Adaptive Design For Clinical Trials

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Adaptive Designs for Confirmatory Clinical Trials - Cyrus Mehta 2013-08-23

Stage-Wise Adaptive Designs - Shelemyahu Zacks 2009-05-11
An expert introduction to stage-wise adaptive designs in all areas of statistics Stage-Wise Adaptive Designs presents the theory and methodology of stage-wise adaptive design across various areas of study within the field of statistics, from sampling surveys and time series analysis to generalized linear models and decision theory. Providing the necessary background material along with illustrative S-PLUS functions, this book serves as a valuable introduction to the problems of adaptive designs. The author begins with a cohesive introduction to the subject and goes on to concentrate on generalized linear models, followed by stage-wise sampling procedures in sampling surveys. Adaptive forecasting in the area of time series analysis is presented in detail, and two chapters are devoted to applications in clinical trials. Bandits problems are also given a thorough treatment along with sequential detection of change-points, sequential applications in industrial statistics, and software reliability. S-Plus functions are available to accompany particular computations, and all examples can be worked out using R, which is available on the book's related FTP site. In addition, a detailed appendix outlines the use of these software functions, while an extensive bibliography directs readers to further research on the subject matter. Assuming only a basic background in statistical topics, Stage-Wise Adaptive Designs is an excellent supplement to statistics courses at the upper-undergraduate and graduate levels. It also serves as a valuable reference for researchers and practitioners in the fields of statistics and biostatistics.
Principles and Practice of Clinical Trials - Steven Piantadosi 2022-07-19
This is a comprehensive major reference work for our SpringerReference program covering clinical trials. Although the core of the Work will focus on the design, analysis, and interpretation of scientific data from clinical trials, a broad spectrum of clinical trial application areas will be covered in detail. This is an important time to develop such a Work, as drug safety and efficacy emphasizes the Clinical Trials process. Because of an immense and growing international disease burden, pharmaceutical and biotechnology companies continue to develop new drugs. Clinical trials have also become extremely globalized in the past 15 years, with over 225,000 international trials ongoing at this point in time. Principles in Practice of Clinical Trials is truly an interdisciplinary that will be divided into the following areas: 1) Clinical Trials Basic Perspectives 2) Regulation and Oversight 3) Basic Trial Designs 4) Advanced Trial Designs 5) Analysis 6) Trial Publication 7) Topics Related Specific Populations and Legal Aspects of Clinical Trials The Work is designed to be comprised of 175 chapters

and approximately 2500 pages. The Work will be oriented like many of our SpringerReference Handbooks, presenting detailed and comprehensive expository chapters on broad subjects. The Editors are major figures in the field of clinical trials, and both have written textbooks on the topic. There will also be a slate of 7-8 renowned associate editors that will edit individual sections of the Reference.

Small Clinical Trials - Institute of Medicine 2001-01-01

Clinical trials are used to elucidate the most appropriate preventive, diagnostic, or treatment options for individuals with a given medical condition. Perhaps the most essential feature of a clinical trial is that it aims to use results based on a limited sample of research participants to see if the intervention is safe and effective or if it is comparable to a comparison treatment. Sample size is a crucial component of any clinical trial. A trial with a small number of research participants is more prone to variability and carries a considerable risk of failing to demonstrate the effectiveness of a given intervention when one really is present. This may occur in phase I (safety and pharmacologic profiles), II (pilot efficacy evaluation), and III (extensive assessment of safety and efficacy) trials. Although phase I and II studies may have smaller sample sizes, they usually have adequate statistical power, which is the committee's definition of a "large" trial. Sometimes a trial with eight participants may have adequate statistical power, statistical power being the probability of rejecting the null hypothesis when the hypothesis is false. Small Clinical Trials assesses the current methodologies and the appropriate situations for the conduct of clinical trials with small sample sizes. This report assesses the published literature on various strategies such as (1) meta-analysis to combine disparate information from several studies including Bayesian techniques as in the confidence profile method and (2) other alternatives such as assessing therapeutic results in a single treated population (e.g., astronauts) by sequentially measuring whether the intervention is falling above or below a preestablished probability outcome range and meeting predesigned specifications as opposed to incremental improvement.

