

by a due diligence team from a potential buyer. Since this book is designed as a monograph with case studies, it would make a useful companion volume to a previous book by the same author, *Introduction to the Due Diligence Process*, published in 2010.

## Review of IND Submissions: A Primer

Brown-Tuttle M. *IND Submissions: A Primer*. Needham, MA: Barnett International; 2009. 530 pages plus CD-ROM.

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DOI: 10.1177/0092861512462022

The subtitle of this book is “An in-depth guide to writing, editing, tracking, and submitting the original IND and applicable IND amendments.” This book is a clear and thorough guide to the preparation, writing, publishing, submission, and monitoring of documents that FDA requires drug sponsors to submit. Although the title and subtitle focus on IND submissions, in fact the book covers in depth a few other types of FDA submissions as well, such as orphan drug applications and FDA meeting requests.

The book is set up like a training manual for those who are entering regulatory affairs for drug products, and it is a good one. It would be useful as a textbook for a regulatory affairs course or to study for certification. Although it is very basic, it might also be useful as a desk reference for a regulatory affairs department for a quick look at an applicable chapter when a quick answer is needed.

Topics include all aspects of INDs, including administrative aspects of submissions (creating style guides and templates; tips on writing and coordinating writing by a group; FDA forms), paper and electronic submissions, tracking submissions, managing references, CTD format, electronic document management systems, FDA meetings, dispute resolution, expanded use INDs, exploratory INDs, IND amendments, protocols, transfers of obligations, investigator’s brochures, safety reports, fast-track designation, responding to clinical holds, special protocol assessments, statistical analysis plans, filing at [clinicaltrials.gov](http://clinicaltrials.gov), CMC issues, orphan drug issues, USAN and proprietary name development, inactivating and reactivating an IND, and drug master files.

The book does not seem to miss any IND-related topics, and everything I read was very accurate and also easy to read. The organization of the book is roughly along the lines of how one would go about initiating and maintaining an IND. However, surprisingly many introductory concepts are not introduced until chapters 22, 26, and 27.

This is a sizable book, with 530 pages of relatively large dimensions (approximately 11” × 12”). It has a plastic spiral binding, but that is mounted within an attractive solid hardcover backing. The spiral binding appears intended to allow readers to remove the spiral-bound pages from the hard cover so that pages can be turned back on the spiral. Each of the 62 chapters is marked with a thick-tabbed divider with each topic clearly marked on the tab, which is extremely convenient and makes its use as a reference tool easier, particularly since the book lacks an index. Its 33-page detailed table of contents partially compensates for this as well.

One of the most impressive aspects of this book is the accompanying CD-ROM, containing template documents, arranged by chapter, for 54 of the chapters. With artificial “samples” of FDA meeting requests, completed FDA forms, etc, as well as a sample style guide and examples of the types of letters that FDA sends to drug sponsors, this CD-ROM collection could be worthwhile for any new regulatory affairs department to obtain.

There is no information about author Meredith Brown-Tuttle in the book. A quick search on the Internet reveals that she has been active in regulatory affairs as a consultant and at a number of consulting firms over the years, was on the Board of Editors at the Regulatory Affairs Professionals Society (RAPS) for many years, and teaches regulatory affairs at the University of California, Santa Cruz.

## Review of Clinical Trial Design: Bayesian and Frequentist Adaptive Methods

Yin G. *Clinical Trial Design: Bayesian and Frequentist Adaptive Methods*. Hoboken, NY: John Wiley & Sons; 2012. 336 pages.

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DOI: 10.1177/0092861512462372

The escalating costs of conducting clinical trials coupled with the increasing likelihood of late-stage failure has led the pharmaceutical industry to re-examine the drug development process. As a result, a great deal of recent attention has focused on adaptive clinical trial designs.<sup>1</sup> In contrast to traditional clinical trials that employ fixed sample sizes and constant treatment allocation probabilities, adaptive designs utilize data from the ongoing trial to modify various features of the study.<sup>2</sup> For example, these adaptations could allow for early termination of a study in cases where the drug under investigation is particularly efficacious, or for those instances when there is little hope of showing both a clinically and statistically

significant difference against the control arm (ie, futility). By no means exhaustive, other modifications include sample size re-estimation using an updated estimate of variability from the current trial, adaptive randomization methods where changing allocation probabilities allow subjects to be randomized to more effective treatment arms with increasing likelihood as the trial progresses, seamless phase I/II or II/III trials, or dose escalation/de-escalation methods for identifying the maximum tolerated dose.

*Clinical Trial Design: Bayesian and Frequentist Adaptive Methods* is an excellent overview of commonly used adaptive design methodologies. The book is well-organized with a very intuitive structure, and like many texts on clinical trial design, a majority of the examples are derived from trials in oncology. Though not presented as such, the book is comprised of three “sections.” Section I (chapters 1-3) provides background to the adaptive methods described in the book: a brief history of clinical trials and drug development; fundamentals of clinical trials, including discussion on study objectives and eligibility, power and sample size, blinding and randomization, key features of parallel and crossover designs, and a description of clinical trial phases I-IV; and a summary of Frequentist and Bayesian statistical methods for continuous, binary, and time-to-event endpoints. Each chapter of section II (chapters 4-6) describes adaptive design methodologies for a specific phase of drug development (phases I-III). Finally, section III (chapters 7-10) can be considered “special topics” for methods that warrant particular attention or those that span across the development phase structure of section II. These topics include adaptive randomization, late-onset toxicity, drug combination trials, and targeted therapy designs.

The text has two very important features. First, each chapter includes a series of exercises to test the knowledge of chapter material and to provide the reader an opportunity to examine the operating characteristics of various adaptive clinical trial designs. After a brief review of similar texts over the Internet, I believe this to be the first book on adaptive designs to provide exercises. The second important feature is the use of software from the Department of Biostatistics at M.D. Anderson. Not only is the software available for free (requires user registration), but the programs are easy to use and designed using straightforward graphical user interfaces. This allows

individuals with minimal programming experience the opportunity to design and evaluate various adaptive designs.

I have one minor, nitpicky point about the book: I wished the author had referenced recent regulatory guidance documents on adaptive designs.<sup>3,4</sup> Clinical trials are a collaborative effort using the expertise of many disciplines and individuals, and the views of FDA or EMA are important to consider, particularly for adaptive designs. For example, these documents make it clear why chapter 6 is dominated primarily by Frequentist methodologies. However, despite this minor point, the author does address concerns raised within these guidance documents: prespecification of study adaptations, control of type I error, potential bias of adaptations, the use of DMCs to evaluate unmasked data, and the use of extensive simulations to evaluate clinical trial properties.

Given the exercises, the detailed examples, and the author's thorough approach of describing traditional clinical trial methods prior to detailing adaptive methods, this book would make an excellent choice for courses in clinical trial design or as a resource for the practicing statistician. Further, the use of software from M.D. Anderson allows other quantitative researchers with minimal programming experience to benefit from the text. The author should be commended; the text is well written and packed with information that belies the book's trim size.

## References

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