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Data and Safety Monitoring Committees in Clinical Trials
Second Edition

Jay Herson
Johns Hopkins Bloomberg School of Public Health
Baltimore, Maryland, USA
To the patients who volunteer for clinical trials—past, present, and future.
Contents

Preface to the First Edition ................................................................. xvii
Preface to the Second Edition ............................................................. xxi
List of Abbreviations ........................................................................ xxiii

1 Introduction ..................................................................................... 1
   1.1 What Is a Data Monitoring Committee (DMC)? ...................... 1
   1.2 Some Definitions ...................................................................... 2
   1.3 DMC in Federal Government–Sponsored Clinical Trials versus Pharmaceutical Industry Clinical Trials .......... 3
   1.4 Stewardship .............................................................................. 5
   1.5 Some Recent History ................................................................. 5
      1.5.1 Development of DMCs in the Pharmaceutical Industry .... 5
      1.5.2 Guidance Documents: FDA, NIH, and ICH ..................... 6
      1.5.3 Other Vehicles for Patient Protection ............................. 7
   1.6 A DMC’s Place in the Drug Development Cycle ....................... 7
      1.6.1 Phases of Drug Development ........................................... 7
      1.6.2 Limitations of a Clinical Program for Revealing Safety Issues ................................................................. 7
      1.6.3 Postmarket Safety Actions ............................................... 10
      1.6.4 Role of DMCs in Exploratory and Confirmatory Trials ...... 10
      1.6.5 Blurring of Phases I, II, and III ......................................... 12
      1.6.6 Investigator-Sponsored Trials ......................................... 12
      1.6.7 Open Label Trials ............................................................ 13
      1.6.8 Emerging Trial Designs of Interest .................................... 13
   1.7 Pharmaceutical Industry Demographics ................................... 13
      1.7.1 Size of Companies ............................................................. 13
      1.7.2 Public versus Private Companies ...................................... 14
   1.8 In Conclusion ............................................................................. 15
DMCounselor .................................................................................... 15

2 Organization of a Safety Monitoring Program for a Confirmatory Trial .................................................................................. 19
   2.1 Members of the Safety Monitoring Team .................................... 19
      2.1.1 The Sponsor ........................................................................ 19
      2.1.2 Data Monitoring Committee ............................................. 20
      2.1.3 Data Analysis Center .......................................................... 21
      2.1.4 Institutional Review Board ............................................... 22
      2.1.5 Other Committees That Might Be Involved ....................... 22
      2.1.6 Scope of DMC Authority .................................................... 23
   2.2 How Is a DMC Created? ............................................................ 23
## Contents

2.3 Membership ........................................................................................................ 24  
2.3.1 Physicians ........................................................................................................ 24  
2.3.2 Biostatisticians ............................................................................................... 25  
2.3.3 How Many Members Are Needed? ................................................................... 25  
2.3.4 Ad Hoc Consultants ...................................................................................... 25  
2.3.5 Ubiquitous DMC Members ........................................................................... 26  
2.3.6 Disclosure of DMC Membership ................................................................... 27  
2.3.7 Multiple Sponsorship .................................................................................... 27  
2.3.8 From Where Are DMC Members Recruited? .............................................. 28  
2.4 Term ...................................................................................................................... 28  
2.5 Conflicts of Interest and DMC Independence from Sponsor ............................ 28  
2.6 Compensation ..................................................................................................... 29  
2.7 Liability and Indemnification ............................................................................ 30  
2.8 Sponsor-DMC Relationship ............................................................................. 30  
2.9 Interdisciplinary Training .................................................................................. 31  
2.10 In Conclusion ..................................................................................................... 31  

DMCounselor .............................................................................................................. 31

3 Meetings .................................................................................................................. 37  
3.1 DMC Charter ......................................................................................................... 37  
3.2 Types of Meetings ................................................................................................. 37  
3.2.1 Orientation or Organizational Meeting .......................................................... 38  
3.2.2 Data Review .................................................................................................... 39  
3.2.3 Ad Hoc ............................................................................................................ 39  
3.3 Orientation Meeting ............................................................................................. 39  
3.3.1 Chair for Orientation Meeting ....................................................................... 39  
3.3.2 Introduction of the Safety Monitoring Team ................................................... 39  
3.3.3 Appointment of DMC Secretary ................................................................... 39  
3.3.4 Presentation of DMC Charter ....................................................................... 40  
3.3.5 Masking Policy ............................................................................................... 40  
3.3.6 Investigator Brochure .................................................................................... 41  
3.3.7 Protocol ........................................................................................................... 41  
3.3.8 Informed Consent .......................................................................................... 42  
3.3.9 Data Flow ........................................................................................................ 42  
3.3.10 Useful Software ........................................................................................... 43  
3.3.11 Review of Integrated Summary of Safety .................................................... 43  
3.3.12 Policy on Review of Publications and Package Inserts .............................. 44  
3.3.13 Data Review Plan .......................................................................................... 44  
3.3.14 Schedule First Data Review Meeting ........................................................... 45  
3.4 Data Review Meetings .......................................................................................... 45  
3.4.1 Attendance ...................................................................................................... 46  
3.4.2 Open Session .................................................................................................. 46  
3.4.2.1 Study Progress ......................................................................................... 46  
3.4.2.2 Data Quality ............................................................................................. 47  
3.4.2.3 Update on Pending Action Items ............................................................. 47
Contents

3.4.2.4 Questions for the DMC .............................................. 47
3.4.2.5 Sample Agenda for Open Session .............................. 47
3.4.3 Closed Session .......................................................... 48
3.4.4 DMC Meetings for Open Label Trials ............................ 48
3.4.5 Scheduling of Next Meeting ........................................ 48
3.4.6 Minutes ................................................................. 52
3.5 Ad Hoc Meetings .......................................................... 52
3.6 In Conclusion .................................................................. 52
DMCounselor .......................................................................... 53

4 Clinical Issues ..................................................................... 63
4.1 Goals of Safety Analysis .................................................. 63
4.2 Definitions ................................................................. 64
4.2.1 Adverse Event ............................................................ 65
4.2.2 Serious Adverse Event ................................................ 65
4.2.3 Adverse Event Tiers ................................................... 65
4.2.4 Serious Adverse Event Reporting Requirements ............. 65
4.2.5 Serious Unexpected Suspected Adverse Reactions (SUSARs) ........................................................................ 66
4.3 Safety Data ....................................................................... 67
4.3.1 Pharmacovigilence Groups ......................................... 67
4.3.2 Case Report Forms ..................................................... 67
4.3.3 Adverse Event Dictionary ............................................ 67
4.3.4 Adverse Event Severity .............................................. 68
4.3.5 Adverse Event Summary ............................................. 69
4.3.6 SAE Narratives .......................................................... 71
4.3.7 Titration to Dose ........................................................ 72
4.4 Deaths ............................................................................. 72
4.5 Impact of Multiregional (Global) Trials ............................. 72
4.5.1 Cultural Issues ........................................................... 73
4.5.2 Political Issues ........................................................... 73
4.5.3 Medical/Surgical Practices Issues ............................... 74
4.5.4 Data Quality Issues .................................................... 74
4.6 In Conclusion ..................................................................... 74
DMCounselor .......................................................................... 76

5 Statistical Issues .................................................................. 81
5.1 Goals of Statistical Analysis ............................................. 81
5.2 Useful Data Displays ....................................................... 82
5.2.1 Enrollment by Center, Ethnicity, and Stage of Disease ... 83
5.2.2 Graph of Cumulative Patient Enrollment by Month ....... 84
5.2.3 Graph of Cumulative Patient Exposure to a Study Drug ... 84
5.2.4 Treatment-Emergent Adverse Events ......................... 85
5.2.4.1 Classification ........................................................... 85
5.2.4.2 Example: The APPROVe Trial ............................... 86
## 7 Data Monitoring Committee Decisions

