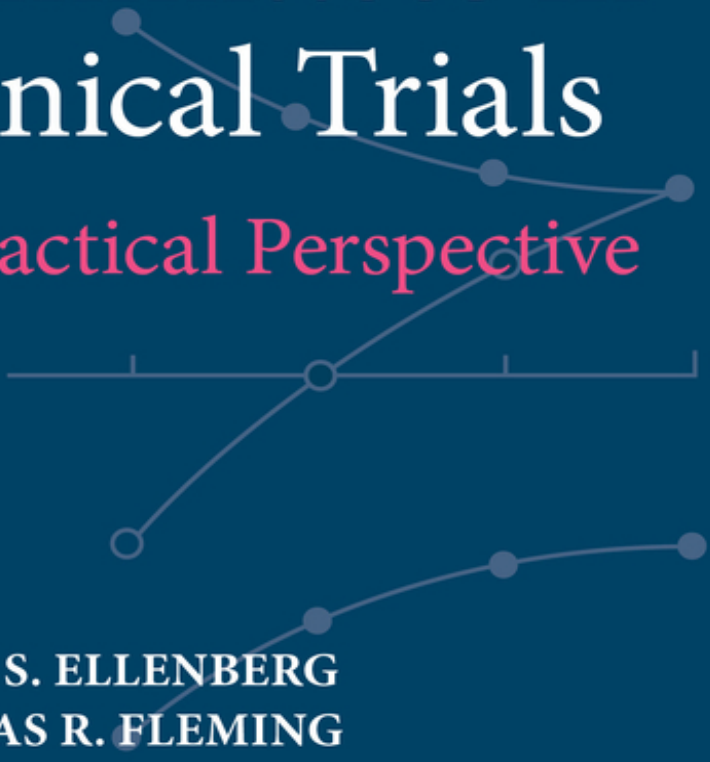
2nd Edition

Data Monitoring Committees in Clinical Trials

A Practical Perspective



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A Practical Perspective

SECOND EDITION

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Preface to the Second Edition

We were gratified by the positive reception given to the First Edition of this book, and believe it remains a useful guide to the principles and practices of clinical trial data monitoring committees. Since the time of its publication, however, there have been a number of new developments that impact on the conduct of these committees. Some of these include guidances issued by regulatory and funding agencies, new types of trial designs that impose new demands as well as limitations on DMC functioning, and many more journal publications addressing DMC issues and illustrating the types of difficult issues that DMCs may face. Thus, several years ago it appeared that an update of the book was needed. In this new edition, we have added material to each chapter to provide the most current information about policies related to DMC operations, to describe experiences of recently published trials relevant to DMC decision-making, and to address special issues in monitoring trials using newly emerging designs. We have also added a chapter focusing on legal issues affecting DMC members, motivated by increasing concerns about litigation related to clinical research generally.

We are grateful to our many colleagues who have written, and continue to write, about their experiences serving on DMCs for trials that presented challenging situations.

These publications inform and enlighten the clinical trials community, especially as they relate to emerging issues in clinical trials, such as new types of clinical trial designs.

The oversight of clinical trials remains an extremely important responsibility. We hope this book will be useful to those engaged in DMC activities, whether as members, sponsors, or investigators reporting to these committees.

Preface to the First Edition

The randomized clinical trial has been recognized as the gold standard for evaluation of medical interventions for only half a century (Doll, 1998). Over the past several decades, the increasingly central position of randomized clinical trials in medical research has led to continual advances in the development of methodology for the design, conduct, and analysis of these studies. An enormous body of literature relating to clinical trials methodology is now available, a professional society focusing on clinical trials has been established (Roth, 1980; www.sctweb.org), and a large number of statisticians, clinicians, and epidemiologists consider clinical trials as their primary area of research and/or application.

One area of clinical trials that has received relatively little attention but that can be critical to the ethics, efficiency, integrity, and credibility of clinical trials and the conclusions of such trials is the process of interim monitoring of the accumulating data. To an increasing extent, interim monitoring is becoming the province of formally established committees. While a great deal has been written about statistical methods for interim data monitoring, the practical aspects of who should serve on data monitoring committees (DMCs) or otherwise be involved in the monitoring process, what data

should be monitored and how frequently, and what are the necessary and appropriate lines of communication have received limited discussion. Since DMCs are given major responsibilities for ensuring the continuing safety of trial participants, relevance of the trial question, appropriateness of the treatment protocol, and integrity of the accumulating data, it is important to understand the ways in which these committees meet such responsibilities.

