Data Monitoring in Clinical Trials

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Editors

Data Monitoring in Clinical Trials

A Case Studies Approach

With 40 Illustrations

Springer

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Preface

Monitoring of clinical trials for early evidence of benefit and harm has gotten considerable attention.[1] More formal guidelines and requirements[2–4] have evolved in recent years, but in fact monitoring of trials is a practice that has been going on for almost four decades.[5] For trials that involved conditions or interventions with serious risks, such as mortality or major morbidity, the tradition and policy has been to have an independent monitoring committee to review accumulating data for evidence of harm or convincing benefit that would require modifying or terminating a trial early. During the past four decades, many trials have had monitoring committees to assume this responsibility. With the new emphasis on monitoring, this type of activity is increasing dramatically as the number of clinical trials being conducted to evaluate new interventions for patients or participants with serious risk or serious outcomes also increases. For example, policies of the National Institutes of Health (NIH) in the United States (US) call for monitoring committees for all phase III trials.[2] Guidelines of the US Food and Drug Administration suggest such committees for trials of high-risk interventions or patients at high risk.[3]

As the number of monitoring committees increases, the challenge exists to pass along the experiences and best practices of the monitoring process to colleagues who are assuming this responsibility for the first time. Textbooks such as the one by Ellenberg, Fleming, and DeMets[6] provide many of the basic principles for monitoring committees. Other texts such as those by Friedman, Furberg, and DeMets;[7] Meinert;[8] Pocock;[9] Jennison and Turnbull;[10] and Piantidosi[11] provide statistical fundamentals and methods for the design, monitoring, and analysis of clinical trials. This text is intended to complement those texts by providing a collection of examples or case studies of monitoring experiences from a variety of trials across different disease disciplines. Each case study will describe the background of the individual trial, summarize the overall results, review the critical issues that emerged in the monitoring of the trial, and finally reflect on the lessons learned from that trial. All of the examples presented share the complexity of the process of monitoring and the lesson that no single rule or algorithm can replace the wisdom and judgment of a monitoring committee. Through these examples, we hope to share the experience of these past committees and pass along some of their sometimes hard-earned wisdom.

Selection of the case studies was largely based on the collective experiences of the editors and their interactions with colleagues involved with clin-

ical trials. Many of the 29 examples are from the field of cardiology, where the practice of monitoring committees was established early. However, there are examples from other disciplines. Regardless of the disease, many of the lessons learned and practices are useful for any trial. Individual colleagues were invited to present the monitoring experience of a trial they were involved with as they saw it and experienced it. Their presentations and discussions do not necessarily represent the official view of either the trial sponsor, the trial investigators, or the trial monitoring committee. We have tried to get representation from each of these constituencies on many of the trials when possible.

For most of the past four decades, the existence and practice of monitoring committees has not been widely recognized or understood. Our belief is that clinical research will benefit with better understanding of the process by both the research community and the interested public. The intended audience for this book are those who are planning to serve on a monitoring committee or are already on one and wish to gain further insight into the monitoring and decision-making process. We also believe that these examples will be useful to investigators as they design their trials and propose monitoring procedures; to sponsors, who typically receive monitoring committee recommendations, and to regulatory agencies, who often must review the results of trials that have been monitored by a committee. In addition, Institutional Review Boards may benefit from these case studies since they ultimately have responsibility for protecting participants at the local level but must rely on the monitoring committee process for most multicenter trials and increasingly for institutional trials. Journal editors, sciences writers, and practicing physicians may also find these case studies instructive.

Over the past four decades, many individuals have served on monitoring committees and participated in the monitoring of many challenging studies. We wish to thank all of those individuals who have contributed directly or indirectly to the practice of monitoring and from whose experience we all have benefitted. We have listed in Appendix 1 the individuals who have served on the committees for the trials presented as case studies in this book and wish to thank them in particular.

ACKNOWLEDGMENTS

We also want to thank the many contributors to the drafting of these case studies. We have listed them in the section which follows. They contributed their experiences because of their commitment to clinical trials, the monitoring process, and to teaching the next generation of clinical trial researchers about the important process of monitoring trials for early evi-

dence of benefit or harm. We are grateful that they accepted our invitation and persevered through the drafts and editing process.

