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 requirements²⁻⁴ 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 DeMets⁶ 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 Piantadosi¹¹ 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.

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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 **1**

Introduction/Overview