

Editorial

Data Safety Monitoring Boards

The dramatic withdrawal of rofecoxib (Vioxx®) by Merck on 30 September 2004 was the result of a recommendation by a Data Safety Monitoring Board (DSMB) to terminate a placebo-controlled study of this drug in the prevention of colonic polyps because of a statistically significant increase in adverse cardiovascular outcomes.¹ Another drug trial terminated around that time (17 December 2004) was by Pfizer, of celecoxib in the prevention of colonic polyps, because it showed statistically significant evidence for increased cardiovascular event rates.² In 2002, a large, multicentre randomized controlled trial (RCT) testing hormone replacement therapy in healthy, postmenopausal women was terminated because it was felt that the evidence already generated from the trial should be made available to the current and future trial participants to help them make decisions about future use of hormone replacement therapy.³ In all three cases, the decision to discontinue the trials was based on the recommendation of a small group of people who constituted an independent DSMB.

India's increasing participation in global clinical trials has seen a steady expansion in relevant infrastructure and human resources. Since very few studies have been initiated on product development in India, the concept of having DSMBs for clinical trials is still nascent. The Indian Good Clinical Practice (GCP) guidelines⁴ issued in 2001 suggest that 'The sponsor may consider establishing an Independent Data Monitoring Committee (IDMC) to assess the progress of the study.' The revised *ICMR Ethical Guidelines for Biomedical Research on Human Participants* (2006)⁵ specifically mandate the constitution of a DSMB to review data emerging from research on interventions in emergency situations.

A DSMB (also known as an Independent Data Monitoring Committee [IDMC], Data Monitoring Committee [DMC] or Data Review Board [DRB]) is an independent, advisory committee established by the sponsor of a study to assess the progress of a clinical trial, the safety data and critical efficacy end-points at pre-determined intervals, and to recommend to the sponsor whether to continue, modify or stop a trial.

It is important to distinguish the roles and responsibilities of a DSMB from those of an Ethics Committee (EC)/Institutional Review Board (IRB). Although the primary aim of both the EC and the DSMB is to safeguard research participants' well-being—and in this regard their roles are complementary—there are important differences in their functioning. All clinical trials need to be overseen by an EC/IRB whereas a DSMB is required only for certain types of trials (*see below*). As per the current guidelines, EC/IRB members (e.g. biostatistician and other experts) may not have the scientific or subject expertise to monitor safety and efficacy data emerging from a clinical trial. Appointed by the institution, an EC is independent of the sponsor and communicates primarily with the investigator. On the other hand, a DSMB is usually appointed by the sponsor and reports to the sponsor.

The concept of a formal independent committee to monitor accumulating data in clinical trials and to review interim analyses of these data was first mooted in the USA in the Greenberg Report (1967).⁶ In the UK, the establishment of DSMBs coincided with the start of the era of large, multicentric clinical trials⁷ such as the ISIS (International Study of Infarct Survival) trials of interventions to reduce the risk of

death following myocardial infarction. The constitution of a DSMB became more popular with an increase in the number of large, multicentric trials. In 1996, the International Conference on Harmonization (ICH) of GCP Guidelines recommended the constitution of DSMBs in randomized trials. In 1998, the UK Medical Research Council (MRC) made the establishment of an independent DSMB mandatory for all its trials. In the USA, the National Institutes of Health (NIH) recommended the establishment of DSMBs for multisite phase III clinical trials funded by them when the trials involved interventions that entailed potential risk to the participants.⁸ DSMBs have become popular because of a larger number of clinical trials with end-points such as death, national governments mandating such boards for studies funded by them, and because they have contributed considerably to the design of clinical trials.⁹

A DSMB for any trial is set up to have a group of experts, independent of the trial, who could objectively review data generated during the trial with a view to ensuring the safety of the trial participants as well as the integrity and validity of the data. An important question is: Do all trials require a DSMB? Simply put, the answer is 'no'. As the primary responsibility of all stakeholders in clinical trials is patient safety, all clinical trials should have a Data Safety Monitoring Plan (DSMP) in place to stipulate how and by whom the safety of the research participants will be monitored. A DSMB forms a part of a DSMP only when relevant, depending on the type and duration of the study, and the level of risk. For example, the policy of the National Heart, Lung, and Blood Institute of the NIH recommends a DSMB in all phase III trials, phase II trials with specific safety or data monitoring issues and when a novel drug, device or therapy with a high or unknown safety profile is being tested. It also states that large or complex observational studies may require monitoring boards.¹⁰ Studies that should have a DSMB include RCTs evaluating the efficacy and safety of a new intervention intended to reduce severe morbidity or mortality, those in which the available data raise concerns about potential serious adverse outcomes, studies where the design or expected data accrual is complex, or where there may be ongoing questions regarding the impact of accrued data on the study design and participants' safety, studies where the data justify early termination, studies conducted in emergency situations (now mandated in the 2006 ICMR guidelines),⁵ and studies in vulnerable populations.