A word about terminology. Committees to monitor accumulating data from clinical trials go by a variety of names. The two most frequent of these are probably "data and safety monitoring board" and "data monitoring committee," but there are many other variations (Ellenberg, 2001). We have arbitrarily selected "data monitoring committee," in part because of its simplicity and in part because this is the term used by international regulatory authorities (http://www.ifpma.org/ich1.html).

From time to time, papers describing the experience of particular DMCs, as well as papers addressing general approaches for operating and serving on such committees, have been published; a number of these are referenced in Chapter 1.

These papers have provided some valuable insights into the monitoring process. In 1992 an international workshop was held at the National Institutes of Health to discuss different approaches to data monitoring that had been or were being used in a variety of settings, and the proceedings were published as a special issue of the journal *Statistics in Medicine* (Ellenberg et al., 1993). At this workshop, individuals with substantial practical experience in interim data monitoring reported on their preferred operating models, and there was substantial discussion of the advantages and disadvantages of the different approaches presented. Up to

now, those workshop proceedings plus the aforementioned papers have constituted the primary references for those interested in learning about the various operating models in use for DMCs, as well as the diversity of issues these committees may consider.

The use of DMCs has continued to grow, especially with respect to trials sponsored by pharmaceutical companies. The demand for individuals to serve on these committees is high; it is increasingly difficult to ensure that any DMC will include at least some members with prior experience on other DMCs. As individuals with extensive experience coordinating and/or serving on such committees, the authors of this book are frequently asked for advice concerning their operation (from trial organizers/sponsors) and the scope of responsibilities of committee members (from new members of such committees). The increasing interest in these issues led us to believe that a comprehensive reference on the practice of interim data monitoring and the structure and operation of DMCs was needed; that was our primary motivation for writing this book.

The book is intended for those involved with or otherwise interested in the clinical trials process. We expect this group will include statisticians, physicians and nurses, trial administrators and coordinators, regulatory affairs professionals, bioethicists, and patient advocates. The issues are relevant to trials sponsored by government funding agencies as well as by pharmaceutical and medical device companies, although approaches taken may differ in different contexts.

We also believe this book should be of interest to those involved in the evaluation and reporting of trial results – for example, medical journal editors and science journalists for lay publications – as the process of trial monitoring has important implications for the interpretation of results.

We have attempted to keep the material non-technical, so as to make it accessible to as large a part of the clinical trials community as possible.

Every chapter in the book addresses an issue that has been debated among those with DMC experience in different settings. Our intent is to describe the issues clearly as well as to describe the arguments that have been made for and against different approaches that might be taken. We will identify areas where there appears to be a general consensus, and occasionally recommend a particular approach even when there is no widespread consensus on that issue. For the most part, however, our goal is to clarify the types of decisions that must be made in implementing DMCs and not to provide a prescription for their operation. There is no "one size fits all" for DMCs; different models may be needed for different situations.

We begin with some introductory background and some historical notes on the use of DMCs in different contexts. Next, we address the scope of responsibilities that may be assigned to a DMC. Some committees are charged with reviewing outcome data only (or even safety data only); others are asked to review the initial protocol, monitor the conduct of the study by assessing accrual, eligibility, compliance with protocol, losses to follow-up, and other issues that are ultimately relevant to the value and credibility of a trial. The specific responsibilities delegated to a committee monitoring a particular trial will influence other operational aspects, such as committee composition.

In Chapter 3 we consider the committee membership: what types of expertise should be represented on all committees, other relevant factors in selecting committee members, optimal committee size, methods of selecting committees (and committee chairs). An important issue regarding

committee membership that we discuss in some detail is conflict of interest.

Chapter 4 continues the consideration of conflicts of interest in the broader context of the independence of the committee. We discuss what is meant by an "independent" committee, and the potential consequences for the trial and its credibility when the committee's independence is called into question. We also discuss the various types of trials for which independence of the DMC may be most critical.

Chapter 5 deals with one of the most controversial issues relating to the interim monitoring of clinical trial data: the extent to which any interim data, and unblinded interim data in particular, should be released to individuals or groups other than the committee itself. It has been argued that there may be a "need to know" for some groups such as the sponsor or the regulatory authority; it has also been argued there is a "right to know" for participating investigators, study subjects, and the general public. Others believe that limiting access to interim results is essential to the successful completion of clinical trials. This chapter focuses on such debates, and their potential implications for trial integrity.

