Ensuring Patient Safety and Scientific Credibility in Clinical Trials

Operating behind the scenes as clinical trials of new treatments progress, data safety and monitoring committees (DSMCs) assure that studies are safe, well run, and will yield a reliable answer when complete. The DSMC should assure subjects and the public, as the trial is underway, that continued use of the investigational treatments either doesn't cause harm or is so overwhelmingly beneficial that it is unethical to continue randomization to the standard therapy. They are meant to resolve the tension between the study subject, who has volunteered to be involved in an experiment with the assumption that the test will be safely carried to its conclusion, and the investigator, who may be tempted to publish or disseminate the results too early, before they are assured that the results are real and not due to a chance occurrence.

Investigators and the public are often unaware of the DSMC's important role in maintaining scientific integrity and safeguarding patients unless they learn that a trial is halted because of evidence of unacceptable harm. Although all trials should be monitored for safety and for appropriate data procedures, not all trials require the level of scrutiny that DSMCs provide. DSMCs play a critical role in large, multicenter, randomized trials (typically phase III trials) that examine treatments intended to prolong life or reduce the risk of a major adverse health outcome, such as cancer relapse or death. Phase III studies, where mortality and/or major morbidity are study end points, and phase II trials with multiple end points, typically incorporate DSMC monitoring into their design. Members of DSMCs are experienced clinical trialists, but are not otherwise materially associated with the trial.

The Women's Health Initiative, the large-scale national study that examined the benefits and risks of hormone replacement therapy on many end points, including breast cancer, is a recent high-profile example that illustrates the importance of evaluations or "peeks" at the data as it develops. With each planned peek, there is a predetermined statistical test with its associated significance or *P* value. If the developing data show results that cross one of these boundaries, the DSMC can recommend to the investigators that the trial be stopped or otherwise modified to protect the interests of the participants. The Women's Health Initiative was set to conclude in 2005, but in May 2002, it was halted because the trial's data monitoring committee found that the risk of invasive breast cancer exceeded the predetermined stopping boundary for this adverse effect.

"An oncologist needs to know that a data monitoring committee examines data right through the course of the study," said Susan Ellenberg, PhD, Associate Dean of Clinical Research and professor of biostatistics at the University of Pennsylvania. "The committee's role is to watch the data." Specifically, she explained that the fundamental roles of a DSMC are to examine accumulating efficacy and toxicity data, to recommend study termination or continuation, to advise on other study notifications, to review and approve the study protocol, to assess study conduct, and recommend pertinent additional analyses. Dr Ellenberg has served as statistician on many National Institutes of Health DSMCs, and she has also written extensively about them.[1]

Regarding a National Cancer Institute (NCI)–funded cooperative group randomized trial, "when a patient asks you how a trial is doing, you can honestly tell them that an independent data monitoring committee is reviewing the trial every six months for untoward toxicity," said Mark Green, MD, vice chair of the Cancer and Leukemia Group B (CALGB) and chair of its DSMC. "If an interim analysis gives any safety or efficacy signal, we have the opportunity to stop the trial early." Built into the standard operating procedures of the committee are mechanisms for real-time monitoring and, according to Dr Green, "This adds another level of protection for the individual and integrity of the trial."

A DSMC has several options when it is alerted to safety and efficacy concerns. For example, Dr Ellenberg pointed out "If an interim analysis of a drug with multiple disease end points shows that in the highest dose, toxicity is too high to be tolerated, that study arm might be dropped." Eligibility might be narrowed or consent forms adjusted as more information becomes available.

Independence and Objectivity

In selecting committee members, it is essential to pick candidates that are independent and objective. Importantly, members should be free of any major conflicts of interest, whether financial, intellectual, or patient involvement, according to Dr Ellenberg. Members should show no bias for a specific trial result and uphold the standard that the interim data should be considered highly confidential. At least one biostatistician, and oftentimes more, serve on most DSMCs. The biostatisticians on board should be facile in working with clinical trial statistics and sequential analysis of study data.