Group Sequential and Confirmatory Adaptive Designs in Clinical Trials - Gernot Wassmer 2016-07-04

This book provides an up-to-date review of the general principles of and techniques for confirmatory adaptive designs. Confirmatory adaptive designs are a generalization of group sequential designs. With these designs, interim analyses are performed in order to stop the trial prematurely under control of the Type I error rate. In adaptive designs, it is also permissible to perform a data-driven change of relevant aspects of the study design at interim stages. This includes, for example, a sample-size reassessment, a treatment-arm selection or a selection of a pre-specified sub-population. Essentially, this adaptive methodology was introduced in the 1990s. Since then, it has become popular and the object of intense discussion and still represents a rapidly growing field of statistical research. This book describes adaptive design methodology at an elementary level, while also considering designing and planning issues as well as methods for analyzing an adaptively planned trial. This includes estimation methods and methods for the determination of an overall p-value. Part I of the book provides the group sequential methods that are necessary for understanding and applying the adaptive design methodology supplied in Parts II and III of the book. The book contains many examples that illustrate use of the methods for practical application. The book is primarily written for applied statisticians from academia and industry who are interested in confirmatory adaptive designs. It is assumed that readers are familiar with the basic principles of descriptive statistics, parameter estimation and statistical testing. This book will also be suitable for an advanced statistical course for applied statisticians or clinicians with a sound statistical background.

Classical and Adaptive Clinical Trial Designs Using ExpDesign Studio - Mark Chang 2010-06-15

ExpDesign Studio facilitates more efficient clinical trial design This book introduces pharmaceutical statisticians, scientists, researchers, and others to ExpDesign Studio software for classical and adaptive designs of clinical trials. It includes the Professional Version 5.0 of ExpDesign Studio software that frees pharmaceutical professionals to focus on drug development and related challenges while the software handles the essential calculations and computations. After a hands-on introduction to the software and an overview of clinical trial designs encompassing numerous variations, Classical and Adaptive Clinical Trial Designs Using ExpDesign Studio: Covers both classical and adaptive clinical trial designs, monitoring, and analyses Explains various classical and adaptive designs including groupsequential, sample-size reestimation, dropping-loser, biomarker-adaptive, and response-adaptive randomization designs Includes instructions for over 100 design methods that have been implemented in ExpDesign Studio and step-by-step demos as well as real-world examples Emphasizes applications, yet covers key mathematical formulations Introduces readers to additional toolkits in ExpDesign Studio that help in designing, monitoring, and analyzing trials, such as the adaptive monitor, graphical calculator, the probability calculator, the confidence interval calculator, and more Presents comprehensive technique notes for sample-size calculation methods, grouped by the number of arms, the trial endpoint, and the analysis basis Written with practitioners in mind, this is an ideal self-study guide for not only statisticians, but also scientists, researchers, and professionals in the pharmaceutical industry, contract research organizations (CROs), and regulatory bodies. It's also a go-to reference for biostatisticians, pharmacokinetic specialists, and principal investigators involved in clinical trials. ERRATUM Classical and Adaptive Clinical Trial Designs Using ExpDesign Studio By Mark Chang The license for the ExpDesign Studio software on the CD included with this book is good for one-year after installation of the software. Prior to the expiration of this period, the software will generate a reminder about renewal for the license. The user should contact CTriSoft International (the owners of ExpDesign Studio) at www.CTriSoft.net or by email at license@ctrisoft.net, about renewal for the license. This should have been made clear in the first printing of this book. We apologize for this error.