We would also like to acknowledge the substantial contributions by Ms. Suzanne Parman for her editorial and logistical support. Without her dedication this text could not have been completed in a timely fashion.

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Section 4: Special Issues

SECTION 1

Introduction/Overview

CHAPTER 1

Monitoring Committees: Why and How

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INTRODUCTION

Monitoring of clinical trials encompasses many concepts. Among these concepts are oversight of trials to ensure that the protocol meets high standards, is feasible, ethical, and is being adhered to; that participant enrollment is satisfactory; that study procedures are being done properly; and that the data are of high quality and complete. Most importantly, however, monitoring is done to make certain, to the extent possible, that participants are not being unduly harmed, either directly by the intervention or indirectly by not receiving the current standard of care. Investigators cannot wait until the end of a clinical trial to examine the data and discover that a particular intervention was beneficial, when they could have made that discovery earlier, and taken appropriate action to help people receive the better treatment. Perhaps even more importantly, investigators cannot wait until the end of a trial to discover that a new treatment that was thought to be beneficial was, in fact, harmful. They must make those decisions as early as possible in order to save lives and preserve the health of the volunteer participants. This is a moral obligation of all who are involved in clinical trials. Once a decision to stop a study has been made, study participants expect, and have a right, to be informed of that decision in a timely manner.

The kind and amount of monitoring depend on the phase of the trial (early or late), organizational structure (single or multi-center), nature of the intervention (how safe it is known to be), whether the trial is open or blinded (sometimes termed "masked"), duration of the trial, and the types of participants being studied (how vulnerable they are thought to be). Many small, single-institution trials can be adequately monitored by Institutional Review Boards (IRBs) that rely on day-to-day oversight by investigators or other individuals tasked with the responsibility. Other trials, however, are best monitored by formally established committees, which provide input to IRBs. These committees go by a variety of names, including Data and Safety Monitoring

Boards, Safety and Monitoring Efficacy Committees, and Data Monitoring Committees. These committees are commonly used for late-phase clinical outcome trials, which are typically multi-center; early-phase trials involving invasive or potentially dangerous interventions; and trials that enroll participants who are particularly vulnerable, such as children, extremely sick patients, and others incapable of providing true informed consent.

HISTORY

The concept of having committees monitor clinical trials goes back at least to the mid-1960s. Among the first trials using such a group was the Coronary Drug Project, or CDP[1] (also see Case 12). The CDP, which began enrolling participants in 1965, was a clinical trial comparing five lipid-modifying drugs against placebo in 8,341 participants who had had a myocardial infarction. The trial included 53 clinical sites, a data coordinating center, and central laboratories, plus an administrative office at the then National Heart Institute of the National Institutes of Health (NIH). Because of the large size and many participating units, the CDP had a formal committee structure, which included a Steering Committee of selected investigators, to help manage the trial. Importantly, there was a Policy Board that oversaw the trial and advised the National Heart Institute. This group was composed of nationally respected scientists representing different fields of expertise who were not involved in the actual trial. As stated in the CDP protocol (see reference 1 for a summary of the protocol), the "Policy Board is to act in a senior advisory capacity to the Technical Group [the committee of all the investigators] in regard to policy questions on design, drug selection, ancillary studies, potential investigators and possible dropping of investigators whose performance is unsatisfactory."

Because of uncertainty as to the best way of organizing and overseeing the CDP, the National Heart Institute, in 1967, commissioned a report, entitled, "Organization, Review, and Administration of Cooperative Studies."[2] This report is also known as the Greenberg Report, after the chairman of the committee that developed it, Bernard Greenberg. This report contained many recommendations, including several that are relevant to trial oversight and data monitoring:

> A Policy Board or Advisory Committee of senior scientists, experts in the field of the study but not data-contributing participants in it, is almost essential.
>
> 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.

