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.
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> A mechanism must be developed for early termination if unusual circumstances dictate that a cooperative study should not be continued.
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> 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-

fits and harms. Even though the primary outcome may not be clear, secondary outcomes or other clinical measures may strongly trend positively or negatively. The committee must decide if adverse events are such that continuing the study cannot be justified. This is often less a statistical decision than a medical and ethical judgment. Another important ethical issue concerns the tension between responsibilities to the study participants, to those yet to enter the study, and to the public. The data from a trial may not be sufficiently persuasive to change entrenched medical practice, but because of adverse trends, the monitoring committee has concerns about the safety of the participants already in the study and may be reluctant to allow enrollment of additional participants. If the study is stopped too early, medical practice may not be altered, and the study participants will have been put at risk to no purpose. If the study is not stopped early, additional harm may come to the study participants. The World Medical Association Declaration of Helsinki[12] clearly states that the well-being of trial participants takes precedence over societal interests. Often, however, the decisions are not clear-cut, and monitoring committees often must wrestle with these difficult issues.

A second principle, and one that drives much of data monitoring, is the concept of repeated looks at the data. Ethically, investigators and sponsors, by means of the monitoring committees, are bound to examine trends in the data during a trial. Unfortunately, the more we look at accumulating data, the greater the possibility of observing a nominally significant result by chance. Therefore, we increase the false-positive rate above that with which the study was designed (e.g., 0.05 or 0.01). For example, if a study is designed with at a 5% level of significance, and the data are looked at twice, the true false-positive, or type 1 error rate is not 5%, but about 8%; if the data are examined five times, the false-positive error rate would be about 14%.[13] Various statistical approaches to this problem have been developed, some of which will be used in the examples in the book. We will not go into detailed statistical issues here. The key point, however, is that because repeated testing of the data can affect statistical interpretation, the issue must be part of data monitoring.

Similarly, monitoring committees look at many outcomes, not just the primary one, and they usually look at different subgroups of participants. As with looking many times at a single outcome, when multiple outcomes, or multiple comparisons, are considered, the standard level of significance does not apply. Care and judgment must therefore be used in making decisions based on nominally significant results from these outcomes. As noted before, however, the safety of the participants is paramount. Therefore, the monitoring committee needs to pay serious attention to adverse events, even if they are of questionable statistical significance or have not been prespecified as outcomes of interest.

Investigators usually want to be very sure when they make claims about the benefits of a new drug or device, but they generally are not interested in proving something is harmful, using the usual level of statistical significance. Therefore, monitoring may be "asymmetric," in the sense that a different level of assurance is used for benefit than for harm.[7]

No clinical trial is done in isolation. Clinical trials are only started after there is considerable basic research, animal studies, and epidemiologic work. And of course, other clinical trials may be addressing the same or similar questions. The monitoring committee needs to be alert, not only to research done in the past that may have led to the clinical trial it is monitoring, but to ongoing research elsewhere that may affect the conduct and feasibility of, or indeed the ethical justification for, the trial. Information from other studies can necessitate modifying the protocol, revising the consent form, or even stopping the study. An example of this last situation is given in Case 24.

Finally, there are a variety of factors that affect the interpretation that the monitoring committee brings to the data it is reviewing. Among these are baseline characteristics of the study participants, including balance between the study groups, use of concomitant therapy by the participants, adherence to medication or procedures, and timeliness of the data that are being monitored. Monitoring committees need to consider these factors when making recommendations to change the protocol or discontinue the study.[3,7]

As noted, monitoring committees can make various recommendations in the course of the study. If the study is progressing reasonably well, with no clear evidence of major toxicity or overwhelming benefit, the committee would recommend continuing the trial without any changes to the protocol. Some circumstances may lead to a recommendation to continue, but with a protocol modification. For example, participant entry criteria may be restricted if it is noticed that certain subgroups of participants seem to be unduly harmed (see Case 23). Or additional measures of possible toxicity could be added. Or if an adverse event not mentioned in the protocol or consent form is observed and thought to be related to the intervention, the investigators and IRBs would be notified and the consent forms appropriately changed (see Case 17).