Group Sequential Methods with Applications to Clinical Trials - Christopher Jennison 1999-09-15

Group sequential methods answer the needs of clinical trial monitoring committees who must assess the data available at an interim analysis. These interim results may provide grounds for terminating the study-effectively reducing costs-or may benefit the general patient population by allowing early dissemination of its findings. Group sequential methods provide a means to balance the ethical and financial advantages of stopping a study early against the risk of an incorrect conclusion. Group Sequential Methods with Applications to Clinical Trials describes group sequential stopping rules designed to reduce average study length and control Type I and II error probabilities. The authors present one-sided and two-sided tests, introduce several families of group sequential tests, and explain how to choose the most appropriate test and interim analysis schedule. Their topics include placebo-controlled randomized trials, bio-equivalence testing, crossover and longitudinal studies, and linear and generalized linear models. Research in group sequential analysis has progressed rapidly over the past 20 years. Group Sequential Methods with Applications to Clinical Trials surveys and extends current methods for planning and conducting interim analyses. It provides straightforward descriptions of group sequential hypothesis tests in a form suited

for direct application to a wide variety of clinical trials. Medical statisticians engaged in any investigations planned with interim analyses will find this book a useful and important tool.

Randomization in Clinical Trials - William F. Rosenberger 2015-10-28

Praise for the First Edition “All medical statisticians involved in clinical trials should read this book...” - Controlled Clinical Trials Featuring a unique combination of the applied aspects of randomization in clinical trials with a nonparametric approach to inference, Randomization in Clinical Trials: Theory and Practice, Second Edition is the go-to guide for biostatisticians and pharmaceutical industry statisticians. Randomization in Clinical Trials: Theory and Practice, Second Edition features: Discussions on current philosophies, controversies, and new developments in the increasingly important role of randomization techniques in clinical trials A new chapter on covariate-adaptive randomization, including minimization techniques and inference New developments in restricted randomization and an increased focus on computation of randomization tests as opposed to the asymptotic theory of randomization tests Plenty of problem sets, theoretical exercises, and short computer simulations using SAS® to facilitate classroom teaching, simplify the mathematics, and ease readers’ understanding Randomization in Clinical Trials: Theory and Practice, Second Edition is an excellent reference for researchers as well as applied statisticians and biostatisticians. The Second Edition is also an ideal textbook for upper-undergraduate and graduate-level courses in biostatistics and applied statistics. William F. Rosenberger, PhD, is University Professor and Chairman of the Department of Statistics at George Mason University. He is a Fellow of the American Statistical Association and the Institute of Mathematical Statistics, and author of over 80 refereed journal articles, as well as The Theory of Response-Adaptive Randomization in Clinical Trials, also published by Wiley. John M. Lachin, ScD, is Research Professor in the Department of Epidemiology and Biostatistics as well as in the Department of Statistics at The George Washington University. A Fellow of the American Statistical Association and the Society for Clinical Trials, Dr. Lachin is actively involved in coordinating center activities for clinical trials of diabetes. He is the author of Biostatistical Methods: The Assessment of Relative Risks, Second Edition, also published by Wiley.

Practical Considerations for Adaptive Trial Design and Implementation - Weili He 2014-10-15

This edited volume is a definitive text on adaptive clinical trial designs from creation and customization to utilization. As this book covers the full spectrum of topics involved in the adaptive designs arena, it will serve as a valuable reference for researchers working in industry, government and academia. The target audience is anyone involved in the planning and execution of clinical trials, in particular, statisticians, clinicians, pharmacometricians, clinical operation specialists, drug supply managers, and infrastructure providers. In spite of the increased efficiency of adaptive trials in saving costs and time, ultimately getting drugs to patients sooner, their adoption in clinical development is still relatively low. One of the chief reasons is the higher complexity of adaptive design trials as compared to traditional trials. Barriers to the use of clinical trials with adaptive features include the concerns about the integrity of study design and conduct, the risk of regulatory non-acceptance, the need for an advanced infrastructure for complex randomization and clinical supply scenarios, change management for process and behavior modifications, extensive resource requirements for the planning and design of adaptive trials and the potential to relegate key decision makings to outside entities. There have been limited publications that address these practical considerations and recommend best practices and solutions. This book fills this

