CLINICAL INVESTIGATION

Data and safety monitoring boards of randomized trials: evolving principles and practical suggestions

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Randomized trials designed *a priori* to test particular hypotheses provide the most reliable evidence concerning the most plausible small-to-moderate effects of drug therapies or interventions and are a necessary component of a totality of evidence upon which to make rational clinical decisions for individual patients and policy decisions for the health of the general public. As the methodology for the design, conduct and analysis of randomized trials continues to evolve, so do the principles and practical suggestions for their Data and Safety Monitoring Boards (DSMB)s. The implementation of these principles and practical suggestions should enhance the functioning of DSMBs, trial investigators and sponsors, protect the safety of the randomized subjects as well as the independence and integrity of the randomized trials.

Keywords: Data and Safety Monitoring Boards • practical suggestions • principles

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Introduction to evolving principles for Data & Safety Monitoring Boards

There is an increasing need for large scale randomized evidence without undue emphasis on small trials, their meta-analyses as well as subgroup analyses or observational studies of small-to-moderate effects, especially those designed for administrative, not research purposes [1]. In this context, Data and Safety Monitoring Boards (DSMBs) have been a crucial component of the success of large scale randomized trials of drugs for several decades [2–4]. As a consequence the organizational structure and functions of DSMBs as well as the design features and relevant statistical methods for randomized trials are evolving [4–7]. In addition, policies for DSMBs have been suggested by governmental sponsors [8,101] and regulators [102]. Finally, examples of recent DSMB experiences have also been summarized [9]. Thus, as the roles and responsibilities of DSMBs continue to expand and evolve, it seems important and timely to emphasize some evolving principles and practical suggestions.

Evolving principles for DSMBs

■ Role as independent scientists

Data and Safety Monitoring Board members are independent scientists whose primary role is to ensure the safety of randomized subjects. DSMB members should serve the subjects, the trial, the independent investigators conducting the trial as well as the sponsor, whether industry or government [4]. In the USA, safety monitoring is mandated for all randomized trials under the jurisdiction of the US FDA or funded by the NIH [10]. This standard has been adopted, at least informally, internationally and regardless of the funding source. For multicenter trials, especially those with higher risk patients, or testing drugs with potentially serious adverse events or novel interventions, the FDA guidelines recommend an independent DSMB as well as an independent Statistical Data Analysis Center (SDAC) [9].

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For single institution trials, safety monitoring is formally a responsibility of the institution through the Institutional Review Board (IRB). Nonetheless, few IRBs have either the multidisciplinary expertise or infrastructure to do so properly [11]. While it is the responsibility of the individual Principal Investigator (PI) to provide adequate safety monitoring, this task can be daunting. Thus, we believe that a DSMB would be helpful for singly institution trials. In fact, in the US, the NIH provides grants from the Clinical Translational Science Award as well as the National Cancer Institute to fund infrastructures for DSMBs for single institution trials. We believe that DSMBs for single institution trials should report to the PI who in turn should report to the IRB.

Advisory role

Data and Safety Monitoring Board members should serve in an advisory role to the independent scientists conducting the trial and the sponsors who fund the trial whether government or industry [12]. Their agreements should not be as consultants to the sponsor but rather as independent scientists preferably to the independent Study Chair (SC), or alternatively, to a Chair of an independent Executive Committee (EC) of trial investigators. The advisory role is meant to maintain the independent roles of the DSMB monitoring the trial, investigators conducting the trial and the sponsor funding the trial. DSMBs should monitor the progress of the trial, which includes numbers randomized, adherence to the intervention, follow-up and other data quality measures. DSMBs function optimally as an independent and multidisciplinary group of experts, which includes methodological and subject matter expertise. In the unlikely event that DSMB members cannot come to a consensus in their recommendations or the investigators or sponsors question or challenge DSMB recommendations, mediation should be attempted [12,13]. If mediation is unsuccessful the DSMB should probably resign.