### 7.1 Types of DMC Decisions

### 7.2 Decision-Making Environment

### 7.3 Risk versus Benefit Analyses

### 7.4 When a Safety Issue Arises

#### 7.4.1 Unmasking

#### 7.4.2 “Dear Investigator” Letter

#### 7.4.3 Modification of Informed Consent

#### 7.4.4 Protocol Modification

#### 7.4.5 Trial Termination

#### 7.4.6 Unmasking the Sponsor

### 7.5 Information beyond the Present Trial

### 7.6 Meta-Analysis

### 7.7 Planned Interim Analyses Regarding Efficacy

### 7.8 Final Meeting

### 7.9 Special Problems with Infant Pharma Companies

### 7.10 In Conclusion

## 8 Emerging Issues

### 8.1 Introduction

### 8.2 Issues in New Clinical Trial Designs and Technologies

#### 8.2.1 Adaptive Designs

##### 8.2.1.1 Dropping a Dose or Treatment Group

##### 8.2.1.2 Adaptive Assignment to a Treatment Group

##### 8.2.1.3 Changing Objectives: Superiority to Noninferiority

##### 8.2.1.4 Seamless Transition: Phase II to Phase III

##### 8.2.1.5 Change in Effect Size of Interest

##### 8.2.1.6 Further Thoughts on Adaptive Designs

#### 8.2.2 Novel Designs in Oncology

#### 8.2.3 Dynamic Treatment Strategies (DTS) and a Sequential Multiple Assignment Randomization Trial (SMART)

#### 8.2.4 Pragmatic Trials and Patient-Reported Outcomes of Safety

### 8.3 Biosimilar Designs

### 8.4 *In Vitro* Companion Diagnostic Devices

### 8.5 Real-Time SAE Reporting Using the Internet

### 8.6 Centralized Risk-Based Monitoring

### 8.7 Causal Inference

### 8.8 Unmasking Potential of Biomarkers

### 8.9 Issues Due to Maturing of DMC Processes and Evolution of the Pharmaceutical Industry

#### 8.9.1 Training of DMC Members

#### 8.9.2 Cost Control
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.9.3 DMC Audit</td>
<td>184</td>
</tr>
<tr>
<td>8.9.4 Internal Safety Review Committees and Still More Committees</td>
<td>184</td>
</tr>
<tr>
<td>8.9.5 Mergers and Licensing</td>
<td>185</td>
</tr>
<tr>
<td>8.9.6 Journal Policies Regarding Independent Reviews</td>
<td>186</td>
</tr>
<tr>
<td>8.9.7 Fraud Detection</td>
<td>186</td>
</tr>
<tr>
<td>8.9.8 Compensation of DMC Members</td>
<td>187</td>
</tr>
<tr>
<td>8.10 Resignation from a DMC</td>
<td>188</td>
</tr>
<tr>
<td>8.11 In Conclusion</td>
<td>189</td>
</tr>
<tr>
<td>DMCounselor</td>
<td>190</td>
</tr>
<tr>
<td>Glossary</td>
<td>195</td>
</tr>
<tr>
<td>Appendix</td>
<td>209</td>
</tr>
<tr>
<td>References</td>
<td>217</td>
</tr>
<tr>
<td>Index</td>
<td>231</td>
</tr>
</tbody>
</table>
Preface to the First Edition

This is a book about best practices in safety monitoring through data monitoring committees (DMC) in pharmaceutical industry clinical trials. It will be useful for those who have served on DMCs and are interested in what was done well and what could have been done better and those contemplating serving on their first committee.

I can still remember that winter morning 20 years ago in San Antonio, when Frank Rockhold asked me at a biostatistical meeting we were attending if I could organize a DMC for a gastrointestinal drug his company was developing. Frank, his talented colleagues, and I worked out a plan and the first DMC in pharmaceutical industry trials was born. At the time, I headed a contract research organization (CRO) in Houston known as Applied Logic Associates (ALA). Since then, that company has provided statistical support to more than 50 DMCs and I have served as statistical member on DMCs for about 30 additional trials. The art and science of safety monitoring through DMCs has reached adolescence and it is time to review, and perhaps debate, best practices. There can be no better time than now, when regulatory agencies worldwide are facing considerable challenges in drug safety for both premarket and postmarketed drugs.

In the world of drug development, clinical issues and statistical issues cannot be separated. All issues are scientific. All use applied logic. This is the approach to this book. It is written in the style of my Herson’s Handout column that appeared in the ALA newsletter Under the Curve, 1991–2004. This was a style appropriate for all drug development professionals regardless of degrees held. The book assumes that the reader has a basic knowledge of clinical trials, clinical operations, and good clinical practices.

Chapter 1 is introductory. It points out the differences between clinical trials sponsored by the federal government and those sponsored by pharmaceutical firms. These differences explain why DMCs operate a little differently for private sector–sponsored trials. We learn that pharmaceutical companies themselves differ by their size and the terms Big Pharma, Middle Pharma, and Infant Pharma are defined. Another important definition is that of stewardship. If there had to be one word to define the role of DMCs it would be stewardship. We also learn the limitations for uncovering safety issues in a single premarket clinical program and provide a rule of thumb for assessing the sensitivity of a clinical program to uncovering adverse events.

Chapter 2 details the organization of safety monitoring describing the interactions of the sponsor, the DMC, the Data Analysis Center (DAC), the Institutional Review Board (IRB), and the regulatory agencies. Tables in the chapter offer checklists of desirable characteristics of a sponsor
representative, a DAC organization, questions to ask oneself, and the sponsor before agreeing to join a DMC.

Chapter 3 explains the nature of DMC meetings. Of special importance is the orientation meeting. In this section, the items usually included in the DMC Charter are listed. From this, the extent of DMC responsibilities for the trial, reporting procedures, serious adverse event data flow, masking (blinding) policy, and many other important agreements that must be made between the sponsor, DAC, and DMC at the outset of the trial are detailed in the text and tables. Another table presents a sample agenda format for DMC meetings that has proven more useful than a mere list of topics to be discussed.

Chapter 4 is an introduction to clinical issues. Here, we will see how the safety data reviewed by DMCs arise. We learn the important distinction between adverse events, serious adverse events, and severity of adverse events. The current state of the art of adverse event coding is described. The impact of multinational trials and the cultural, political, and medical practice issues relevant to DMC operations are described.

In Chapter 5, we investigate statistical methods useful for DMCs. It is emphasized that statistical significance of a treatment difference for a safety parameter is neither a necessary nor sufficient reason to terminate a trial. We see some useful graphical and tabular data displays and review statistical methods for testing hypotheses and creating confidence intervals for various measures of treatment differences in safety. The methods are illustrated with data from an actual clinical trial. Every DMC faces problems of multiplicity and this concept is explained and use of the false discovery rate is presented as a means of controlling multiplicity. The chapter includes an introduction to likelihood methods for assessing evidence. Much of the work in this area has been done by my graduate school advisor, Professor Richard Royall. I have found the methods useful for DMC work. I am excited to be able to present the methods here. The chapter closes with a brief description of the role of Bayesian methods for safety analysis. A table is presented summarizing all methods discussed in the chapter along with their advantages and disadvantages for DMC use.

Chapter 6 continues in the inference vein with a description of the biases and pitfalls in analyzing safety data. Sources of bias arise from unmasking, incomplete follow-up, spontaneous versus solicited adverse event data collection, early termination due to efficacy, and the problems introduced by slicing and dicing the adverse event descriptions into many subgroups within a body system (granularity). Finally, the concept of competing risks in adverse event incidence is presented, particularly in the case where there is differential follow-up between treatment groups due to a treatment effect in a primary efficacy endpoint.

We now arrive at Chapter 7, where we apply our knowledge from prior chapters to data monitoring committee decisions. We review the types of decisions that DMCs can make as well as the environment in which they are made. We see the steps that can be taken when a safety issue arises and
the potential pitfalls in incorporating data from past clinical trials into the
decision-making process.

Chapter 8 might also be called an epilogue. It deals with emerging issues
in drug development that affect DMC operations. The issues are divided into
those that arise from advances in technology and those that arise through the
maturation of the DMC process. In the former, we take up adaptive designs. Of
particular importance is the situation when an adaptive change is taking place
on the basis of efficacy but, due to safety, the DMC feels that this change will
not be in the interest of patient safety. Other technology changes are the advent
of real-time SAE reporting and the potential of certain adverse events to be
biomarkers for efficacy. In the area of maturation of DMC processes, training
of DMC members, CROs, DACs, and even sponsor representatives to the DMC
paradigm is very important and how can we create the supply of qualified indi-
viduals to meet the demands. Sponsors have encountered problems with cost
control as DMCs ask for more data than was originally planned. Suggestions
are given for dealing with this situation. What happens when pharmaceutical
companies merge or out-license the product the DMC is deliberating? How do
we ensure that independent review of patient safety will continue? New medi-
cal journal policies requiring DMCs and independent statistical review will
also affect DMC operations and are covered here as well.