The monitoring committee could recommend stopping the study (or, in the case of a multi-armed study, dropping one arm) for any of several reasons. These include such overwhelming evidence of benefit from the intervention that the study hypothesis was answered earlier than expected or sufficient evidence of unexpected serious harm. Several examples of these are provided in this book. The committee may also recommend stopping early because there is little or no chance that the hypothesis can be adequately addressed. This may happen because participant recruitment is extremely

slow, because compliance with the intervention is poor or there are a great many "cross-overs," or because the control group event rate is much lower than expected. It may also happen because even if the study were to continue to its scheduled end, no clinically useful information would be derived. In all these cases, if the usefulness of what will be learned is so limited that it does not outweigh the discomfort and possible harm to which the participants are being subjected, it is inappropriate to continue the study. Finally, the monitoring committee may recommend early stopping because other research studies have answered the question being posed, and the trial is no longer important or continuation would be unethical (e.g., proven therapy is being withheld).

In rare circumstances, the monitoring committee might recommend extension of the trial beyond its scheduled duration. Typically, this happens when the control group event rate is lower than planned, and a relatively short extension would yield enough outcome events to answer the question. An alternative to this is to design a trial that continues until a pre-specified number of events occurs. This alternative is preferable from a study-design perspective, and has been successfully used in some trials (see Case 8 and the REMATCH study[14]), but for fiscal and management reasons, the uncertainty of duration may be difficult for a sponsor to accept.

INTERACTIONS BETWEEN THE MONITORING COMMITTEE AND OTHERS

Because of its central role in ensuring safety and the integrity of the trial, the monitoring committee has direct or indirect interactions with several other groups. It may be appointed by, and report to, the sponsor of the trial. This is the case with most NIH funded trials. It may also be appointed by and/or make recommendations to an executive committee of the investigators.

If the monitoring committee advises the sponsor, rather than the investigators, the relationship between the monitoring committee and the investigators is indirect. The sponsor of the trial, after receiving the committee recommendations, would communicate with the investigators, informing them either that the study is proceeding well, or that certain changes need to be made. The study investigators, in turn, would inform the study participants of any recommendations, including, potentially, providing them with a revised consent form.

The IRB at each clinic has the legal responsibility to oversee the protocol at that clinic, and to ensure local participant safety. In multi-center trials, this responsibility is generally ceded to the monitoring committee, which is the only group that knows the outcome data across the entire study. When

initially reviewing trial protocols, the IRBs should be informed about the plans for monitoring, so that they are comfortable that it will be done in an appropriate manner. In return for the authority to conduct the monitoring, the monitoring committee must keep all IRBs informed of its recommendations, and of any unexpected adverse events or protocol changes. For studies sponsored by the NIH, a policy requires that reports of the recommendations and any safety concerns of the monitoring committee be sent to all involved IRBs after each monitoring committee meeting.[15] We recommend that a similar policy be adopted for all industry-sponsored trials.

When the clinical trial is being conducted under the auspices of drug and device regulatory agencies, those agencies must also be kept informed of serious adverse events. Reports summarizing the committee recommendations and any protocol modifications must be communicated to the regulatory agencies, typically through the study sponsor.

Finally, it should be emphasized that except for these communications, all members of monitoring committees are expected to maintain confidentiality. Discussions of data or study issues outside of the meetings or with anyone else are completely inappropriate.

SUMMARY

This chapter reviews several key issues with regard to monitoring committees, so that the examples and discussions in the rest of this book may be better understood. The primary purpose of independent monitoring committees is to ensure, to the extent possible, that participants in clinical trials are not unduly harmed. A secondary purpose is to enhance study quality and integrity. The use of monitoring committees in late-phase and selected early-phase clinical trials has become commonplace. The compositions of these committees and the monitoring process they follow have also become more standardized, although some differences remain. Principles underlying data and safety monitoring, namely, maintenance of ethical and biostatistical standards and of public trust, and the need for considerable judgment and interpretation, are essential in the committee process. The monitoring committee also operates in the context of a larger research and participant safety environment. Therefore, recommendations from the committee must be implemented in that context.

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