DSMB Charter

A DSMB Charter that describes its structure and functions should be initially drafted, ideally by the SC or Chair of the EC. The DSMB and SDAC should then revise and approve the Charter prior to randomization of the first subject. The DSMB Charter generally describes the terms of reference as well as the principles, not rules, by which the committee intends to function, which includes the primary role of independent judgments based on the totality of evidence. The DSMB Charter should not and, indeed, cannot be viewed as a legal document covering all possible contingencies simply because it is not possible to conceive *a priori* all the possible scenarios that may emerge during a trial. The DSMB must apply the principles and practical suggestions to the specific scenario that emerges in any given randomized trial [9].

Independent SDAC

The SDAC should be independent, and preferably academically based, to perform the necessary statistical analysis of accumulating interim data and provide scientific and service functions to the DSMB [4,7]. The SDAC must have access to the accumulating data as well as the responsibility and authority to conduct analyses described in the DSMB Charter as well as those in response to the requests of the DSMB, which are likely to evolve as the trial progresses. The DSMB analyses should be both independent of, yet considerate of, and to the extent possible, consistent with, the more detailed and comprehensive analysis plans of the SC and sponsor.

Early termination of trials

Randomized trials should, in general, continue to their scheduled termination or until a DSMB recommends alteration or termination based on the totality of evidence, which includes the emerging unblinded safety and efficacy data from the trial including the primary, prespecified outcome, secondary outcomes, as well as individual components of the primary and other data quality measures including randomization, adherence and follow-up rates [4,14–16,101]. This totality of evidence should also include results from prior research, relevant research just completed as well as new and emerging research. While perfect consistency cannot be expected, general internal and external consistency is highly desirable.

Primary emphasis on totality of evidence

Periodic and systematic reviews of the totality of evidence should also include the worldwide safety experience, as well as protocols of ongoing trials and protocols and final reports of all completed trials. This information should be provided to the DSMB and updated at each open session meeting by the SC, Chair of the EC or sponsor. If the totality of evidence is not sufficient to make rational clinical decisions for individual patients and policy decisions of the general public, then it is appropriate to remain uncertain and the DSMB recommendation should be that there is no cogent evidence to recommend alteration or early termination of the trial.

Statistical stopping guidelines

All statistical stopping guidelines for assessing harm, benefit or futility in the accumulating data, should always be just one component of the overall judgment of the DSMB and, thus should never be rules [3,4,14,15], This is because a decision to terminate a trial early by a DSMB should be based on the totality of evidence,

not just the emerging unblinded data for a primary outcome, and certainly not just a finding of statistical significance, no matter how extreme the p-value.

Monitoring for safety, efficacy & unblinding

Since safety of trial participants is paramount, DSMBs should frequently monitor the emerging data by treatment group and periodically monitor the data for early convincing evidence of efficacy as well as the overall progress of the trial. It is certainly possible for DSMBs to remain partially blinded. This situation is certainly not optimal and DSMBs should never be prohibited from knowing the identity of the treatment arms. IF a DSMB chooses to review data by labeled intervention arms but without knowledge of the identity of the labels, unblinding should be done before any recommendation to alter or terminate the trial is made [17].

Indemnification of DSMB

There should be a commitment by any sponsor to defend, indemnify and hold harmless the DSMB against any third party suits, actions, legal or administrative proceedings, claims, liens, demands, damages, liabilities, losses, costs, fees, penalties, fines and expenses, including without limitation attorneys' fees and expenses and costs of investigation, litigation, settlement and judgment claims arising out of the performance of services, except in judicial finding of willful misconduct or failure to comply with terms of the DSMB Charter [18]. This principle is a logical consequence of legal actions that have resulted in DSMBs being identified as parties in lawsuits as well as being subpoenaed.