At the end of each chapter, the reader will find a Q & A section called
DMCounselor. The questions provide a behind-the-scenes glimpse of DMC
meetings, interactions with sponsors, multinational issues, personality con-
flicts, and especially the problems that Infant Pharma faces in providing inde-
pendent review in the same manner as Big Pharma. All cases raised in this
section are real. They were either my own personal experience or those of oth-
ers. All details of the cases have been changed for confidentiality but the conun-
drums remain. Some readers may not agree with the solutions that I provide in
my answer but at least they can see issues they may not have thought of before.

A glossary is presented giving definitions of most of the technical terms
used in the text and the appendix contains a table of adverse events reported
for selected marketed drugs in placebo-controlled trials. It is referred to at
various points in the text to illustrate safety concepts.

I explain in the text that I use the term sponsor where others might use
company. I use the term patient as the clinical unit in our trials. I realize that
in some indications subject would be more appropriate but I chose patient for
consistency. I use the term drug as a synonym for intervention. The latter term
would include biologics and medical devices. I felt that most readers are used
to this terminology. Indeed, the Food and Drug Administration and the Drug
Information Association deal with interventions broader than just drugs.

About a year after completing my first statistics course as an undergradu-
ate, I noticed that the professor had published his own textbook on the subject.
When I asked him how long it took him to write the book, he replied “Well it
is hard to say, I have been teaching for twenty years.” I now understand what
he meant. Although writing this book may have taken 1 year it represents
20 years of experience. This also means that it will be impossible for me to thank all those people who I have learned from. I certainly must thank Frank Rockhold for introducing me to the DMC concept. The many employees of ALA, too numerous to name here, for their insight into the details, such as MedDRA and related software, their development of efficient methodology, and the realization that protecting patient safety was just as important as hitting a home run in efficacy. During my years as president of ALA, I became intimately aware of the issues facing Infant Pharma and am grateful for the opportunity to present them here. There have been many DMCs. If I had to single out one DMC experience it would be the one that lasted longest. My hat goes off to ophthalmologists Alan Bird, Don D’Amico and Ron Klein, DAC biostatistician Emmanuel Quinaux, and sponsor representative Harvey Masonson for all they taught me while we had the privilege of working on the first vascular endothelial growth factor used in ophthalmology. It was a very educational 6 years.

I am so grateful for the Biostatistics Department at the Johns Hopkins Bloomberg School of Public Health in Baltimore for welcoming me into the department after my semiretirement and offering me the physical and intellectual environment conducive to writing a book. Among the Johns Hopkins family, Scott Zeger brought me into the department in 2004 and Richard Royall not only introduced me to likelihood methods when I was his student but set the example for me by writing such a fine book on the subject. Jeff Blume and Elizabeth Garrett-Mayer also shared a lot of ideas about likelihood and were a help with the graphs.

I thank biostatisticians Dennis Dixon, Janet Wittes, and Marc Buyse not only for our long friendship but also for teaching me the differences between government and private industry trials. I thank Janet also for her official responsibility of reviewing this manuscript and making so many important suggestions and corrections.

This book would never have come about if David Grubbs of the Taylor & Francis Group had not approached me about writing a book and offering me encouragement along the way. Taylor & Francis could not have provided me with a better project coordinator than Marsha Pronin.

Last, but certainly not least, I must thank my wife Linda for enduring my writing obsession and providing so much encouragement for what is the equivalent of a second doctoral dissertation some 37 years after the first. Yes Linda, I’ll clean up the room now.

I hope that the many drug development professionals who read this book will find it useful in starting a dialog on best practices beyond the point of just writing a charter and scheduling meetings. I hope that those talented readers who have not yet served on a DMC will consider doing so. It is an important and rewarding experience.

Jay Herson, PhD
July 15, 2008
Preface to the Second Edition

When the first edition of this book was published in 2009, a second edition was the furthest thing from my mind. However, in the past 2 years alone, we have seen a huge impetus of regulations and books on safety in drug development. The big push is to guide safety monitoring and analysis toward risk (adverse events) versus benefit (efficacy) and to reduce the paperwork in expedited reporting of adverse events. Terms such as SUSARs, SMQs, PSAP, companion diagnostics, safety assessment committees, and so forth, did not exist, at least in my vocabulary, when I created the first edition in 2008.

The new regulations have been complemented by the development of new statistical methods, which are also described here so that DMC members will have a reference if they should appear at a meeting. Meta-analysis, use of outside data, Bayesian methods, and causal inference are more common today than they were in 2008, so I have given them more ink.

The first edition mentioned the efficacy analysis responsibilities of DMCs but gave no details. This edition provides the statistical elements of planned interim analysis with group sequential methods, conditional power, futility, and so on.

I have introduced some new ideas of my own. While I applaud the SPERT recommendation of the PSAP (Program Safety Analysis Plan), I see much of that as a sponsor guide toward a final safety analysis. Thus, I have introduced the notion of a Data Review Plan (DRP), which would be solely for DMC use. For those who have been concerned about DMC independence from the sponsor, I introduce the ideas of the DMC members being appointed jointly by sponsor and regulators but compensated by regulators. We have seen more than a few cases of data fraud in clinical trials and we expect more cases to come up in the future with the advent of centralized statistical monitoring. Thus, I have added my idea of a Fraud Recovery Plan, which could be used to salvage a clinical trial when some cases of data fraud are found. These items have been added with the objective of beginning what I think would be useful discussions of these issues, something like a draft guidance issued by a regulatory agency.

I have participated in many more DMCs since the first edition and have greatly expanded the popular DMCounselor Q&A at the end of every chapter with new scenarios representing my recent experiences and those of others. As with the first edition, the details of the clinical trials have been changed to protect the innocent.

At the end of Chapters 3 through 8, I have added tables to indicate useful DRP items and potential DMC responsibilities implied in that chapter. I have aggregated these chapter tables in Appendix Table A.2 for the DRP.
and Table A.3 for the DMC. I hope these will be useful to sponsors and DMC members in preparing DRPs and DMC Charters.

Once again, I must thank David Grubbs and his talented colleagues at Chapman & Hall/CRC Press for encouraging me to write the second edition and for all of the support along the way. My hat also goes off to the many people who have written books on statistical methods for drug safety over the past few years. I have referenced so many of their chapters. I must paraphrase a much-quoted Groucho Marx phrase “I would never serve on a committee that would have me as a member.” I do not like committee work but stand in awe of those who toil on industry panels such as SPERT, BRAT, and PRISMA all of which are spelled out in this edition. Their work has really moved the field forward. Our colleagues in the regulatory agencies have put much thought into the new drug safety guidelines and it has been my pleasure to relate their words to DMC responsibilities.

My association with the Biostatistics Department at the Johns Hopkins Bloomberg School of Public Health continues to be rewarding and to provide the stimulating environment for this undertaking and for the many ideas I get from faculty and present and former students.

Again, I thank my wife, Linda, for putting up with my obsession with still another book. Fortunately it did not prevent us from doing the travel we enjoy so much.

Like the first edition, the second edition is about best practices. I hope this book will help those of us who work on drug development and understand how best practices have evolved.

Jay Herson, PhD
# List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>AESI</td>
<td>adverse event of special interest</td>
</tr>
<tr>
<td>ALA</td>
<td>Applied Logic Associates</td>
</tr>
<tr>
<td>APD</td>
<td>aggregate patient data</td>
</tr>
<tr>
<td>APPROVe</td>
<td>Adenomatous Polyp Prevention on Vioxx</td>
</tr>
<tr>
<td>AUC</td>
<td>area under the curve</td>
</tr>
<tr>
<td>BRAT</td>
<td>Benefit Risk Action Team</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CHW</td>
<td>Chi Hung Wang method of sample size reestimation</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CIOMS</td>
<td>Council of International Organizations of Medical Sciences</td>
</tr>
<tr>
<td>CRA</td>
<td>clinical research associate</td>
</tr>
<tr>
<td>CRF</td>
<td>case report form</td>
</tr>
<tr>
<td>CRO</td>
<td>contract research organization</td>
</tr>
<tr>
<td>CTCAE</td>
<td>Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>DAC</td>
<td>Data Analysis Center</td>
</tr>
<tr>
<td>DFDR</td>
<td>double false discovery rate</td>
</tr>
<tr>
<td>DFS</td>
<td>disease-free survival</td>
</tr>
<tr>
<td>DRP</td>
<td>Data Review Plan</td>
</tr>
<tr>
<td>DTS</td>
<td>dynamic treatment strategy</td>
</tr>
<tr>
<td>DMC</td>
<td>Data Monitoring Committee</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>ETASU</td>
<td>Elements to Assure Safe Use</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FDR</td>
<td>false discovery rate</td>
</tr>
<tr>
<td>FRP</td>
<td>fraud recovery plan</td>
</tr>
<tr>
<td>FWER</td>
<td>family-wise error rate</td>
</tr>
<tr>
<td>HDL</td>
<td>high-density lipoprotein</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>ICH</td>
<td>International Collaboration on Harmonisation</td>
</tr>
<tr>
<td>IFPMA</td>
<td>International Federation of Pharmaceutical Manufacturers and Associations</td>
</tr>
<tr>
<td>IPD</td>
<td>individual patient data</td>
</tr>
<tr>
<td>IQWiG</td>
<td>German Institute for Quality and Efficiency in Health Care</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>ISRC</td>
<td>Internal Safety Review Committee</td>
</tr>
<tr>
<td>ISS</td>
<td>integrated summary of safety</td>
</tr>
<tr>
<td>ITE</td>
<td>insufficient therapeutic effect</td>
</tr>
<tr>
<td>LDL</td>
<td>low-density lipoprotein</td>
</tr>
<tr>
<td>LR</td>
<td>likelihood ratio</td>
</tr>
</tbody>
</table>
List of Abbreviations

