

CLINICAL RESEARCH
LAW AND COMPLIANCE
HANDBOOK

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CLINICAL RESEARCH LAW AND COMPLIANCE HANDBOOK. JOHN E STEINER JR, ESQ, EDITOR. SUDBURY, MA: JONES AND BARTLETT; 2006. XXX + 460 PAGES. HARDCOVER \$89.95. ISBN 0-7637-4725-4.

Published data are as good as the research behind them. In human-subjects research, the scientific soundness of the protocol is one element that contributes to the value of a study. Another critically important element is the extent to which human-subjects protection is maintained throughout the study's development and performance.

A fitting subtitle for *Clinical Research Law and Compliance Handbook* might be *How We Wish All Human-Subjects Research Were Done*. The book, edited by John E Steiner Jr, the chief compliance officer and privacy official at the Cleveland Clinic Health System, provides a solid overview of the regulatory and legal issues pertinent to the conduct of clinical trials involving human subjects. Strict adherence to the principles described in the book would go a long way toward ensuring human-subjects safety and high-quality data.

However, the text also provides an appreciation of just how difficult it can be to abide by the regulations that govern research. The clinical-research regulatory environment is complex and demanding. Each of the book's 12 chapters, written by different authors with experience in the field, addresses a different aspect of clinical-research compliance.

Although the first chapter describes the key compliance issues facing academic medical organizations, the issues it describes are not limited to academic settings. The authors open the chapter by defining the term *good clinical practice*, which is often interpreted differently by different people in research compliance. These authors describe good clinical practice, or GCP, as "a term coined by the pharmaceutical and medical device industry to encompass international and federal regulations, as well as industry-accepted standards, that govern the conduct of clinical trials on humans". The rest of the chapter describes methods that can be used to meet GCP requirements. The methods include development of standard operating procedures (SOPs), adequate training of investigators and staff, and quality-assurance auditing and would be appropriate for all potential research environments,

not just academic medical organizations. Checklists and sample SOPs are included, and the information provided is extensive and helpful. Unfortunately, it doesn't include any magic words of wisdom on how to achieve and implement this level of compliance given the realities of limited budgets and busy staff.

Chapter 1 covers only the basics of study conduct. The next three chapters cover several aspects of the business side of research, including clinical-research billing, contract concerns, and operational and budget issues involved in clinical trials. As the book mentions, principal investigators and study staff are typically most concerned about the level of care provided to patients and study volunteers. Therefore, adequate resources must be in place to address those perhaps lower-profile, but highly important, aspects of the research process.

Interesting—or perhaps, depending on one's perspective, potentially alarming—discussion of fraud and abuse follows in Chapter 5. The two federal statutes of greatest relevance to fraud and abuse cases are the federal Antikickback Statute and the False Claims Act. The authors write that those statutes apply not only to financial matters but also to the overall conduct of research. "Sham researchers and authors, inadequate oversight, faulty safety precautions, and study misdesign now are considered fraud and abuse issues in much the same way as a straightforward kickback or inappropriate claim for government research money", the authors write. Two paragraphs in the chapter are devoted to disclosure requirements implemented by journals; these are helpful but of course not sufficient to reflect the amounts of work and thought that go into the development of conflict-of-interest guidelines developed by journal editors.

Later chapters delve more deeply into the regulations that apply specifically to the day-to-day review and conduct of research. Chapter 7 discusses postmarketing studies, those done to gather data in addition to those provided to support companies' marketing applications and label changes, as

the authors describe them. In some cases, the Food and Drug Administration (FDA) requires companies to gather additional safety data as a condition of its approval of the original marketing application. However, as the authors point out, there must be a legitimate research purpose for the postmarketing studies; a study that is designed only to raise awareness (or market share) of a product may run afoul of the Antikickback Statute. One potential red flag is a study overseen by a company's promotion and marketing departments, the authors caution.

Institutional review boards, conflicts of interest, technology in clinical trials, and international clinical trials are discussed in later chapters. The book closes with a discussion of court cases that have arisen out of clinical research.