Until 1968, CDP investigators were informed of accumulating outcome data. But in April of that year, the Policy Board recommended that such data not be made available to the investigators. Consistent with recommendations from the Greenberg Report, it further recommended that a Safety Monitoring Committee be formed to review those data on a regular basis. If safety issues arose, they were to be referred to the Policy Board, which considered them and made recommendations to the National Heart Institute. Initially, the members of the Safety Monitoring Committee were staff of the National Heart Institute, data coordinating center staff, the chairman of the study Steering Committee, the director of the electrocardiogram reading center, and a statistician from outside the study. Others with relevant expertise from outside the study were added subsequently. Both the Safety Monitoring Committee and the Policy Board met regularly to review study progress and accumulating data, but the Safety Monitoring Committee performed a more in-depth review of the data. It made recommendations to the Policy Board with regard to protocol changes or safety concerns.[3]

The Greenberg Report was extremely influential, in that, essentially, all future cooperative clinical trials funded by the National Heart Institute and its successor incarnations incorporated the idea of a separate committee that reviewed outcome data and made recommendations with regard to trial continuation or modification.

Although the details varied among institutes, other NIH institutes then developed monitoring systems over the years. Indeed, the concept of having an external, independent data-monitoring committee spread to clinical trials supported by industry and internationally. The NIH and the U.S. Food and Drug Administration have also developed guidelines for use of such committees.[4,5]

STRUCTURE AND OPERATIONS OF MONITORING COMMITTEES

Usually, voting members of monitoring committees are independent of the study investigators and sponsor. That is, no one who is involved with either the conduct of the trial or its funding and management should serve as a voting member on the committee. The committee may need to make recommendations that go against the interests of investigators and sponsors. These recommendations may range from dropping poor-performing centers, to alerting participants about safety concerns, to stopping the trial because

of adverse events. Investigators and sponsors who have financial or intellectual interests in particular outcomes have a potential conflict of interest and should not make such recommendations or be involved in the deliberations. How uninvolved a member needs to be is a matter of judgment. Can a member be from the same academic department as an investigator? Can they be from the same university? Is it appropriate for a member to be from the same organization as the sponsor, but in a different office or division from the one managing the trial? As a general rule, the more distant and independent, the better. But complete independence should not come at the expense of needed expertise. If the best person to serve on the committee is from the same university as one of the investigators, then that could outweigh concerns over potential or perceived conflicts of interest. In such cases, there needs to be sufficient care to ensure there are no real and important conflicts of interest on the part of the member and to minimize perceived conflicts.

The issue of conflict of interest applies to more than just the organization to which the committee member belongs; it also applies to financial holdings of the member and to future potential profits through holding of patents. All prospective members must be willing to disclose publicly, on an ongoing basis, their financial holdings and consulting or other relationships with companies that manufacture the drug, device, or biological being tested or with companies that manufacture direct competitor products. Having such holdings or relationships would not automatically exclude someone from serving on a monitoring committee, but there needs to be an open assessment of these potential conflicts and their magnitude. If conflicts do exist, it would be inappropriate for the member to vote on issues that relate specifically to that conflict.

What sorts of people should serve on a monitoring committee? The needed expertise is of several kinds. First, one or more experts in the scientific field of inquiry, including knowledge about the intervention, are necessary. Also essential are one or two experts in clinical trial design and biostatistics. Beyond that, monitoring committees often have bioethicists and/or patient advocates, especially for NIH-sponsored trials. Above all, at least some of the members should have served before on a monitoring committee. Experience in that activity is invaluable.

Others who may attend portions of meetings of the monitoring committee, but who are not formal, voting members, include senior investigators, representatives of the sponsor, and, although uncommon, someone from a drug (and device) regulatory agency. Attendance by someone from a regulatory agency can become complicated when the trial is multinational.