In Chapter 6 we deal with the logistical issues – how often a committee should meet, how long the meetings need to be, how they are conducted, the content of the report the committee is to consider, the preparation and content of meeting minutes, and a number of other issues. Many groups who regularly sponsor and/or coordinate clinical trials have developed their own approaches to these issues, but these approaches can be quite different, even for similar types of clinical trials. Some might consider these types of issues part of the "minutiae" of clinical trials; our experience, however, is that the quality and reliability of the monitoring process may depend very heavily on just these types of issues.

Chapter 7 addresses the very important but little discussed topic of how the DMC interacts with other trial components. There are many constituencies involved in any given trial, including the sponsor(s), the investigators, the statistical coordinating center, the study steering committee, the institutional review board(s), and of course the patients. There is also a variety of modes of interaction, both formal (e.g. submitting reports) and informal (e.g. attending meetings of other components where unstructured discussion may take place).

Chapter 8 provides an overview of the various statistical approaches for interim monitoring of clinical trial data, and some discussion of why some approaches may be more useful in some circumstances than others. In this chapter, we also discuss the rationale for using these statistical tools in the monitoring process, as they have been widely but not universally adopted by DMCs. This discussion includes consideration of the different philosophies that have been expressed regarding the appropriateness of stopping clinical trials before they have collected all the information that was specified at the outset, a discussion that of necessity brings in the ethical issues that have been brought to bear on this determination.

In Chapter 9 we consider in more detail the monitoring approaches best suited to different types of trial and describe an alternative to an independent monitoring committee that has been found useful in some settings.

Finally, in Chapter 10 we review regulatory considerations that may affect the operation of a DMC. There is very little in the US Code of Federal Regulations concerning DMCs; they are certainly not mandated except in one very limited circumstance. But there are aspects of the regulatory process that are important for DMCs to be familiar with, and there have been occasions when interactions between regulatory

authorities and DMCs have occurred. Such interactions raise important questions about where certain responsibilities may optimally reside.

Shortly before this book went to press, the Food and Drug Administration issued a draft guidance document on the establishment and operation of DMCs, and that document is briefly summarized.

The reader will find real-life examples throughout the book. Many of these examples come from the direct experience of the authors and have not been written about previously; others have been described in prior publications. We hope these examples will demonstrate the types of decisions and dilemmas DMCs frequently face, and the consequent difficulty of establishing a set of fixed rules for the operation of these committees. Our goal with this book is to assist those who establish DMCs, those who serve on them, those who are participating in trials and depending on their judgment, as well as those who read, interpret, and use the results of clinical trials.

The book has benefited enormously from the constructive advice of those who graciously agreed to read drafts and provide comments. Baruch Brody, Lawrence Friedman, Alan Hopkins, Desmond Julian, James Neaton, Stuart Pocock, David Stump, and Janet Wittes reviewed drafts of most chapters and their input led us to make many improvements. Robert Temple, Jay Siegel, Scott Emerson, Tom Louis, Paul Canner, and Jonas Ellenberg provided extremely helpful input on specific chapters. Diane Ames assisted in producing many of the figures.

Sue Parman coordinated much circulation of material, arranged meetings and teleconferences, and assisted with the preparation of several chapters.

Thanks are also due to Helen Ramsey of Wiley, who encouraged the development of this book, and to Wiley

editors Sharon Clutton, Siân Jones and Rob Calver for their assistance and collegiality throughout the process. We also appreciate the work of Richard Leigh, our copy editor, for the many modifications he suggested and queries he raised that improved the flow of the book and eliminated errors and ambiguity.

We are indebted to all our colleagues with whom we have served on DMCs, with whom we have worked in preparing reports to DMCs, and who have served on DMCs to which we have reported. Whatever value there may be in these pages derives from the fundamentally collaborative experience of monitoring clinical trial data and the mutual learning that ensues.

We would like to acknowledge partial support from National Institutes of Health grants NIHR37AI129168 (T.F.) and NIHR01CA18332 (D.D).

Finally, we are particularly grateful for the forbearance and support of our families – particularly our spouses, Jonas, Joli, and Kathy – during the process of writing, rewriting, arguing, negotiating, and nitpicking as we made our way to the final manuscript.

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1

Introduction

Key Points

- The purpose of data monitoring committees (DMCs) is to protect the safety of trial participants, the credibility of the study, and the validity of study results.
- DMCs have a long history in trials sponsored by government agencies in the USA and Europe.
- Pharmaceutical companies use DMCs in many trials of investigational drugs, biologics, and medical devices.
- Statistical methods have been developed for interim monitoring of clinical trials.
- While not all trials need DMCs, trials that address major health outcomes and are designed to definitively address efficacy and safety issues should incorporate DMC oversight.

