randomized controlled clinical trial (*see* **Clinical Trials, Overview**) has become a standard as a research method during the past four decades to evaluate the risk–benefit ratio of novel or existing interventions or therapies. The results of a new or existing intervention are compared with a standard or a control, using clinically relevant outcome measures such as survival, morbidity, or quality of life. Most interventions or therapies should be evaluated by this rigorous comparative methodology before being widely accepted or used in practice. Such evaluation is often required for regulatory approval, especially for drugs and biologics.

For some trials the outcome of the disease or the risks of the therapy may be irreversible. Several issues in the design and conduct of a clinical trial were carefully considered by the Heart Special Projects Committee [12], commissioned by the National Heart Institute of the National Institutes of Health (NIH). The report of this committee is often referred to as the Greenberg Report. One of the recommended principles is that comparative trials should be carefully monitored for patient safety and for evidence of benefit. The process is often carried out by a committee, which we shall refer to as the Data and Safety Monitoring Board (DSMB). The principles used today in monitoring a randomized control clinical trial are largely influenced by the Greenberg Report. The experience with DSMBs has been discussed from several perspectives at an NIH workshop and is described in the Proceedings [7]. Fleming & DeMets [9], DeMets [4], Pocock [19], Fleming [8], Armstrong & Furberg [1], and DeMets et al. [5] discuss various aspects of data monitoring and the role of the DSMB. The Task Force of the Working Group on Arrhythmias of the European Society of Cardiology [21] discusses the causes, consequences, and control of early termination, including the role of the DSMB. This article describes the rationale, responsibilities, and issues that involve the DSMB for most trials.

Rationale for Data Monitoring

The goals of a randomized controlled clinical trial are to evaluate the effectiveness of a new intervention, and to assess its safety, so as to estimate the ratio of benefits to risks. One of the ethical principles of clinical trials is that they should continue no longer than necessary to meet the objectives stated in the trial protocol. This is especially true for trials with serious outcomes, such as mortality, morbidity requiring hospitalization, and irreversible adverse effects. Trials may be modified or terminated early if there is overwhelming evidence for a positive benefit to risk ratio, if the evidence strongly suggests harm or a negative benefit to risk ratio, or if the trial has no chance of resolving the primary objectives. Furthermore, if the observed data are not close to the design assumptions, then the trial may need to be modified, such as increasing the sample size, in order to preserve the integrity of the trial. If recruitment goals cannot be achieved in a reasonable time frame, then the viability of the trial must be reassessed. In some cases, logistical or data quality issues must be resolved or the credibility of the trial may be severely jeopardized. All of these aspects must be monitored carefully and considered in the continuation of any trial.

The decision to make protocol modifications, including early termination, is a complex process and several factors must be taken into consideration. This has been discussed by the Coronary Drug Project Research Group [3] and more recently by Fleming & DeMets [9]. Factors include the balance in risk factors between the intervention and control groups, potential biases in outcome ascertainment, compliance to intervention, consistency of results across primary and secondary outcome measures and across clinically relevant subgroups, consistency of results with external information, the effect of repeatedly testing a single outcome or testing multiple outcomes on false positive results, and the impact of early termination on trial participants and future users of the intervention. Examples of these complex decisions have been described for the Coronary Drug Project [3], the Beta Blocker Heart Attack Trial [6], the Cardiac Arrhythmia Suppression Trial [10], and the Physicians Health Study [2]. All of these trials involved early termination, either for an early benefit, an unexpected harmful effect, or for lack of an effect in the primary outcome. In all cases the decision process was complex and difficult.

A particularly difficult issue is how much evidence indicating potential harm should be allowed to accumulate. In some cases, the choice may be between stopping a trial with a negative trend at the

point when the trial has little or no chance to prove treatment beneficial, or continuing a trial with a negative trend until the evidence becomes convincing that the treatment is harmful. In the PROMISE trial [16], which evaluated the drug milrinone in congestive heart failure patients, the trial continued until a statistically significant harmful result was obtained. A similar experience occurred in the PROFILE trial [17], which involved the drug flosequinan in congestive heart failure. Part of the rationale for continuing to this level of evidence was that, unless shown to be convincingly harmful, other beneficial effects of each drug would encourage their continued use in a large patient population. In contrast to this experience, the CONSENSUS II trial [20] with the drug enalapril in congestive heart failure terminated with a negative trend before it became statistically significant. Here, the rationale was that the method of drug delivery would not be used unless it was beneficial. Once the point was reached where that outcome was highly unlikely, there was no reason to continue. In all three cases many factors had to be considered. Another difficult decision is whether the same degree of evidence is required to prove harm as is required for benefit. If the decision process is inherently asymmetric, then the statistical guidelines for data monitoring should also reflect that asymmetry.

