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Seminar article

Independent data monitoring committees: An update and overview

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Abstract

An independent data monitoring committee's (IDMC's) duty is to ensure that the interests of the patients entered in the trial are being well served (i.e., the risk-benefit ratio is appropriate) and that the scientific integrity of the trial is maintained during the interim between trial initiation and trial completion. Industry sponsors form IDMCs to ensure an independent assessment to assure that the study participants are not exposed to unnecessary or unreasonable risks because of their trial participation and to ensure that the study is being conducted according to highest scientific and ethical standards. IDMCs are needed to analyze interim data for large randomized studies, in particular those that involve multiple sites and important clinical end points such as survival or disease progression. Ethical principles mandate that clinical trials begin with uncertainty as to which treatment is better (clinical equipoise). This uncertainty should be maintained during study conduct and analysis unless there are compelling data that emerge during the conduct of the trial. Group sequential statistical designs offer a mechanism to consider terminating a trial early and the results made public if the interim data become sufficiently compelling. Interim monitoring of safety and efficacy data is an integral part of modern clinical trials.

Keywords: Data monitoring committee; Interim analysis; Group sequential design; Statistics; Clinical trials

Introduction, history, and context

The history of data monitoring committees (DMCs) or independent DMCs (IDMCs) can conceptually be traced back to the "Greenberg Report." This report was made from the Heart Special Project Committee to the National Advisory Heart Council (part of the National Heart Institute) in 1967 and was prepared by an expert committee, headed by Dr. Bernard Greenberg, a statistician from the University of North Carolina. The report was designed to address the management of complex multi-institutional clinical trials and specifically addressed the need for an independent advisory committee that could help to manage large, complex clinical trial endeavors funded by the National Heart Institute. The report was not intended for publication, and it was not actually published in a citable form until 1988 [1]. Even today, that report encapsulates many of the relevant concerns in the organization and execution of large clinical trials.

In 1979, the National Institute of Health (NIH) issued a policy developed by the NIH Clinical Trials Committee [2] and made note that "every clinical trial should have prevision for data and safety monitoring." What was novel then is now accepted as part of the normal conduct of large, complex, multi-institutional trials. A workshop convened by the US Food and Drug Administration (FDA) in 1992 [2] reviewed operational aspects of these committees, and the policy was further developed by a 1994 report by the NIH Office of External Research, which established a committee on clinical trials monitoring. Then, it was generally agreed that monitoring should be proportional to risk, and that risk associated with participation and research should make every attempt to maximize the opportunity for benefit while minimizing the risk to the participants and future participants. In 1998, the NIH issued an updated policy for data and safety monitoring committees [3] and noted that data safety monitoring committees were required for multisite clinical trials involving interventions that entailed potential risk to the participants.

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In 2006, the FDA issued a guidance document for clinical trial industry sponsors on the establishment and operation of clinical trial DMCs. The current FDA guidance was initially issued in draft form in November 2011, and a guidance entitled "Guidance for clinical trials sponsors: On the establishment and operation of clinical trial data monitoring committees" is available on their current web site [4], and this document (or subsequent ones should this version be updated) is essential for sponsors to review before initiating a trial oriented toward regulatory approval.

Today a variety of federal regulations are specific regarding the sponsors of new drugs requiring an IDMC when evaluating new drugs, biologics, or devices. These federal regulations regulate a variety of factors around trial conduct that extend beyond the IDMC's issues. For instance, federal regulations 21 CFR 56.103, 21 CFR 312.66, 21 CFR 812.40, and 21 CFR 812.150(a) govern how the sponsors or individuals conducting a trial are responsible for informing the various institutional review boards (IRBs) regarding significant new information that arises during the conduct. Information such as the IDMC's recommendations after interim data reviews should be communicated to the various IRBs responsible for managing the risks and benefits of the trial at individual sites.

When to engage an IDMC

The primary purposes of the IDMC are to assure that the interests of patients entered in the trial are being well served (i.e., the risk-benefit ratio is appropriate) and the scientific integrity of the trial is maintained during interim analysis. Virtually, all clinical trials potentially pose some risk to patients under treatment. Given that sponsors have vested interests in trial results, it is generally agreed that IDMCs are needed for randomized studies, in particular those that involve multiple sites and end points such as survival or other critically important health outcomes. If there are particular concerns about risks because the treatment may involve toxicity, or there is a relative lack of experience with an agent, making assessments somewhat unpredictable, then these issues need to be taken into consideration when contemplating whether an IDMC is needed.

The clearest reasons to establish an IDMC is to enhance the safety of trial participants where safety concerns may be unusually high. In this case, there is a clear need for regular analysis of interim data in a way that shields the sponsors and steering committee from data that may lead to unblinding. As noted previously, for interim analyses outside the statistical analysis plan (SAP), the trial sponsor should be kept blinded to the data. For SAP-related intermediate end points, the sponsor may have access to binary (yes/no) outcomes of the analyses. The trial then should continue in accordance with the original design and SAP.

It is not just the agent and experience with the intervention that determine risks, certain populations are more fragile than others are, including children, pregnant women, or the elderly, and extra measures of IDMC protection may be necessary regardless of the perceived risks of the drug under study.

The members of the IDMC

The IDMC typically comprises 3 to 5 individuals with extensive clinical experience both in the disease under study and in the management of large, complex clinical trials that represent different expertise and points of view (e.g., patient advocate). Each trial has an IDMC appointed by the trial sponsor, and each trial should have a distinct IDMC. Larger committees have been suggested by some, but the necessity for in-depth discussions and the practicalities of ensuring availability suggest that a small group of committed individuals is best; 2 clearly designated positions are typically present, these positions being the chair and the statistician. The chair is expected to lead the IDMC in deliberations (especially in "closed sessions"), sign the official minutes (after review by all IDMC members), and be responsible for communications to the sponsor. He/she should have considerable experience in both serving on IDMCs and the disease under investigation. Given that many adverse events in patients with cancer are not due to drugs, but rather due to the underlying disease, and that adverse events are typically reviewed in the interim without causal attributions (to the drug or the disease), experienced clinicians familiar with the disease under study are critical for appropriate decision making. A statistician expert in the disease under study might or might not be available, but having an expert with both statistical expertise and disease expertise is clearly optimal. Individuals without experience in the disease under study can be a clear liability during deliberations.

Expert statistical input is an absolute requirement for optimal IDMC function, and it is best if that statistician has experience in the nuances of the disease being addressed. In all instances, for large registrational-type trials, some prior IDMC experience should be a requirement for all IDMC members, given the often complex decision making that can occur during the interim data analysis.

Group sequential monitoring: Why do we need them

The statistical problem is that the type I error rate increases with repeated testing of a hypothesis performed on sequential data from a clinical trial [5]. Type I error is defined as the probability of rejecting a null hypothesis when it is true. Multiple sequential testing of data always increases the probability of a false-positive result if no adjustment is made on the type I error rate. To illustrate this concept, suppose that an investigator would like to analyze