1.1 MOTIVATION

In randomized clinical trials designed to assess the efficacy and safety of medical interventions, evolving data

Data Monitoring Committees in Clinical Trials: A Practical Perspective, Second Edition.
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are typically reviewed on a periodic basis during the conduct of the study. These interim reviews are especially important in trials conducted in the setting of diseases that are life-threatening or result in irreversible major morbidity. Such reviews have many purposes. They may identify unacceptably slow rates of accrual or high rates of ineligibility determined after randomization, protocol violations that suggest that clarification of or changes to the study protocol are needed, or unexpectedly high dropout rates that threaten the trial's ability to produce credible results. The most important purpose, however, is to ensure that the trial remains appropriate and safe for the individuals who have been or are still to be enrolled. Unacceptable levels of treatment toxicity may require an adjustment of dosage or schedule of administration, or even abandonment of the study. Efficacy results, too, must be monitored to enable benefit-to-risk assessments. Interim results may demonstrate that one intervention group has such unfavorable outcomes with regard to survival or a major morbidity endpoint that its benefit-to-risk profile is clearly inferior to that of the comparator treatment. In such cases, it may be appropriate to terminate the inferior intervention or the entire trial early so that current study participants, as well as future patients, will no longer be provided with inferior treatment.

Relatively early in the development of modern clinical trial methodology, some investigators recognized that, despite the compelling ethical need to monitor the accumulating results, repeated review of interim data raised some problems. Repeated statistical testing was seen to increase the chance of a "false positive" result unless nominal

significance levels were somehow adjusted. In addition, it was recognized that awareness of the pattern of accumulating data on the part of investigators, sponsors or trial participants could affect the course of the trial and the validity of the results. For example, if investigators were aware that the interim trial results were favoring one of the treatment groups, they might be reluctant to continue to encourage adherence to all regimens in the trial, or to continue to enter patients on the trial, or they might limit the types of patients they would consider entering. Furthermore, influenced by financial or scientific conflicts of interest, investigators or the sponsor might take actions that could diminish the integrity or credibility of the trial. For example, a sponsor observing interim data showing that the new treatment had little if any effect on the pre-specified primary endpoint but a much stronger effect on an important secondary endpoint might be tempted to switch the designation of these two endpoints.

A natural – and practical – approach to dealing with these problems is to assign sole responsibility for interim monitoring of data on safety and efficacy to a committee whose members have no involvement in the trial, no vested interest in the trial results, and sufficient understanding of trial design, conduct and data-analytical issues to interpret interim analyses with appropriate caution. These "data monitoring committees" (DMCs) have become critical components of many clinical trials.

The interim monitoring experience of an early AIDS clinical trial illustrates some of the inherent difficulties and challenges that arise in the review of accumulating data from clinical trials.

Example 1.1: Treatment for HIV infection

Trial 002 of the Community Programs for Clinical Research in AIDS (CPCRA) was designed to compare the efficacy of two antiretroviral agents, zalcitabine (ddC) and didanosine (ddI), in HIV-infected patients who did not derive benefit from zidovudine (AZT), at that time the first-line treatment for HIV infection (Abrams et al. 1994). When the trial was initiated, ddI was considered the first-line treatment in this patient population; the goal of the trial was to determine whether ddC was approximately equivalent to ddI by seeing whether as much as a 25% advantage for ddI in the time to disease progression or death could be ruled out. A total of 467 patients were randomized to receive either ddI or ddC. To achieve the desired level of statistical power, it was calculated that patient follow-up would be needed until 243 patients had been observed to reach the endpoint of disease progression or death.

This trial was initiated in December 1990, at a time when little in the way of effective treatments for this population was available, when the numbers of new HIV infections and deaths were increasing, and when both the patient community and their physicians were increasingly desperate to identify treatments that could buy a little more time for those suffering from this disease. Patients entering such trials were generally young men who were facing a very premature death from a disease they may not have even known about at the time they contracted it. Further, more pharmaceutical companies were initiating drug development for treatment of HIV, but with a great deal of caution, as would be expected in a completely new disease area. While there are inherent tensions in all trials testing new agents for serious diseases,

the atmosphere surrounding early trials of AIDS treatments, such as this one, was particularly "high pressure." Trial 002 was monitored by the DMC that had been established by the National Institute of Allergy and Infectious Diseases (NIAID) to oversee all of its extramural trials of treatment for HIV infection (DeMets et al. 1995). The CPCRA was a clinical trials group funded by NIAID; therefore, access to interim data was limited to DMC members – none of whom were treating patients on this or any other NIAID-funded AIDS trial, or had any financial stake in the trial outcome – and to a limited number of NIAID staff.