LRC    lipids research clinics
MD     doctor of medicine
MACE   major adverse cardiac event
MedDRA Medical Dictionary for Regulatory Activities
MOOC   massive online open course
MSSO   Maintenance Support and Service Organization
NCI    National Cancer Institute
NIAID  National Institute of Allergic and Infectious Disease
NICE   National Institute of Health and Clinical Excellence
NIH    National Institutes of Health
NNH    number needed to harm
NNT    number needed to treat
NSAID  nonsteroidal anti-inflammatory drug
OS     overall survival
PAC    pulmonary arterial catheter
PDUFA  Prescription Drug User Fee Act
PFS    progression-free survival
PharmD doctor of pharmacy
PhD    doctor of philosophy
PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRO-CTCAE patient-reported outcome version of CTCAE
PSAP   Program Safety Analysis Plan
R&D    research and development
RB     risk–benefit
REMS   risk evaluation and mitigation strategy
SAC    Safety Assessment Committee
SAE    serious adverse event
SAP    statistical analysis plan
SC     Steering Committee
SE     standard error
SMART  sequential multiple assignment randomized trial
SMP    safety monitoring plan
SMQ    standardized MedDRA query
SOC    system organ class
SOP    standard operating procedure
SPERT  Safety Planning, Evaluation, and Reporting Team
SUSAR  Serious Unexpected Suspected Adverse Reaction
UK     United Kingdom
U.S.   United States
VA     Veterans Administration
WHO    World Health Organization
Introduction

PREVIEW  The data monitoring committee is the keystone of the stewardship and the scientific/ethical integrity of a clinical trial. The independent review of safety in clinical trials began in the public-funded clinical trials and has become the mainstream in pharmaceutical industry clinical trials today. After acknowledging the limitations of a single clinical trial to find rare adverse events, a rule of thumb for measuring the sensitivity of a clinical program that observes adverse events of various frequencies is presented. Issues involved in safety monitoring may differ between the size of industry sponsor and public versus private company.

KEY WORDS: adverse event, Big Pharma, confirmatory clinical trial, data monitoring committee, Infant Pharma, masked, Middle Pharma, serious adverse event, sponsor

1.1 What Is a Data Monitoring Committee (DMC)?

Professor Jerome Cornfield once defined a clinical trial as cogent description (Cornfield 1973). It has become clear that objectivity in reviewing accumulating data in clinical trials is extremely important in maintaining cogency. One factor that can operate against cogency is bias. We will discuss the concept of bias in Chapter 6, but for now, let’s define it as a conscious or unconscious lack of objectivity due to a sponsor staff’s interest in getting the experimental treatment approved by regulatory agencies. Clinical trial sponsor staff can introduce bias into trial conduct if they review efficacy data during the trial and may have a tendency to underplay the importance of adverse events that present during the trial. This is especially true in oncology trials which are usually conducted with sponsor staff, investigators, and patients all aware of treatment assignment. Although sponsors tended to claim that their trial management did not introduce bias, the current feeling is that if clinical trial results are to be persuasive to regulatory agencies, practicing physicians, and the general public, even the appearance of bias must be avoided. The problem is complicated by the fact that investigators and others associated with the trial can also introduce bias. While bias reduction is important for scientific and regulatory reasons, it has also become evident that objective review of accumulating data is necessary to protect patient safety.
In the late 1980s, following the example of clinical trials run by the U.S. federal government through agencies such as the National Institutes of Health (NIH), the Veterans Administration (VA) and the Centers for Disease Control and Prevention (CDC), the British Medical Research Council, and the French INSERM, the pharmaceutical industry began to form DMCs. These committees took on various names and were of various forms. Initially some of these committees included members who were sponsor staff but regulatory agencies took a dim view of this practice. Eventually, membership evolved to individuals who were not members of the sponsor staff but were physicians of appropriate specialties and experienced clinical trial biostatisticians who could be trusted to review efficacy and safety data in such a way that bias is minimized. In subsequent chapters, we will review “best practices” for minimizing bias and for DMC operations in general. This book will concentrate on the safety role of the DMC in industry-sponsored trials. Safety data constitute 85% of data collected in clinical trials submitted to the U.S. Food and Drug Administration (Rochester 2008), are evaluated more subjectively than efficacy data, and, experience shows, constitute about 90% of DMC operations.

A recent draft guidance by the FDA on safety assessment practices introduces the term “Safety Assessment Committee (SAC).” The role of this committee is broader than that of the DMC. While the DMC will consist entirely outside consultants, the SAC will consist of sponsor internal as well as outside experts and will integrate safety information from a development program with information from other clinical trials of the same or similar drugs, preclinical studies, epidemiologic studies, and so on, in order to form a complete impression on emerging adverse events. There is also considerable overlap between DMC and SAC responsibilities and there may be some common members to both committees. There is no reason that a DMC cannot be a subcommittee of an SAC. Until there is some experience with the SAC concept, there is likely to be confusion as to who has the last word on the experimental drug’s safety profile. For now, it is important to note that the DMC is smaller and more focused than the SAC. We will continue to refer to the key safety committee as the DMC but, going forward, the reader should expect to see the term safety assessment committee appear in the literature (U.S. Food and Drug Administration 2015a).

1.2 Some Definitions

It will be useful to provide some brief definitions of important terms. We will return to these terms to provide more rigorous definitions later in the book.

The sponsor of a trial is the organization that has the ultimate responsibility for reporting the results to the regulatory authorities. For our purposes, it will most often be a pharmaceutical or biotechnology company but it
could be a university, government agency, or, in the case of orphan drugs, a patient–parent support group.

An adverse event (AE) is any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not considered related to the drug. An adverse event is deemed treatment-emergent if the adverse event is not a manifestation of a condition that existed prior to the clinical trial. It is not always easy to make this distinction. A serious adverse event (SAE) is any untoward medical occurrence that, at any dose, results in death, is life-threatening, requires inpatient hospitalization, or prolongation of existing hospitalization. This is the regulatory definition. We will see in Chapter 4, that this definition may generate different types of adverse events as serious in different countries due to differences in hospitalization policy.

The reader will be familiar with patients and possibly investigators being blinded to treatment assignment. In deference to our ophthalmology colleagues, we will use the term masked as a synonym for blinded. When treatment assignment is not masked to anyone we usually use the term open label.

The term monitoring is used in several different contexts in the pharmaceutical industry. Statistical monitoring refers to making calculations on accumulating efficacy data to justify early termination of a clinical trial (Proschan, Lan, and Wittes 2006) and/or sample size reestimation (Chuang-Stein, Anderson, Gallo et al. 2006). Safety monitoring by sponsor staff and DMC members refers to continual review of accumulating safety data during the trial. Site monitoring is a quality control procedure applied periodically during the trial by sponsor or contract clinical research associates (CRAs) (Woodin and Schneider 2003). In Chapter 8, we will review the newly emerging science of centralized statistical monitoring.