Monitoring committee meetings are typically divided into open, closed, and executive sessions. During the open session, no blinded outcome data

are disclosed or discussed (even if the trial itself is open, or unblinded). Rather, administrative issues, study progress, problems in participant enrollment, baseline data, participant adherence, and other similar matters are discussed, with a study investigator present to answer any questions. Unblinded outcome data, by study group, are presented and discussed during the closed session. Usually, attendance at this session is restricted to committee members and a study biostatistician who presents the data. It is generally accepted that if the sponsor is a drug or device company, attendance by that representative at the closed session is not a good idea. An exception would be if the study biostatistician is an employee of the company. In this case, however, rules as to what the statistician is and is not allowed to communicate to the sponsor must be established in advance. If the sponsor is a government agency with no commercial interests in the trial outcome, such as the National Institutes or Health or the Department of Veterans Affairs in the United States, some have argued that attendance is permissible, whereas others think that the same rules as apply to industry-sponsored studies should pertain. There is also disagreement as to whether the biostatistician presenting the data should be part of the investigator group, part of the study data analysis group but separate from the daily study management activities, or completely independent of the investigators. This chapter will not review the reasons for these differing views, but simply recognize that they exist.[6]

Finally, there may be an executive session, where only the voting members of the committee and perhaps an executive secretary are present. This session allows the members to discuss issues more freely. If there are no contentious problems, however, the executive session may be unnecessary. The committee members can decide that at the time of the meeting.

There are two general models for monitoring committees. In the first, a committee is specifically established to monitor an individual trial. This is usually done when the trial is large and likely to go on for several years. In the second, a committee will monitor more than one trial. This is common in the case of networks of investigators that develop and conduct several or even many related protocols, such as for cancer and AIDS trials, and for IRB-appointed institution-wide monitoring committees. The advantages of the former are that the monitoring committee members have expertise in precisely the area of study and they can devote sufficient time to monitoring that single study. The primary advantage of the latter is that it is more efficient to have one committee monitor multiple protocols.

The frequency with which monitoring committees meet is determined by what is necessary to ensure the safety of the participants. The nature of the condition being studied, the kind of intervention, and how rapidly new data accumulate all influence that frequency. Typically, committees that monitor long-term trials meet every six to twelve months or when a speci-

fied percentage of participants have been accrued or a specified number of events have occurred. In addition, the option to review safety data in between, either in person or through telephone conference calls, should exist. Often, ongoing reports of individual adverse events are provided to the chairperson of the committee, who can decide whether or not to convene the full committee.

MONITORING PROCESS

It is not possible to foresee and prevent all harm. But the main purpose of monitoring is to make sure that no avoidable harm comes to the study participants as a result of being in the study. No study is risk free, but any potential harm must be counterbalanced or outweighed by potential benefits. To that end, the monitoring committee must be satisfied that the study is designed in as optimal a fashion as possible, with all reasonable safety precautions. After the study is underway, the committee regularly looks at accumulating data. In particular, it monitors study outcomes—both primary and secondary endpoints—and potential adverse events, including laboratory data, as appropriate. The committee must expect that unforeseen adverse events can and will occur, and must be prepared to modify its procedures to prevent or minimize the consequences of unexpected events.

In addition, because a study that is not well conducted cannot justifiably put participants at risk, the monitoring committee reviews study progress, in order to ensure the integrity of the trial. For example, is accrual of participants proceeding on schedule, and if not, how long will it take and will enough participants be entered eventually to address adequately the study hypotheses? Are study forms being completed and are the data of high quality? Are study procedures being done in a timely fashion? Are the analyses up-to-date? Are the participants taking the study medications as prescribed?

Monitoring committees must consider several principles. Various textbooks cover these in some detail,[7-10] so we will only summarize them here.

First, of course, are ethical standards. The trial must begin in a position of clinical equipoise.[11] That is, the informed scientific and medical communities do not know which of the approaches being tested in the trial is preferable. As the data begin to accumulate, the monitoring committee may decide that the trends in the primary outcome are so strong in one direction or another (i.e., in favor of or against the new intervention) that clinical equipoise is no longer tenable and the study must be stopped before its scheduled end. The study has achieved its goal of providing an answer. The sections that follow discuss many examples. Judgment, as well as science and statistics, enter into the decision. Connected with that is a balance of bene-