"One thing that is important [for oncologists to realize] is that not all people sitting on a monitoring committee are oncologists," said Alan Lyss, MD, an oncologist at Missouri Baptist Cancer Center (St Louis, Missouri) who enrolls

patients onto clinical trials through the NCI CALGB. "There are also patient advocates," added Dr Lyss. "The goal is to make the committee completely independent. None of the participants are really stakeholders."

Committee Charter

Before a clinical trial begins, the study sponsor and DSMC should establish a charter describing its standard operating procedures. The charter should outline the interim monitoring procedures, format for meetings and data reviews, procedures for evaluating conflicts of interest for potential committee members, and access to ongoing data of the committee. The trial sponsor may also consider submitting the charter to the Food and Drug Administration (FDA) and other regulatory bodies with jurisdiction.

FDA Guidance on DSMCs

The FDA issued a Final Guidance on the Establishment and Operation of Data Monitoring Committees in March 2006.[2] Although the information is broad, one area that is spelled out in great detail concerns access to interim comparative data.

According to the report, "sponsor exposure to unblinded interim data, through the DSMC or otherwise, can present substantial risk to the integrity of the trial. One concern is that unblinding of the sponsor increases the risk of further unblinding, for example of participants, potential participants, or investigators, thereby potentially compromising objective safety monitoring, equipoise, recruitment, administration of the intervention, or other aspects of the trial."

Another reason for ensuring that study data is highly confidential is that sponsor access to data could introduce bias or impair trial management or make the trial results uninterpretable as a result.

In cases where the sponsor sees a compelling need to review data, the sponsor should discuss the request with the FDA and the Monitoring Committee in advance.

The CALGB Data and Safety Monitoring Board Experience

Dr Mark R. Green says that the DSMC has dealt with some challenging decisions during his 11-year tenure on the committee, for example, the early release of data from CALGB 9344 concerning the potential benefit of the addition of paclitaxel after "standard" doxorubicin and cyclophosphamide as adjuvant therapy for selected patients with resected breast cancer.

"We have a well-defined charter, good SOPs [standard operating procedures], consistent administrative support, and committed medical professionals, statisticians, and lay people from within and outside of CALGB who are all critically important," he said. The CALGB-DSMC consists of approximately a dozen people from many different backgrounds, including a physician and a statistician from the Cancer Treatment Evaluation program through NCI and a representative from the Division of Cancer Prevention and Control as nonvoting members. "In my view, we have worked very well together. Although each person is initially appointed for a 3-year term, we often ask people to stay on for 6 years," according to Dr Green. "To my knowledge, we have had no breaches of confidentiality and no *soto voce* 'minority reports.'"

In selecting people for the DSMC, "it is best to be careful to tell candidates up front that the work can be time intensive and that they may be called on to make decisions that can be uncomfortable." Dr Green has helped CALGB Chair Richard L. Schilsky, MD, select candidates for consideration. In addition, "you want to draw in individuals from a variety of venues, representing different kinds of experience, who are sophisticated about the process, and provide perspectives that reflect all stakeholders," said Dr Green. He considers outside lay people critically important in the DSMC process.

Taking a step back, Dr Green asked: "Have we always been 100% prescient about outcomes emerging down the road? Clearly, the answer to that is no. But with the benefit of hindsight and mature data, does it still seem that process (and patients) has been very well served? Here, I think the answer is a resounding yes."

DOI: 10.1200/JOP.0824604

References

1. Ellenberg SS, Fleming TR, DeMets DL: Data monitoring committees in clinical trials: A practical perspective. London, United Kingdom, John Wiley & Sons, 2002

2. FDA guidance for clinical trial sponsors: Establishment and operation of clinical trial data monitoring committees, March 2006. http://www.fda.gov/cber/gdlns/clintrialdmc.htm