1.3 DMC in Federal Government–Sponsored Clinical Trials versus Pharmaceutical Industry Clinical Trials

DMCs had long been included in federal government–sponsored clinical trials before they appeared in pharmaceutical industry clinical trials. The latter took on a different form from the former due to differences in the characteristics of the trials being conducted (Herson 1993). Table 1.1 provides a summary of differences between federal government–sponsored trials and private industry sponsored trials. The federal government trials that are primarily research or science oriented with a public audience are sometimes community based (see, e.g., Djunaedi, Sommer, Pandji et al. 1988) and most often involve drugs already approved such as the Women’s Health Initiative progestin trial (Writing Group for the Women’s Health Initiative Investigators 2002; Wittes, Barrett-Connor, Braunwald et al. 2007). Industry
Data and Safety Monitoring Committees in Clinical Trials

trials are patient based and development or product oriented with the goal of convincing regulatory agencies that a new product should be approved and then reaching a market segment of patients through physicians. To illustrate this distinction consider the NIH-sponsored Lipids Research Clinics (LRC) trials (Lipids Research Clinics Program 1984a,b). At the LRC, design stage researchers asked the question “Does cholestyramine treatment to lower low density lipoprotein (LDL) for patients with hyperlipidemia have an effect on mortality and morbidity?” After 10 years of research, a positive result was found. Then, private industry was able to follow with development trials of fewer patients and shorter duration to show that lovastatin, for example, was effective in lowering LDL (Havel, Hunninghake, Illingworth et al. 1987). This conclusion was considered acceptable for approval since the NIH trial had established that lowering LDL had a positive effect on a clinically significant endpoint. When this pivotal trial began, the sponsor research staff “knew” the answer, that is, on the basis of the preliminary trials, they had confidence that the construct they designed would result in a positive outcome.

DMCs in NIH-sponsored trials are usually involved in trial design, sample size requirements, data analysis methods, data quality, publications policy, investigator evaluation, and so on, in addition to efficacy and safety review. These responsibilities become more complicated when, in addition to DMCs, the NIH trials include steering committees and endpoint adjudication committees.
The duties of DMCs operating within private industry trials are narrower in scope. However, some industry-sponsored trials also have these two types of committees. The roles of these committees will be described further in Chapter 2.

Lachin (2004) has indicated that there is more of a chance for conflict of interest in private industry trials than in government-sponsored trials. Pharmaceutical firms have learned that good science and objectivity are the best strategies for shortening the time to approval. Thus, DMCs in the pharmaceutical industry evolved as “blue ribbon” panels for independent certification on issues such as adjudication of efficacy endpoints, conduct of planned interim analyses, and safety monitoring. DMCs in the pharmaceutical industry are a node in an aggressive drug development process leading to marketing. There are considerable financial consequences in the outcome of the trial and numerous opportunities for bias and/or conflict of interest.

1.4 Stewardship

While sponsors retain DMCs to add to the objectivity and credibility of trials, DMC members can best fulfill their obligations to sponsors and patients by considering themselves responsible for the stewardship of the trial. This implies both the preservation of credibility of the trial and the aegis of patient safety. How this stewardship can best be carried out will be covered in later chapters of this book. For now, it is sufficient to note that DMC members must be proactive and consider themselves “board of directors” of the trial if they are to fulfill their responsibilities to the patients and sponsor.

1.5 Some Recent History

1.5.1 Development of DMCs in the Pharmaceutical Industry

One of the first-known DMCs in pharmaceutical industry clinical trials was the cimetidine stress ulcer clinical trial in 1988–1989 (Herson, Ognibene, Peura et al. 1992). This trial was conducted in intensive care units and was designed to compare cimetidine to placebo for prophylaxis of upper gastrointestinal bleeding due to stress (Martin, Booth, Karlstadt et al. 1993). The primary efficacy endpoint for this trial was prophylactic failure defined as the appearance of bright red blood and other bleeding-related outcomes. A supplementary definition of failure was “insufficient therapeutic effect” (ITE) which investigators could invoke at their discretion to remove a patient from the study if they feared the patient might begin to bleed. The sponsor
decided to create a DMC for independent and masked certification of bleeding data and determination if ITE decisions were made according to usual clinical practice and safety monitoring including judgments on whether or not death was disease related. The decision to involve a DMC in this trial came from the sponsor’s experience on earlier clinical trials for this product where the possibility of bias in sponsor staff efficacy classifications raised credibility issues with FDA. The sponsor and consultants used some aspects of DMCs on NIH-sponsored trials to write the charter for their DMC.

Physicians chosen for this committee had expertise in gastrointestinal disease and emergency medicine. The data for DMC review were sent by the sponsor to a contract research organization (CRO) with treatment assignments coming from a manufacturing office of the sponsor rather than from those sponsor staff involved in the trial. All data processing for the DMC was performed by the CRO. When the trial ended the DMC presented the results to the sponsor. However, those sponsor staff members still evaluating safety were not informed of results to avoid introduction of bias in ongoing safety evaluations.

1.5.2 Guidance Documents: FDA, NIH, and ICH

Since DMCs first appeared in pharmaceutical trials in the early 1990s, much has been written about the role of DMCs. Examples include the FDA guidance finalized in 2006 (U.S. Food and Drug Administration 2006), the International Conference on Harmonisation (ICH) E-3 guideline on clinical study reports (International Conference on Harmonisation 1995), the E-6 guideline on good clinical practices (International Conference on Harmonisation 1996), and the E-9 guideline on statistical principles (International Conference on Harmonisation 1998). The E2A guideline on clinical data safety management (International Conference on Harmonisation 1994) provides some useful definitions but the vocabulary and expedited reporting requirements have been superseded by some recent FDA guidances to industry all of which have implications for DMC responsibilities. In addition to the safety assessment guidance referred to above, these would include the guidance on safety-reporting requirements (U.S. Food and Drug Administration 2012), a risk-based approach to monitoring (U.S. Food and Drug Administration 2013), and risk evaluation and mitigation strategies (U.S. Food and Drug Administration 2015b). We will return to these guidances in later chapters.

Hemmings and Day (2004) provide a good discussion of regulatory issues related to DMCs. Literature oriented toward NIH-sponsored trials would include the NIH guidelines (U.S. National Institutes of Health 1998, 1999, 2000), the DAMOCLES literature search (Sydes, Spiegelhalter, Altman et al. 2004), and books by Ellenberg, Fleming, and DeMets (2002) and DeMets, Furberg, and Friedman (2006). Recently some prestigious medical journals have adopted a policy of not publishing results of industry-sponsored
Phase III trials unless an independent DMC was involved (Fontanarosa, Flanagin, and DeAngelis 2005).

1.5.3 Other Vehicles for Patient Protection

DMCs are not the only source of protection of patient safety. Each clinical trial site (hospital, clinic, and doctor’s office) comes under the auspices of an Institutional Review Board (IRB) or Ethics Committee which reviews protocols and their amendments and receives periodic safety reports. Each sponsor has internal safety review mechanisms and some larger medical institutions have internal DMC-like committees who review safety on ongoing trials regardless of sponsorship. The relationship between these entities and DMCs will be covered later in this book.

1.6 A DMC’s Place in the Drug Development Cycle

1.6.1 Phases of Drug Development

Drug development is often broken into several phases—molecular, preclinical, exploratory, confirmatory, and postmarket (Scheiner 1997). The exploratory and confirmatory phases include those clinical trials that will be used for drug approval. The exploratory trials are often referred to as phase I and II. These trials are primarily proof of concept trials which establish dosage (maximum tolerated dose) and efficacy (minimum effective dose). Some prefer to call these trials test of concept rather than proof but in any case it is important to consider these early trials as learning trials. These are followed by the confirmatory trial(s) known as phase III. Here, we apply what we learned in earlier phases regarding dose, schedule, and appropriate patient populations to design a trial that is expected to demonstrate efficacy and safety with statistical precision. Phase III trials are sometimes called pivotal trials because they are the trials that will form the basis of the regulatory decision. The terms confirmatory, phase III, and pivotal will be used synonymously in this book.

1.6.2 Limitations of a Clinical Program for Revealing Safety Issues

The clinical program is conducted to produce evidence of efficacy and safety sufficient for marketing approval by regulatory agencies. This program will provide evidence of serious adverse events that occur with highest frequency. It must be understood that it is the DMC’s role to consider these adverse events but, obviously, not to be responsible for all SAEs that may ever be associated with the drug during its lifetime.
A single pivotal clinical trial designed to demonstrate efficacy will not be able to assess rare events or those that represent delayed effects. The DMC may not gain an understanding of which AEs will become chronic during the duration of a clinical trial. Despite the limitations, several clinical trials have been terminated for safety in recent years. A partial listing is found in Table 1.2. In the period 2008–2010, 19% of phase II trials were terminated due to safety (17 of 87) and 21% of 83 products failed due to safety in phase III or during regulatory review (Arrowsmith 2011a,b).