While carefully monitoring outcome data in a clinical trial is often ethically mandated, the process of repeatedly examining data also increases the rate of a false positive result; that is, claiming that a difference between two interventions or treatments exists when in fact there is none. Typically, researchers set the false positive rate at 1% or 5% before conducting statistical tests and interpreting P values. However, if a particular outcome such as the primary outcome is tested five times using a P value of 0.05 each time as the criteria for significance, then the actual false positive rate is increased to almost 15%. This is clearly much higher than is scientifically acceptable and five interim analyses are not unusual during the course of a large multicenter trial. This issue is often referred to as repeated testing. Another related issue is multiple testing, which refers to conducting statistical tests on multiple outcomes, and focusing attention on the one result which has a P value less than 0.05. Clearly, if 20 independent outcomes are statistically tested, then one will by chance alone have a P value less than 0.05. Thus, the ethical mandate of carefully monitoring the outcomes of a clinical trial must take into account the increased chance of falsely claiming a treatment benefit or harm due to the monitoring process. Statistical methods adjusting for the repeated testing and multiple testing have been developed and are discussed in [18], [15], and [13].

To evaluate these diverse factors thoroughly requires a great deal of expertise and experience in clinical trial design, biostatistics, epidemiology, and the subject-matter or disease process involved. No single individual is likely to possess such vast expertise. For this reason, the concept of a monitoring committee evolved, starting with the suggestions made in the Greenberg Report Heart Special Projects Committee [12]. A recent report by the National Institutes of Health has reconfirmed that recommendation [14].

DSMB Membership and Responsibility

Since several complex issues must be considered at each interim analysis, requiring expertise from several diverse but relevant disciplines, the membership of the DSMB must reflect those disciplines in order to monitor the data and the safety of the patients. The disciplines typically included are the relevant clinical disciplines, laboratory expertise, epidemiology, biostatistics, clinical trials, and medical ethics. Often, three to five individuals are necessary to cover this broad range of expertise. Clinical trial experience by all members of the DSMB is highly desirable, but prior experience of serving on a DSMB by the DSMB chair is essential. Appointment of members may be made by either the sponsor or the trial executive committee, but in either case, the appointments should be acceptable to both parties. The protocol should clearly specify the DSMB appointment process.

The authority of this DSMB is to review the accumulating data and make recommendations to either the study chair or the sponsor, or both. While it is rare for a DSMB recommendation not to be accepted and fully implemented, the DSMB usually does not have the final decision-making authority. That final decision typically resides jointly with the sponsor and the trial executive committee. The trial protocol should carefully specify the lines of the DSMB reporting so that any recommendations by the DSMB can be properly received and rapidly taken into consideration by those with the final decision-making authority. However, regardless of the lines of reporting, both the trial investigators and the sponsor

must be briefed as to the rationale for any DSMB recommendation within a reasonably short period of time. Furthermore, the DSMB should maintain the view in their deliberations and recommendations that they are primarily responsible to the trial participants, next to the investigators who are placing significant responsibility with them for their patients, then to the trial sponsor, and finally to the regulatory authorities. Any DSMB should fully recognize those interests and take them into consideration.

The recommendation of the Greenberg Report was that a trial advisory committee such as the DSMB should be independent of the trial. Members of the DSMB should not be investigators entering patients or participants into the trial. Otherwise, ethical dilemmas arise as trends in data emerge which are not yet scientifically convincing but could disrupt clinical equipoise about the benefits of the treatment or intervention. In some trials the study chair has been allowed to be an ex-officio member of the DSMB, to convey information about the trial to the DSMB and to understand better the recommendations of the DSMB. In such cases the study chair should not be entering or caring for patients in the trial.