Typically, a DSMB is multidisciplinary and is appointed by the sponsor. The size of a DSMB and the expertise required among members depend on the type of trial (phase of the trial, range of medical issues, complexity of design and analysis, and potential level of risk) as well as the scope of the responsibilities given to the DSMB. Experience in clinical trials, ability to commit time for attending DSMB meetings and willingness to maintain confidentiality of the interim results that are reviewed are desirable qualities to seek in prospective members of a DSMB. Prior DSMB experience, especially of the chairperson, is important when considering membership.¹¹ An important issue that influences the choice of members is any potential conflicts of interest that they may have (e.g. financial and/or intellectual relationship to the trial being monitored). A clear policy guideline should address this issue. In general, a DSMB has at least 3 members including one or more specialists in the area being studied in the trial, and one or more biostatisticians with knowledge of and experience in the statistical methods proposed to be used to evaluate interim data from the trial.

The scope of responsibilities of a DSMB is defined in its charter (standard operating procedures), which is the authority under which the DSMB is established. The charter must also describe decision-making procedures and define the relationship of the DSMB with the sponsor and other trial stakeholders, as also the schedule, its format and attendance requirements for its meetings. The method of preparation and circulation of interim analyses, and the methods to assess conflicts of interest in members are also included.

The principal role of a DSMB is to ensure the safety of clinical trial participants. The responsibilities of a DSMB can encompass evaluating accumulating data with regard to efficacy and safety, recommending termination or continuation of the study,

recommending other study modifications, reviewing and approving the study protocol (this is separate from the EC approval and is undertaken when involvement of the DSMB is considered desirable at the planning stage itself), assessing study conduct and recommending additional analyses.

Two important issues that come up in the functioning of a DSMB are its independence and the access to sponsors of interim data and participation in meetings. Independence¹² of the DSMB from the sponsor is essential to ensure objectivity in its functioning. It may also allow for mid-term corrections to be made in the trial, if need be, in response to new information without introducing the sponsor's bias, thus maintaining the scientific integrity of the study.

Three models of independence have been described:¹³ (i) all members involved in the decision-making process are completely independent of the trial and a statistician independent of the sponsor conducts the analyses, (ii) the trial statistician prepares and presents interim analyses to the DSMB in an open session in which all stakeholders participate with free sharing of blinded data emerging from the trial. However, decision-making is limited to members of the DSMB and is done in a closed session when the DSMB reviews data, at times in an unblinded format, and (iii) people involved in the trial including study investigators are members of the DSMB and therefore participate in decision-making. The second model combines the advantages of participation of the team during the open sessions where open data are discussed while still maintaining an acceptable degree of independence of the DSMB, making it probably the preferred model.

Perhaps the most crucial responsibility of a DSMB is to arrive at recommendations after completing a review of the available data. Trials may be stopped because of safety concerns,¹⁴ or because it is clear that it is futile to continue because of lack of efficacy¹⁵ or sometimes because the interim analysis indicates a favourable outcome with a new treatment, making it unethical to not offer it to future patients.¹⁶⁻¹⁸ This mandate, in particular the authority to recommend stopping trials early, is a major responsibility. Thus, decisions need to be taken after careful deliberation, since these can have far-reaching effects on clinical practice. Recently, Slutsky and Lavery⁹ have discussed two important ethical questions related to the recommendations of a DSMB, namely (i) how to balance the need to protect study participants of a particular clinical trial against its duty to patients and clinicians outside the trial, for whom a clear and convincing answer to the clinical question will have important implications, and (ii) the need for disclosure of interim results.¹⁹ Both these tricky issues have been analysed elegantly in the article. The ethical dimensions are even more complex in clinical trials performed in patients with HIV. A recent study has reported, for example, that 10 RCTs were stopped early for harm—however, only 1 trial had stopping guidelines that had been defined *a priori*. The authors concluded that clinicians should interpret RCTs stopped early for harm with caution and interpret the results in light of related evidence and that there was a need for increased transparency of decision-making processes for early stoppage.²⁰

The responsibility on the DSMB is illustrated by a commentary by Cannistra,²¹ who argues that there are instances in which 'stopping rules' can compromise the interpretation of results, thereby jeopardizing the patients that they are designed to protect. The author uses the examples of the Southwestern Oncology Group (SWOG) study 9701 and the oncology trial designed by the National Cancer Institute of Canada Clinical Trials Group.

Conclusion

DSMBs play an important role in clinical trials. By monitoring safety and efficacy parameters of study participants they provide crucial information for all stakeholders. For example, an EC can benefit by the interpretation of adverse events reported during a trial provided by a DSMB. The regulator is assured that the DSMB would formally evaluate data and recommend a course of action that would ensure patient safety. It is time to promote the constitution of DSMBs for clinical trials in India. The Department of Biotechnology, Government of India now requires DSMBs for

multicentric trials funded by it, e.g. stem cell studies and large vaccine trials. It is equally important to stress the need for capacity building in this important area of clinical research.

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