In a clinical program, it is always useful to keep in mind the “rule of 3000/n” where \( n \) = the number of patients exposed to the drug in a clinical program. This calculation yields a lower bound on the sensitivity of the trial to detect adverse events on an incidence/1000 basis. For example if \( n = 1000 \) patients, then, the clinical program is likely to find at least one case of AEs that occurs at an incidence of 3000/1000 (= 3) or 3/1000. If \( n = 500 \), then, the clinical program would be sensitive to find at least one case that occurred with incidence 6/1000. To be able to find an adverse event that occurs at the rate of 1/100,000 a program of 300,000 patients would be required. This type of AE could only be found in postmarket surveillance. Table 1.3 presents a table for sensitivity for AE detection in a hypothetical clinical program for development of a diabetes drug.

### Table 1.2

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication in Trial</th>
<th>Risk</th>
<th>Trial Terminated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torcetrapib</td>
<td>Raise HDL (high-density lipoprotein)</td>
<td>Increase in cardiovascular events and death</td>
<td>2006</td>
</tr>
<tr>
<td>Estrogen + progestin</td>
<td>Prevention of chronic disease</td>
<td>Invasive breast cancer, coronary heart disease</td>
<td>2002</td>
</tr>
<tr>
<td>Tirilazad</td>
<td>Head trauma</td>
<td>Death</td>
<td>1994</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>Polyp prevention</td>
<td>Thrombotic events</td>
<td>2004</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Polyp prevention</td>
<td>Thrombotic events</td>
<td>2004</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Alzheimer’s</td>
<td>Fear of thrombotic events</td>
<td>2004</td>
</tr>
</tbody>
</table>

### Table 1.3

Sensitivity to AE Detection in a Clinical Program for Development of a Diabetes Drug

<table>
<thead>
<tr>
<th>Protocol No.</th>
<th>Description</th>
<th>n for This Protocol</th>
<th>AE Detection Rate/1000</th>
<th>n (Cumulative)</th>
<th>Cumulative AE Detection Rate/1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>26 weeks + 3 months extension</td>
<td>348</td>
<td>8.6</td>
<td>348</td>
<td>8.6</td>
</tr>
<tr>
<td>12</td>
<td>26 weeks + 3 months extension</td>
<td>406</td>
<td>7.4</td>
<td>754</td>
<td>4.0</td>
</tr>
<tr>
<td>21</td>
<td>26 weeks + 6 months extension</td>
<td>510</td>
<td>5.9</td>
<td>1264</td>
<td>2.4</td>
</tr>
<tr>
<td>22</td>
<td>26 weeks + 6 months extension</td>
<td>928</td>
<td>3.2</td>
<td>2192</td>
<td>1.4</td>
</tr>
<tr>
<td>31</td>
<td>52 weeks</td>
<td>604</td>
<td>5.0</td>
<td>2796</td>
<td>1.1</td>
</tr>
</tbody>
</table>
see that the sensitivity of the individual protocols to detect AEs ranges from 3.2 to 8.6/1000. As the program progresses, sensitivity does not drop below 3/1000 until the first 26-week + 6-month extension trial (protocol 21). At the conclusion of the program with 2796 patients, cumulative AE sensitivity is 1.1/1000. There are many potential AE types that would occur at a rate of 1/100,000 and thus the need for postmarket surveillance to clarify the safety profile of the drug.

Table A.1 in the Appendix presents a table of adverse events observed in placebo-controlled trials for marketed drugs together with the number of patients enrolled on each treatment arm. The list reveals that the adverse events observed are the most common and not necessarily most serious. The postmarket phase will reveal the rare and potentially serious adverse events.

We will revisit this table again in various chapters.

Lin, Chern, and Chu (2003) acknowledge this limitation but are concerned that failure to find cases of liver toxicity in a confirmatory trial might lead to a conclusion that the experimental drug is not associated with liver toxicity. They provide useful guidelines for surrogates, such as laboratory values, to liver disease that might be uncovered in a clinical trial. DMC members can, presumably, discuss surrogates for other diseases when appropriate.

Postmarket experience will be needed to uncover SAEs that occur with low incidence. The clinical programs generally enroll patients with much narrower characteristics than for those who will receive the drug after approval. Eligibility requirements specify strict age groups, and prohibit enrollment of patients with certain medical histories, comorbidities, and concurrent medications. As larger numbers and newer types of patients are exposed to the drug postapproval newer SAEs are likely to emerge. In the postapproval era, papers appear in the literature presenting safety profiles of drugs using over many controlled clinical trials. Examples would include Schoenfeld (1999) for gastrointestinal safety of the nonsteroidal anti-inflammatory drug meloxicam, Strampel, Emkey, and Civitelli (2007) for the safety profile of bisphosphonates in the treatment of osteoporosis, and Wernicke, Lledo, Raskin et al. (2007) for the cardiovascular safety profile of duloxetine used to treat major depressive disorder. A summary of limitations of a clinical program to uncover important safety issues is presented in Table 1.4.

**TABLE 1.4**

Limitations of Safety Assessment by a DMC in a Single Clinical Trial

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>DMC is likely to find only AEs that occur immediately and with highest frequency.</td>
</tr>
<tr>
<td>2.</td>
<td>DMC not likely to find rare or delayed effects.</td>
</tr>
<tr>
<td>3.</td>
<td>DMC may not develop an understanding of chronic effects.</td>
</tr>
<tr>
<td>4.</td>
<td>Due to stringent eligibility requirements, clinical trial patients are not representative of those who will be treated with the drug after approval. Different patient types on varying concomitant medications may have a different but more common safety experience than the clinical trial patients.</td>
</tr>
<tr>
<td>5.</td>
<td>DMC may miss subtle signals that involve extensive analysis and additional data on surrogates of AEs.</td>
</tr>
</tbody>
</table>
1.6.3 Postmarket Safety Actions

After FDA approves a drug, there are several actions the agency may take when safety concerns arise. These actions include ordering the drug withdrawn from the market, attaching a black box warning to the drug’s package insert (i.e., label change to highlight the description of the SAE in the package insert), and ordering discontinuation of a dosage form. Carpenter, Zucker, and Avorn (2008) report that during the period 1993–2004, FDA made 11 safety-based withdrawals and 14 black box warnings (21 drugs had either a withdrawal or black box warning or both) and 36 had dosage form discontinuation. Carpenter, Zucker, and Avorn (2008) report that during the period 1993–2004, FDA made 11 safety-based withdrawals and 14 black box warnings (21 drugs had either a withdrawal or black box warning or both) and 36 had dosage form discontinuation. Carpenter, Zucker, and Avorn (2008) report that during the period 1993–2004, FDA made 11 safety-based withdrawals and 14 black box warnings (21 drugs had either a withdrawal or black box warning or both) and 36 had dosage form discontinuation. Carpenter, Zucker, and Avorn (2008) report that during the period 1993–2004, FDA made 11 safety-based withdrawals and 14 black box warnings (21 drugs had either a withdrawal or black box warning or both) and 36 had dosage form discontinuation. Carpenter, Zucker, and Avorn (2008) report that during the period 1993–2004, FDA made 11 safety-based withdrawals and 14 black box warnings (21 drugs had either a withdrawal or black box warning or both) and 36 had dosage form discontinuation. Carpenter, Zucker, and Avorn (2008) report that during the period 1993–2004, FDA made 11 safety-based withdrawals and 14 black box warnings (21 drugs had either a withdrawal or black box warning or both) and 36 had dosage form discontinuation. Carpenter, Zucker, and Avorn (2008) report that during the period 1993–2004, FDA made 11 safety-based withdrawals and 14 black box warnings (21 drugs had either a withdrawal or black box warning or both) and 36 had dosage form discontinuation.

Lasser, Allen, Woolhandler et al. (2002) indicate that there were 548 new chemical entities approved by FDA during the period 1975–1999 and of these, 56 drugs (10.2%) acquired a black box warning or were withdrawn. On the basis of the FDA’s adverse experience reporting system during the period 1969–2002, a total of 75 drugs or drug products were removed and 11 received restricted prescription requirements (Wysowski and Swartz 2005). Table 1.5 presents a partial list of drugs withdrawn from the market for safety reasons during the period 1975–2007.