This book's emphasis is on clinical trials involving drugs and devices. The reader should keep in mind that many of the issues discussed, such as informed consent and adherence to a study protocol, are also important in human-subjects research that does not involve drugs or devices, such as behavioral studies. The first table in the book indicates that the most common problem seen by FDA at clinical sites is

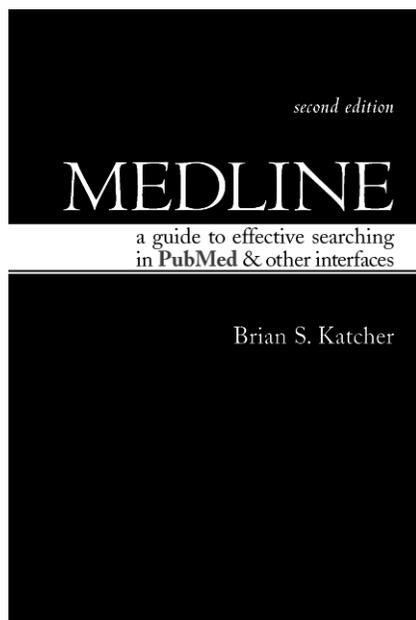
inadequate informed consent, which would be just as important, and potentially cause a similar level of problems, in a behavioral study as in a clinical trial.

The book is a valuable addition to the literature on clinical-trial conduct. However, it is a dense and not inexpensive work and therefore is probably most appropriate for readers with a particular interest in research compliance.

One other thing to keep in mind is that laws and regulations can go only so far. Clinical-research regulations were in place at times of well-known incidents that caused severe harm to, or in some cases the death of, research subjects. Human-subjects research is a resource-intensive enterprise, and the pressures to produce results can be tremendous. A thorough commitment to human-subjects protection, and not just a focus on the regulations, is required to ensure that study volunteers remain protected.

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MEDLINE: A GUIDE TO EFFECTIVE SEARCHING IN PUBMED & OTHER INTERFACES. SECOND EDITION. BRIAN S KATCHER. SAN FRANCISCO: THE ASHBURY PRESS; 2006. XI + 136 PAGES. SOFTCOVER \$31.95/ ISBN 13: 978-0-9673445-1-5, ISBN 10: 0-9673445-1-4.

In the second edition of this book, Brian S Katcher aims to teach readers to “think critically in applying MEDLINE’s power” when searching the elegantly indexed bibliographic database. This book is not meant to replace tutorials and other resources for the novice but rather seeks to cultivate an understanding of MEDLINE’s indexing scheme and the vocabulary needed for querying the database. Katcher writes for the end user in a clear, readable style and intends for the book to be read in its entirety away from the computer. This edition provides up-to-date information on the constantly changing indexes and corrects several omissions for which the first edition was criticized. The result is a thorough yet concise practical guide that may yield a profitable return on a small time investment.

The book opens with an interesting history of MEDLINE’s evolution from the printed *Index Catalogue of the Library of the Surgeon General’s Office* in 1876 to the expansive online literature-retrieval system available today. The first chapter also introduces Boolean logic and the widely used Entrez PubMed interface. Chapter 2 examines each MEDLINE index and presents strategies for combining index terms to construct useful searches. Katcher skillfully articulates the dilemma of precision versus recall and presents helpful examples of various query strategies and resulting citations.

The author follows that chapter with a detailed explanation of Medical Subject Headings (MeSH) and their organization into branching hierarchies. Katcher’s instructive examples are helpful, illustrating the disambiguation of MeSH categories and subheadings. Techniques for increasing recall or precision, such as MeSH term “explosion” and free text searches, and cautions about their use are not neglected. An extensive discussion of the vast Chemicals and Drugs category of MeSH terms and the Pharmacologic Action category, introduced in 2003, although enlightening, may be of little interest to some readers.

Katcher highlights the distinction between publication types and MeSH

terms in Chapter 4. For example, the Publication Type “practice guideline” and the MeSH term “practice guidelines” garner quite different search results, the former leading to published practice guidelines and the latter to information about their development. Aside from that section, Chapters 4 and 5 provide less useful information that is either freely available through online tutorials or innately known. In the last chapter, “Framing Questions and Other Practical Tips”, Katcher intimates that the most common problems for MEDLINE users cannot be resolved by reading a guide: “Perceiving the question that best illuminates a practical problem requires skills that are completely unrelated to MEDLINE but have everything to do with its effective application.” A useful asset is the updated Web-based version of Appendix A, which provides hyperlinks to MEDLINE interfaces on the Web, tutorials, and a sampling of other Web-based health-information resources. When checked on 31 October 2006, the site had been updated within 30 days.

Katcher encourages readers: “Take advantage of all the energy that has gone into organizing the information in MEDLINE. It is a National treasure.” His historical account and explanation of that organization in the first three chapters is the real treasure of this MEDLINE edition. For novice users, the book’s advice on search strategies and tips for refining search results may certainly be useful. However, it is the opinion of this reviewer that for most users, a small amount of interaction with MEDLINE will build the critical thinking skills that Katcher aims to teach.

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