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CAMBRIDGE UNIVERSITY PRESS
Cambridge, New York, Melbourne, Madrid, Cape Town,
Singapore, São Paulo, Delhi, Mexico City

Cambridge University Press
The Edinburgh Building, Cambridge CB2 8RU, UK

Published in the United States of America by Cambridge University Press, New York

www.cambridge.org
Information on this title: www.cambridge.org/9780521762595

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First published 2012

Printed in the United Kingdom at the University Press, Cambridge

A catalogue record for this publication is available from the British Library

Library of Congress Cataloguing in Publication data
Clinical trials in neurology : design, conduct, analysis / edited by Bernard Ravina ... [et al.].
p. cm.
Includes bibliographical references and index.
ISBN 978-0-521-76259-5 (hardback)
1. Neurology – Research – Methodology. 2. Clinical trials. I. Ravina, Bernard.
RC337.C62 2012
616.80072′4–dc23 2012000303

ISBN 978-0-521-76259-5 Hardback

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Preface

The aging population is increasing the global burden of neurological diseases and the need for safe and effective therapeutics for these disorders. While therapeutic targets for neurological disorders are increasingly tractable, neurology also has one of the highest failure rates in late stage clinical trials. There is an increasing need for proficiency in the design, conduct, analysis, and interpretation of clinical trials in neurology. This is especially true in the early and middle stages of therapeutic development, which determine if and how comparative efficacy studies should be conducted.

The goal of this book is to describe how the principles of clinical trials can be applied to the challenges that arise in developing therapies for neurological disorders. The fundamentals of clinical trials are explored in several existing texts and are the same across different fields of medicine. Here we describe the application of those principles to the specific clinical questions that arise with the study of neurological diseases.

There is no one trial design that meets all objectives for a particular phase of development. Rather there are parameters that need to be optimized for each intervention, question, and study. A clinical trial can be defined as an experiment in humans that is designed to test a medical, surgical, behavioral, or other type of intervention. This definition does not presuppose a particular design, type of control group, or analysis plan. When designing a trial and consulting this text for guidance, the reader should carefully consider the clinical question they are facing and how that question fits in the overall program of research for the intervention. The next step is to select a design that can practically and efficiently answer the question and guide decision-making about the intervention and the steps to further develop it.

The underlying motivation for this text is the notion that better clinical trial design and conduct will improve the efficiency of the development process by eliminating interventions with a low likelihood of success and focusing resources on those with more promise. This does not mean that all trials will be positive. By carefully selecting the appropriate dose, design, population, measure, and analytical approach we can best test the intervention's mechanism and its relevance for treating patients with neurological disorders. Rather than a high volume of clinical trials, we seek high quality trials that have the potential to lead to improvements in patient care and quality of life.

Audience

This text is intended for those who conduct clinical trials in academia, the pharmaceutical and biotechnology industries, and government and is written by experts from each of these areas. The intended audience is meant to include the broad spectrum of medical researchers, statisticians, data managers, trial managers, regulators, and program officials. Clinical trials are by nature multidisciplinary, social undertakings that are accomplished by teams. Those teams work most effectively when the members have a common understanding of goals and principles that unite their different areas of expertise.

Organization and terminology

The text is written to emphasize key concepts, with examples from neurology and other fields and references that can provide additional detail. It should be regarded as a starting point for learning about clinical trials and a companion to formal coursework and practical experience.

The text begins with a description of the growing need for progress in the treatment of neurological disorders, the sequence of clinical development, and a discussion of the unique challenges of neurology research, such as measuring drug disposition in the central nervous system. While this is not a book specifically about drug development, any clinical trial must be nested within an overall development plan to determine how to optimize the intervention (learning) and then to actually test it (confirming) for its hypothesized benefit. Subsequent sections focus on core principles of clinical

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trials: control of bias and random error, basic aspects of statistical inference, notable clinical trial designs in the neurology literature, clinical measurement and assessment of outcomes, interim monitoring, ethics, and the regulatory framework for drugs and devices using the US as an example. We then consider how these principles manifest in clinical trials for several common neurological disorders.

We have devoted two chapters to clinical operations, which is unusual in a clinical trials text. It is not sufficient to merely design an elegant experiment. The experiment must be conducted in a manner that ensures the integrity of the intervention and the study data. The steps involved in planning and implementing studies are often neglected in texts and courses and many trials fail on aspects of execution, timeline, and budget. This is especially true for many neurological disorders, where clinical trials are relatively new and researchers are often working in uncharted or unfamiliar territory. Our objective is to provide direction from what has been learned through experience to help researchers avoid costly mistakes. The final chapter of the text focuses on issues of financial relationships and compliance in industry-academic collaborations. This issue is of growing importance and transparency is necessary to facilitate these essential collaborations and ensure trust in the clinical research enterprise.

Disclaimer

Any views or opinions presented in this book are solely those of the authors, and not necessarily those of the US Food and Drug Administration or the authors' employers or institutions.

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Acknowledgements

This is a multi-author text and this diverse group in many ways reflects the multidisciplinary teams needed to conduct clinical trials and develop new therapies. Many of the authors and my co-editors have been mentors and colleagues through my positions at the National Institute of Health (NIH), academic medicine, and now the biotechnology industry. I am grateful to them not only for contributing to this text but for facilitating my own interest in and understanding of clinical trials. The NIH/NINDS Neurology Clinical Trials Methods Course brought many of us together. The focused discussions and debates with faculty and trainees alike have helped to shape my approach to clinical trials. I would like to thank Janine Fitzpatrick and Briana Bouchard for their administrative and technical support and Nancy Richert for the MRI cover image. The otherwise un-named contributor to this text is my wife Joanna. Her unwavering support and critical thinking skills have been essential for this text and for the many studies, large and small, that fill a career in clinical research.

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