Of the 740 new molecular entities approved by FDA in 1980–2009, only 26 were withdrawn for safety reasons (3.5%). An additional 92 products were withdrawn for other reasons. The frequency of safety withdrawals decreased from 50% of withdrawals in the 1980s, 40% in the 1990s to 10% in the 2000s (Quereshi, Seoane-Vazquez, Rodriguez-Monguio et al. 2011).

Lasser, Allen, Woolhandler et al. (2002) list 28 drugs for which black box warnings were issued during the period 1975–2000. The timing of the warnings ranged from 1- to 23-year postapproval. The frequency of black box warnings appears to have accelerated since 2000 with adverse events of new awareness and interest and new sources of safety evidence. For example, since 2000, 50 drugs received black box warnings for suicide risk (Mundy 2008). Rosiglitazone, indicated for diabetes, received a black box warning for cardiovascular risk with much of the evidence coming from a meta-analysis published by an academic cardiologist (Harris 2007; Nissen and Wolski 2007).

There is a considerable controversy about the timing and appropriateness of specific postapproval drug actions (Friedman, Woodcock, Lumpkin et al. 1999; Lurie and Sasich 1999; Lasser, Allen, Woolhandler et al. 2002; Carpenter, Zucker, and Avorn 2008). Much of this controversy stems from a misunderstanding of the extent that a clinical program can reveal safety concerns and the differences of opinion in the ability and methodology to assess early safety signals from clinical trials. The following chapters will explain how DMCs can help in identification of safety signals.

1.6.4 Role of DMCs in Exploratory and Confirmatory Trials

This book will concentrate on DMCs in confirmatory trials where they are used most frequently. There is no doubt that there is a need for safety
TABLE 1.5

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication/Class</th>
<th>Risks</th>
<th>Approved</th>
<th>Withdrawn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pergolide</td>
<td>Parkinson’s disease</td>
<td>Heart valve damage</td>
<td>1988</td>
<td>2007</td>
</tr>
<tr>
<td>Tegaserod maleate</td>
<td>Irritable bowel syndrome</td>
<td>Myocardial infarct; stroke</td>
<td>2002</td>
<td>2008</td>
</tr>
<tr>
<td>Valdecoxib</td>
<td>Pain, anti-inflammatory</td>
<td>Heart attack, stroke</td>
<td>2001</td>
<td>2005</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>Pain</td>
<td>Thrombotic events</td>
<td>1999</td>
<td>2004</td>
</tr>
<tr>
<td>Cervastatin</td>
<td>Lipid lowering</td>
<td>Muscle damage</td>
<td>1997</td>
<td>2001</td>
</tr>
<tr>
<td>Rapacuronium bromide</td>
<td>Injectable anesthetic</td>
<td>Bronchospasm</td>
<td>1999</td>
<td>2001</td>
</tr>
<tr>
<td>Alosetron</td>
<td>Irritable bowel syndrome in women</td>
<td>Intestinal damage</td>
<td>2000</td>
<td>2000</td>
</tr>
<tr>
<td>Cisapride</td>
<td>Night heartburn</td>
<td>Fatal heart rhythm</td>
<td>1993</td>
<td>2000</td>
</tr>
<tr>
<td>Troglitazone</td>
<td>Type 2 diabetes</td>
<td>Severe liver toxicity</td>
<td>1997</td>
<td>2000</td>
</tr>
<tr>
<td>Astemizole</td>
<td>Antihistamine</td>
<td>Fatal heart rhythm</td>
<td>1988</td>
<td>1999</td>
</tr>
<tr>
<td>Grepafoxacin</td>
<td>Antibiotic</td>
<td>Fatal heart rhythm</td>
<td>1997</td>
<td>1999</td>
</tr>
<tr>
<td>Mibefradil</td>
<td>High blood pressure and chronic stable angina</td>
<td>Dangerous interactions with other drugs</td>
<td>1997</td>
<td>1998</td>
</tr>
<tr>
<td>Bromfenac</td>
<td>Pain</td>
<td>Severe liver damage</td>
<td>1997</td>
<td>1998</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>Antihistamine</td>
<td>Fatal heart rhythm</td>
<td>1985</td>
<td>1998</td>
</tr>
<tr>
<td>Fenfluramine</td>
<td>Obesity</td>
<td>Heart valve abnormalities</td>
<td>1973</td>
<td>1997</td>
</tr>
<tr>
<td>Dexfenfluramine</td>
<td>Obesity</td>
<td>Heart valve abnormalities</td>
<td>1996</td>
<td>1997</td>
</tr>
<tr>
<td>Flosequinan</td>
<td>Cardiovascular disease</td>
<td>Increased mortality</td>
<td>1992</td>
<td>1993</td>
</tr>
<tr>
<td>Temafloxacin</td>
<td>Antibiotic</td>
<td>Hemolytic anemia, renal failure, and so on</td>
<td>1992</td>
<td>1992</td>
</tr>
<tr>
<td>Encainide</td>
<td>Antiarrhythmic</td>
<td>Increased mortality</td>
<td>1986</td>
<td>1991</td>
</tr>
<tr>
<td>Nomifensine</td>
<td>Antidepressant</td>
<td>Hemolytic anemia</td>
<td>1984</td>
<td>1986</td>
</tr>
<tr>
<td>Suprofen</td>
<td>Analgesic, NSAID</td>
<td>Pain</td>
<td>1984</td>
<td>1986</td>
</tr>
<tr>
<td>Zomepirac</td>
<td>Analgesic, NSAID</td>
<td>Anaphylaxis</td>
<td>1980</td>
<td>1983</td>
</tr>
<tr>
<td>Benoxaprofen</td>
<td>Analgesic, NSAID</td>
<td>Jaundice</td>
<td>1982</td>
<td>1982</td>
</tr>
<tr>
<td>Ticrynafen</td>
<td>Antihypertensive</td>
<td>Hepatic toxicity</td>
<td>1979</td>
<td>1980</td>
</tr>
<tr>
<td>Azarbine</td>
<td>Psoriasis</td>
<td>Thromboembolism</td>
<td>1975</td>
<td>1977</td>
</tr>
</tbody>
</table>


a Nonsteroidal anti-inflammatory drug.
monitoring in exploratory trials especially since these represent the first use of new drugs in humans. However, it is not clear that this must be accomplished through a completely independent DMC and many feel that engaging a completely independent committee would at this stage slow down the development process. In a paper commissioned by the Society for Clinical Trials, Dixon, Freedman, Herson et al. (2006) give useful guidance on this issue as do Hibberd and Weiner (2004).

The phase I trial uses objective safety data and the protocol team in-house together with participating investigators who can generally handle the safety monitoring with little question of credibility. Phase II does not usually require a completely independent DMC but it often makes sense to include one or two outside members (physician or physician plus biostatistician) to the protocol team with the understanding that one of the outside people will take the role of Chair of the DMC when the drug enters confirmatory trials. This allows for some outside expertise in the first efficacy trials and provides drug familiarity for the confirmatory DMC. Of course, if the trial is first for a novel drug such as a drug-eluting stent or one utilizing gene therapy or nanotechnology, it may be advisable to add to the DMC additional outside reviewers with the particular expertise.

1.6.5 Blurring of Phases I, II, and III

Regulators have become concerned about the recent use of Phase Ib expansion protocols in oncology. One trial that caught their eye is the KEYNOTE-001 trial for the PD-1 inhibitor pembrolizumab (Patnaik, Kang, Rasco et al. 2015) which was initiated in 2011 to determine a dose for phase II trials in advanced solid tumors. As favorable responses were observed, the sample size increased and different tumor types were added until there were over 1200 patients on this Phase 1b protocol. Among these, there were 173 patients with advanced melanoma and this was considered sufficient for accelerated approval. However, as the number of patients increased the sponsor did not add a DMC. Had development progressed in the traditional phase I, II, and III sequence, there would certainly have been a DMC for the confirmatory trial.

1.6.6 Investigator-Sponsored Trials

In the United States, investigator-sponsored trials are those conducted by an academic physician (investigator) using drugs provided by a pharmaceutical company. The investigator, rather than the sponsor, is responsible for all interaction with FDA. Thus, sponsors have little control over investigator-sponsored trials but there is clearly a need for safety review. When the investigator-sponsored trial is conducted within a single institution and that institution has a standing internal DMC to monitor trials that do not otherwise have a DMC, this body would usually be sufficient. If no
such panel exists or the trial is multicenter, investigators might want to consider some of the ideas for exploratory trials above.