The interim results from this trial, shown in Figures 1.1 and 1.2, illustrate how substantially relative risk estimates

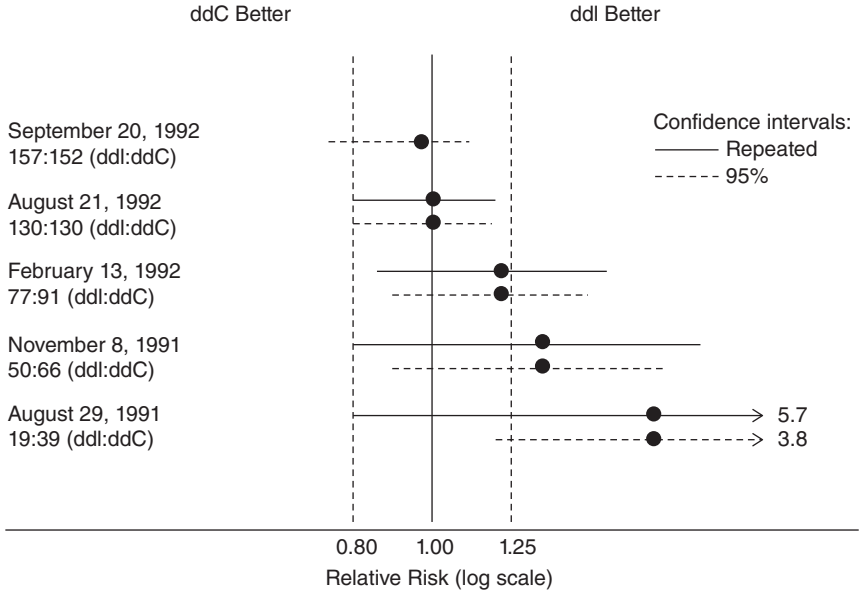

Figure 1.1 Relative risk of progression of disease (including death) by date of DMC review. Numbers to the right of the arrows are upper confidence limits. Source: From Fleming et al. (1995). Reproduced by permission of Lippincott, Williams & Wilkins.

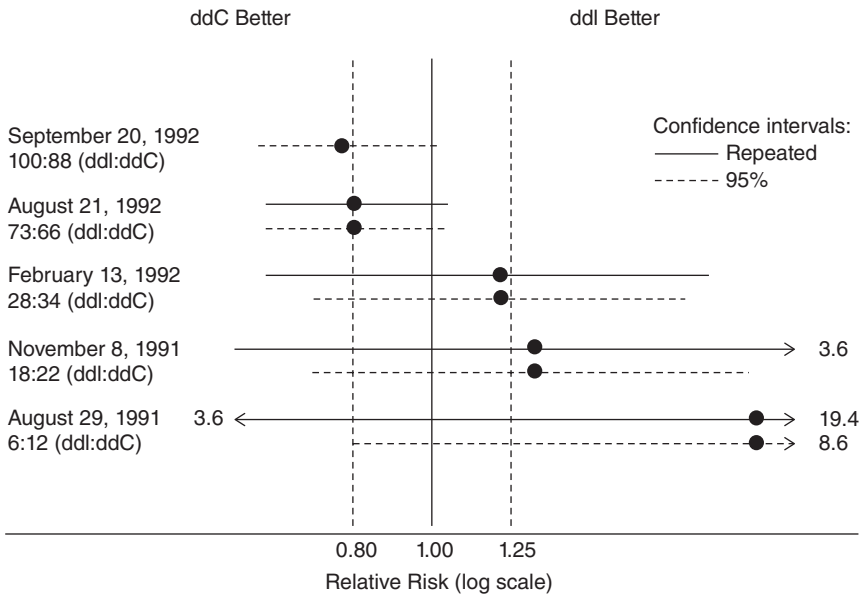

Figure 1.2 Relative risk of death by date of DMC review. Numbers to the right of the arrows are upper confidence limits. Source: From Fleming et al. (1995). Reproduced by permission of Lippincott, Williams & Wilkins.

can change over time. At the first interim analysis in August 1991, the early trial results strongly favored ddI. At that time, the ddI group had experienced many fewer disease progressions (19 versus 39) and fewer deaths (6 versus 12) than the ddC group. The effects on laboratory markers were also more favorable in the ddI group. While the nominal *p*-value for the treatment difference in progressions at this analysis was an impressive 0.009, this value did not approach the protocol-specified early termination criterion at this early stage in the trial. The DMC considered these data as well as available information on toxicities and other relevant outcomes and recommended that the trial continue as designed.