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10 Data and Safety Monitoring

By Susan Partridge, BSN, MBA, CCRC and L. Steven Brown, MS, CPH[1]

Introduction

Data and safety monitoring of a clinical trial consists of oversight of an ongoing study. This oversight ensures that study participants are protected from unforeseen and potentially avoidable risks, and that the trial produces valid data. The premise for data and safety monitoring is that despite one's best efforts in designing a trial, one can never fully anticipate what happens as a study progresses. During the course of a trial, study populations may respond differently than expected, accrual of subjects may be skewed for unforeseen reasons, unexpected operational or compliance problems could impact outcomes, unanticipated adverse events or new drug toxicities may emerge, and minor adverse events may prove to be more important than one thought. As a result, data and safety monitoring has evolved to become one way that the clinical research enterprise can ensure the quality and safety of the trials they conduct.

This type of monitoring is different from sponsor-directed monitoring; the latter is also conducted in real time, but the purpose of sponsor-directed monitoring is to verify study site performance and compliance with the protocol, sponsor requirements, and good clinical practices. Data and safety monitoring is also distinct from the requirement for study review and approval by an institutional review board (IRB).

Data and safety monitoring takes into consideration what could possibly happen during a trial, not just what is expected to happen. Prior to the start of a study, a plan outlines how accumulating data will be reviewed to focus on the following:

1. study participant safety and protection from risks;
2. trial validity and integrity;
3. ensuring that the study continues to be ethical, scientifically valid, worthwhile, and feasible for the entire study period; and,
4. ensuring that the trial is stopped as soon as reliable conclusions can be drawn from the data.

Another important element of effective data and safety monitoring is the ability to objectively assess the data and make recommendations to continue the trial as designed, modify the trial or terminate the trial. Study sponsors and investigators may have recognized or unrecognized interests in the conduct and results of a trial. Ensuring that data and safety monitoring is performed by individuals who are not only knowledgeable but independent of the vested parties is critical to unbiased decision making.

Data and Safety Monitoring: A Background

Data and safety monitoring and the introduction of data monitoring committees (DMCs) can be traced to the 1960s. It started with the Framingham Heart Study, which began in 1948. Starting in the mid-1950s, the study began releasing its findings about the role of cigarettes, high blood pressure, and elevated cholesterol in the risk

of heart disease. Those results led to the development and National Heart Institute (NHI)[2] funding of the Coronary Drug Project, a nine-year trial from 1966-1975. The project was designed to evaluate the long-term efficacy and safety of five lipid-influencing drugs and their impact on the incidence of myocardial infarction (heart attack). To meet statistical requirements, the study methods called for enrollment and long-term follow-up of more than 8,300 subjects, resulting in an operationally challenging study involving 53 study sites. Because trials of this size, complexity, and cost were not typical at the time, there were many questions by study investigators and sponsors about how best to oversee and ensure the participants' safety and the validity of the trial while it was ongoing.

The NIH commissioned an external advisory group to develop a plan for the conduct of these types of trials. Under the leadership of Dr. Herbert Greenberg, the Heart Special Project Committee produced the report in May 1967, titled Organization, Review, and Administration of Cooperative Studies (Greenberg Report): a Report from the Heart Special Project Committee to the National Advisory Heart Council. The committee recognized that interim monitoring of study data was essential for ensuring study participants' safety, and that individuals closely involved in the design, sponsorship, or conduct of the trial may not be fully objective in reviewing that data. The report called for establishing an expert panel of advisors who could review the accumulating data in an unbiased manner and make recommendations. The Greenberg Report recommended that this group of advisors (which we now call a Data and Safety Monitoring Board or Committee) should be "… a Policy Board or Advisory Committee of senior scientists, experts in the field of study but not data-contributing participants in it, is almost essential for a large complex cooperative project."[3]

The Greenberg Report also anticipated that not all studies should be permitted to continue to completion:

> A mechanism must be developed for early termination if unusual circumstances dictate that a cooperative study should not be continued. Such action might be contemplated if the accumulated data answer the original question sooner than anticipated, if it is apparent that the study will not or cannot achieve its stated aims, or if scientific advances since initiation render continuation superfluous. This is obviously a difficult decision that must be based on careful analysis of past progress and future expectation. If the National Heart Institute must initiate such action, it must do so only with the advice and on the recommendation of consultants.[4]

The Greenberg Report and Coronary Drug Project contributed significantly to the way in which clinical research is practiced today. In addition to establishing the concept of formal independent data and safety monitoring, the Coronary Drug Project is also notable for establishing a model for the design, organization, standardization, quality control, and monitoring of multicenter trials.

In summary, the Greenberg Report defined the forerunner of the current DMC: a body of experts independent of the study that conducts ongoing reviews of the study's data in order to ensure the scientific and operational integrity of the clinical trial. The following ideas, generated by the Greenberg Report, became official National Institute Health (NIH) policy by 1979:

1. Every clinical trial should have provision for data and safety monitoring.
2. The mechanism(s) for data and safety monitoring should be presented to and approved by the Institutional Review Board as an integral part of its review of the project proposal. A variety of types of monitoring may be anticipated depending on the nature, size, and complexity of the clinical trial. In many cases, the principal investigator would be expected to perform the monitoring function.

3. Large or multicenter trials and trials in which the protocol requires blinding of the investigators, should have a data and safety monitoring unit. The unit should consist of clinical experts in the disease under investigation, biostatisticians, and scientists from other pertinent disciplines. Physicians engaged in the care of study patients or directly responsible for evaluating clinical status are excluded.[5]

The NIH standard is closely echoed in the 1998 NIH Policy for Data and Safety Monitoring. It is also reflected in the definitions we see today in the FDA guidance of 2006: "A clinical trial DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from one or more ongoing clinical trials. The DMC advises the sponsor regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial."[6]

Likewise, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance of 2005 defines a data monitoring committee as: "A group of independent experts external to a study assessing the progress, safety data and, if needed, critical efficacy endpoints of a clinical study. In order to do so a DMC may review unblinded study information (on a patient level or treatment group level) during the conduct of the study. Based on its review, the DMC provides the sponsor with recommendations regarding study modification, continuation or termination."[7]