1.6.7 Open Label Trials

A clinical trial needn't be masked to require a DMC. Trials for mechanical heart valves, for example, are uncontrolled yet have serious safety problems such as major bleeding events, thromboembolic events, and mortality (Grunkenmeier, Jin, and Starr 2006). It is important that there be independent review of accumulating data. In Chapter 3, we will describe how these meetings are conducted.

For chronic conditions such as epilepsy, Parkinson’s disease, and hypertension, it is common for patients who exit phase II or III trials to be put on open label extension studies. These trials are uncontrolled and have the purpose of obtaining more precision in estimation of incidence of adverse events and, perhaps, to uncover new adverse events encountered in long-term exposure. DMCs may be asked to review data from ongoing open label extension studies while they are reviewing data from controlled trials. At the very least, the DMC should review the extension study results at the end of the final confirmatory trial. Day and Williams (2007) provide insight in the role of the open label extension study in drug development.

1.6.8 Emerging Trial Designs of Interest

As the pace of drug development accelerates, much attention has been drawn to pragmatic trials, biosimilar trials, SMART/dynamic treatment strategy trials, umbrella trials, and basket trials. We will explain the role of DMCs in these trials in Chapter 8, after we get further grounding in DMC operations. For now, it is safe to say that these types of trials, although they present certain challenges, all require independent review of accumulating data.

1.7 Pharmaceutical Industry Demographics

1.7.1 Size of Companies

For the purposes of this book, the global pharmaceutical/biotechnology industry will be divided into three gross size groups. The term “Big Pharma” will apply to multinational companies that have many products in development and many products on the market either as recently approved or generic. “Middle Pharma” will refer to companies with just a few products on the market and several in development. Those companies working in the development of their first product will be called “Infant Pharma.”
1.7.2 Public versus Private Companies

All of the Big Pharma companies and most of the Middle Pharma companies are publicly owned. Many of the Infant Pharma firms are publicly owned and those that are financed by venture capital firms seeking to raise additional rounds of financing while pursuing an exit strategy which would consist of taking the company public or selling it to a larger company. Today’s reality is that, regardless of size, these companies are vulnerable to information that must be reported to investors on company activities and especially R&D (research and development) activities. Actions taken by DMCs can affect the financial status of these companies although differently depending on size. We will return to this important topic at various times in this book. For purposes of contrast, we will be referring to Big versus Infant Pharma in much of what follows. As would be expected, Middle Pharma shares some characteristics of both its big and little brothers. Middle Pharma is very dependent on Big Pharma as a marketing partner for their products and for investment in R&D programs. Middle firms are very dependent on public markets for financing their new products. If a Middle Pharma firm has not had a product approved since it emerged from infancy and has had a string of disappointments since emerging, it would be highly vulnerable to DMC negative decisions. The differences in the three levels of companies are further described in Table 1.6.

TABLE 1.6
Characteristics of Pharmaceutical/Biotechnology Companies by Size

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Big Pharma</th>
<th>Middle Pharma</th>
<th>Infant Pharma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Products on the market</td>
<td>Many products on the market</td>
<td>Some products on the market</td>
<td>None</td>
</tr>
<tr>
<td>Financial organization</td>
<td>Public</td>
<td>Public</td>
<td>Public or venture capital financed</td>
</tr>
<tr>
<td>Corporate goal</td>
<td>Expand product line</td>
<td>Expand product line; create corporate partnerships with Big Pharma</td>
<td>Show progress to increase financing, license the product to the larger company</td>
</tr>
<tr>
<td>Clinical program financing</td>
<td>Complete</td>
<td>Almost complete</td>
<td>Trial-by-trial basis, further funding for pivotal trial might depend on the results of interim analysis</td>
</tr>
<tr>
<td>Vulnerability to negative trial information</td>
<td>Small, unless the drug is the successor to the blockbuster</td>
<td>Modest, especially vulnerable if it has been some time since the last product was approved</td>
<td>Considerable</td>
</tr>
<tr>
<td>DMC procedures</td>
<td>In place</td>
<td>In place</td>
<td>Not well developed, often created as the trial develops</td>
</tr>
</tbody>
</table>
1.8 In Conclusion

We have now seen the rationale and the setting for DMCs in the pharmaceutical industry. In the next chapter, we will learn more about the members of the safety monitoring team and their roles.

DMCounselor

Q1.1 I agreed to serve on a DMC for an Infant Pharma company which has gone public. The drug is a novel approach to pancreatic cancer. The trial is actually phase II but their regulatory consultant feels that if the results are positive, the regulatory agency will consider it phase III. The sponsor has now told us that we will meet only once at the end of the trial because their board of directors is concerned that if we recommend early trial termination due to a safety concern, they would have to include this information in a press release and this would have a bad effect on their stock price. I would like to walk away from this DMC but this is an important drug and I would like to be associated with its development. What should I do?

A I had doubts about this sponsor when I heard that they have a consultant who told them that a phase II trial would count as a phase III trial in this case. It is doubtful that sufficient safety data would arise in a single phase II trial. In any case, this sponsor’s restrictions do not allow the DMC to fill the stewardship role. It is the DMC’s responsibility to decide how often they will meet, not the sponsor’s. The DMC must review accumulated data during the trial so that patients are not put at risk for a trial’s duration if serious concerns arise during the trial. If this sponsor is afraid of an interim recommendation, why would they want a DMC to make an assessment at the end of the trial? You should try to convince the sponsor not to begin the phase II/III until they have more confidence in the safety of this product. At that point, there should be much less financial risk in having a DMC schedule periodic meetings during the trial.

Q1.2 I was asked to serve on a DMC for a phase II trial. I said that I would do so provided I would automatically be placed on the DMC for the phase III trial. The sponsor refused. Why would they do this?

A The sponsor was right in this instance. While it is a good idea to have some continuity between phase II and phase III, it is also good to have some new people on the phase III trials. In choosing which, if any, phase II DMC members would carry over to the phase III DMC
sponsors would usually wait until the phase II trial was concluded at which time they would have learned from that trial what type of expertise was needed for the phase III DMC.

Q1.3 I was asked to serve as a biostatistician member of a DMC. I accepted and found out that the trial was phase I. Is a biostatistician member really needed for a phase I trial?

A Outside members are not usually employed on phase I trials but the sponsor appears to think that it is necessary in this case. Do not think that you are not needed just because you will not be looking at confidence intervals and explaining survival curves to the physician members? Your knowledge of protocols, objectivity, logical thinking, and so on, would be very important to the committee.

Q1.4 I was asked to be a physician member of a DMC for a neurology drug by a Middle Pharma company. I accepted but later found out that the trial was completed 5 months ago without a DMC. The sponsor is now in negotiations to license the drug to a Big Pharma company and the latter insists that there be an independent review of safety before talks can continue. Is this an appropriate use of my time?

A The committee the sponsor is forming is not a data monitoring committee but an ad hoc committee to come in once and make statements about safety presumably by also taking efficacy into account. This committee will obviously be unmasked and will not have had the benefit of considering and scrutinizing safety issues as they arise. If you feel you want to serve, this is OK but make sure that the sponsor does not represent your committee as a DMC. The sponsor must also understand that your committee is not coming together for 2 hours to be a “rubber stamp” on safety. If your committee needs more time and information it must be granted. Also, your committee should not be brought to the table either as individuals or collectively to be part of business negotiations with the company purchasing the license.

Q1.5 I am a physician member of an Infant Pharma co. trial of a new agent for interstitial bladder cancer. This is my first participation in a pharmaceutical industry DMC. I have about 10 years of experience working on DMCs sponsored by NIH. The DMC has been meeting several times over the past 18 months. In that time, there has been an ongoing Securities Exchange Commission investigation of the sponsor, the chief executive officer (CEO) has resigned and left the country, we are now on our third vice president (VP)—chief medical officer, and each time the medical officer resigns, the two or three clinical operations staff members leave as well. Is this typical of Infant Pharma? How can I tell if I am wasting my time on this?

A These things do occur in Infant Pharma but I am not aware of occurrences to this extent. I understand your concern and the culture shock
you must be feeling. However, I think you must separate the officers of
the company from the actual trial operations. In spite of the turnover,
are you getting data of reasonable quality to examine? Do you have any
evidence of fraudulent data? I would expect the clinical operations to
be separate from the corporate-level problems. This would especially
be the case if a CRO (contract research organization) were running the
trial. I would encourage you to discuss your concern with the other
DMC members and your DMC Chair should indicate that the DMC
has a concern with the turnover among clinical operations staff. No, I
do not think you are wasting your time.
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