Walters [22] writes that DSMB independence is essential for a trial to achieve knowledge with maximum objectivity, respecting the contribution of the patients toward that goal. To be independent, the DSMB members should be free of real conflicts of interest, especially since they are reviewing confidential and privileged information. Freedom from any conflict is probably not achievable if the DSMB members are expected to have any expertise and experience with the goals of the trial. However, financial conflicts of DSMB members should be avoided, including stock ownership and transactions, large consulting arrangements with the sponsor, or frequent speaking engagements on behalf of the intervention. DSMB members should at least disclose any consulting or financial arrangements and sources of research funding. If conflicts are identified that could be perceived as serious and possibly damaging to the trial, then the DSMB member should either remove the conflict or not continue to participate on the DSMB. Neither a sponsor nor a member of a regulatory agency should be a member of the DSMB since each has other specific responsibilities and interests and thus is not independent. In some cases, sponsors have been allowed to attend DSMB meetings but their role must be limited.

Since the DSMB has access to interim results, including primary outcome data, absolute confidentiality is of utmost importance. Results of the trial should not be discussed beyond the DSMB meetings and great care must be taken that interim reports are secure. This would include members from sponsoring agencies, should they be allowed to attend. Early in a trial, trends in accumulating data can be quite variable, and any release of early trends could be both misleading and damaging to the conduct of the trial. In some cancer trials, knowledge of interim data and emerging trends had the effect of hampering recruitment and definitive results were not achieved [11]. Of course, if early trends are overwhelming and scientifically convincing, then the DSMB might very well recommend early termination. This was the case in the Cardiac Arrhythmia Suppression Trial [10]. However, the DSMB must keep interim results confidential until the trial is terminated and the results are properly disseminated.

DSMB Meetings

The meetings of the DSMB must be structured so that all of the critical elements of a trial are properly reviewed and the patients' safety thoroughly examined. The DSMB must meet often enough to carry out its responsibilities. For many trials, the DSMB meetings are held at least once a year and may have at least three to five regularly scheduled meetings during the course of the trial. In general, meeting more often than after every 20% increment in patient recruitment or patient outcome is usually unnecessary, and does not lead to substantial gains in early termination. However, it is not unusual to hold an extra meeting if a decision to terminate is approaching. Other considerations such as slow patient recruitment or unanticipated logistical problems may call for additional meetings of the DSMB.

Each DSMB meeting must evaluate patient recruitment progress, data quality, baseline characteristics, patient compliance, primary and secondary outcomes, adverse effects, and other safety measures. Interim reports must reflect all of those considerations and can be quite extensive, depending on the complexity of the trial. The DSMB must have the authority to request any available data from the trial that is necessary to carry out its primary responsibilities. Reports should be provided through a confidential

and secure process to the DSMB prior to the meeting so that members have adequate time to review the analysis and identify concerns.

Attendance at the DSMB meeting has been discussed by the proceedings edited by Ellenberg et al. [7]. The DSMB for the National Institute of Health's AIDS Clinical Trial Group (ACTG) developed a meeting format that addresses most of the concerns of all interested parties [5]. The general format starts with an open session where all interested parties can attend and participate, is followed by a closed session where confidential data are reviewed and discussed by the DSMB with the statistical analysis center that prepared the interim report, and concludes with an executive session for DSMB members only. Following the executive session, the DSMB chair may give the trial chair and sponsor a short briefing on DSMB recommendations and any other concerns raised in the closed or executive session.

At the open session, sponsors, representatives of the investigators, and representatives from regulatory agencies may be present to discuss study progress, including recruitment, general data quality, logistical matters such as drug supply or shipment of laboratory specimens, and general compliance issues. Results of other new studies and their impact on the current trial may be discussed as well.

In the closed session, where confidential data are reviewed, the DSMB and the trial statistician must be present. For many trials sponsored by the NIH, NIH representatives are present during the closed session. The ACTG DSMB did allow NIH representatives to attend, but industrial sponsors who often were also involved did not participate in the closed session. For totally industry-sponsored trials, the practice is not consistent. A few trials have had sponsor representatives present (e.g. PROMISE, PRAISE), but in general this is not recommended routine practice. If representatives of the sponsor do attend, they must abide by the same confidentiality as do members of the DSMB, and must not interfere with the DSMB deliberations or use the information to affect the trial, unless instructed by the DSMB.

The executive session allows the DSMB to deliberate and formulate their final recommendations without other influences. This format has been very effective for the ACTG DSMB meetings, where several trials are considered during a session, and seems to be useful in many other settings as well.

Summary

The DSMB in a clinical trial is central to reviewing accumulating evidence on patient safety and treatment benefit. The complexity of clinical trials makes the decision process to terminate or continue trials challenging and requires a DSMB to have a diversity of expertise and experience. DSMBs have been utilized in many clinical trials over the past three decades and their value to the clinical trial process is now well established.

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