Introduction to evolving practical suggestions for DSMBs

There are several evolving practical suggestions for DSMB functioning and meetings that should be considered. These include an initial open session where investigators and sponsor update the DSMB on trial progress, as well as the worldwide safety experience of the intervention, a closed session with only the DSMB and SDAC present to review interim data and a final open session where the general and specific recommendations are transmitted immediately to the SC or Chair of the EC or the sponsor. The initial meeting should be face to face. In practical terms, the DSMB should meet face to face periodically, at least once per year, but far and away, the vast majority of additional meetings can be accomplished via teleconference. The face-to-face meetings should be at least half a day and the teleconferences for 2–4 h. The important underlying principle is to achieve better and prompt communication concerning the progress of the trial between the DSMB, investigators and sponsor [4,6].

Evolving practical suggestions for DSMBs

Initial open session

At each meeting an 'initial open session' should occur that may be attended by the independent DSMB, the independent SDAC, an independent investigator who serves as SC and the sponsor. Updates are provided to the DSMB on the worldwide safety experience as well as other completed and ongoing trials and by the SC on the progress of the trial, which includes the rate of randomization, adherence, follow-up and adjudication rates based on the overall data, which combines the active treatment with the placebo or other comparison group. After each open session meeting the SDAC and DSMB Chair prepare a draft of minutes that are reviewed and revised by the entire DSMB and approved. Following approval, copies are provided to the SC and sponsor.

Closed session

At each meeting a 'closed session' is held that is restricted to the DSMB and the SDAC, as the investigators and sponsors should remain completely blinded to the emerging data until the termination of the trial. At the closed session, typically the SDAC presents the emerging data by treatment group, which includes recruitment rates, baseline data, adherence rates, follow-up rates, serious and serious unexpected, as well as all, adverse events, and, at prespecified intervals, primary and secondary efficacy data. Following their comprehensive review, the DSMB Chair writes a letter to the SC summarizing their recommendations. In usual circumstances that letter states that based on a review of the totality of evidence, including the emerging unblinded (or partially blinded) data, there are no cogent reasons to recommend alteration or termination of the trial. If, however, such evidence emerges to support a recommendation to alter or terminate the trial the DSMB letter to the SC and sponsor should state their recommendations and their rationale in detail. After each closed session meeting the SDAC and DSMB Chair prepare a draft of minutes that are reviewed and revised by the DSMB and approved. Following approval by the DSMB, copies are archived by the SDAC until the end of the trial, at which time they are provided to the SC and sponsor.

Final open session

At each meeting a 'final open session' should be held by the DSMB in which the overall recommendation as well as specific recommendations and suggestions are discussed with the SC and sponsor. This may also be done by means of a telephone call if this is more convenient. The SC and sponsor request further information from the DSMB so they may understand more fully the rationale for their recommendations.

Future perspective

In the future, protection of the independent judgments of DSMBs about safety and efficacy in emerging data are crucial to protection of human subjects and integrity of randomized trials. As the numbers of DSMBs continue to expand it will be helpful to conduct workshops on DSMB membership to expand the number of academic researchers with knowledge of the principles and practical suggestions. Finally, to prevent erosion of the independence of the DSMBs and their SDAC, standardization of the independent scientist agreements, and the basic components of DSMB Charters as well as format and style of open and closed session reports would be helpful. Such standardization might be achieved as a collaboration between independent academic scientists with experience in the structure and functions of DSMBs and SDACs as well as sponsors, both governmental and industry, and regulatory authorities.

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Executive summary

- This article describes evolving principles and practical suggestions for Data and Safety Monitoring Boards.
- The evolving principles include their role as independent scientists, their role as advisory, their Charter, the need for an independent Statistical Data Analysis Center, early termination of trials, the primary emphasis on the totality of evidence, the role of statistical stopping guidelines, monitoring safety, efficacy and the need for unblinding as well as indemnification.
- The evolving practical suggestions include the format of an initial open session, followed by a closed session and a final open session, as well as the need for workshops and standardization.

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- ■ of considerable interest
- ■■ **Provides guidelines for Data and Safety Monitoring Boards of randomized trials.**

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