publication gap, providing guidance on practical considerations for adaptive trial design and implementation. The book comprises three parts: Part I focuses on practical considerations from a design perspective, whereas Part II delineates practical considerations related to the implementation of adaptive trials. Putting it all together, Part III presents four illustrative case studies ranging from description and discussion of specific adaptive trial design considerations to the logistic and regulatory issues faced in trial implementation. Bringing together the expertise of leading key opinion leaders from pharmaceutical industry, academia, and regulatory agencies, this book provides a balanced and comprehensive coverage of practical considerations for adaptive trial design and implementation.

Adaptive Design of Clinical Trials - Ayesha Naz Khalid 2014

There is great competition for clinical research funding. This is in part due to the National Institute of Health's reduced budget to support such initiatives. It has resulted in a growing trend for clinical research to use adaptive design models to accelerate clinical trials and at the same time reduce overall cost. Although such models have existed for several years, the pace of adoption remains slow, especially for early-stage clinical research. Through a review of relevant literature and interviews with industry experts, this thesis explores the barriers that inhibit the adoption of adaptive design of clinical trials. Reasons uncovered include: a lack of novel funding mechanisms, regulatory uncertainty, logistical difficulties, overly technical communications, a lack of collaboration among stakeholders, and an inability to recruit and retain patients. Then follows a series of possible solutions - some already functioning, others possible - for each of the barriers. This research found that unless efforts are devoted to addressing these underlying barriers, the widespread adoption of adaptive designs for clinical trials will not occur. The thesis concludes with recommendations and suggestions for future research.

Bayesian Adaptive Methods for Clinical Trials - Scott M. Berry 2010-07-19

Already popular in the analysis of medical device trials, adaptive Bayesian designs are increasingly being used in drug development for a wide variety of diseases and conditions, from Alzheimer’s disease and multiple sclerosis to obesity, diabetes, hepatitis C, and HIV. Written by leading pioneers of Bayesian clinical trial designs, Bayesian Adaptive Methods for Clinical Trials explores the growing role of Bayesian thinking in the rapidly changing world of clinical trial analysis. The book first summarizes the current state of clinical trial design and analysis and introduces the main ideas and potential benefits of a Bayesian alternative. It then gives an overview of basic Bayesian methodological and computational tools needed for Bayesian clinical trials. With a focus on Bayesian designs that achieve good power and Type I error, the next chapters present Bayesian tools useful in early (Phase I) and middle (Phase II) clinical trials as well as two recent Bayesian adaptive Phase II studies: the BATTLE and ISPY-2 trials. In the following chapter on late (Phase III) studies, the authors emphasize modern adaptive methods and seamless Phase II–III trials for maximizing information usage and minimizing trial duration. They also describe a case study of a recently approved medical device to treat atrial fibrillation. The concluding chapter covers key special topics, such as the proper use of historical data, equivalence studies, and subgroup analysis. For readers involved in clinical trials research, this book significantly updates and expands their statistical toolkits. The authors provide many detailed examples drawing on real data sets. The R and WinBUGS codes used throughout are available on supporting websites. Scott Berry talks about the book on the CRC Press YouTube Channel.

Bayesian Designs for Phase I-II Clinical Trials - Ying Yuan 2017-12-19

Reliably optimizing a new treatment in humans is a critical first step in clinical

evaluation since choosing a suboptimal dose or schedule may lead to failure in later trials. At the same time, if promising preclinical results do not translate into a real treatment advance, it is important to determine this quickly and terminate the clinical evaluation process to avoid wasting resources. Bayesian Designs for Phase I–II Clinical Trials describes how phase I–II designs can serve as a bridge or protective barrier between preclinical studies and large confirmatory clinical trials. It illustrates many of the severe drawbacks with conventional methods used for early-phase clinical trials and presents numerous Bayesian designs for human clinical trials of new experimental treatment regimes. Written by research leaders from the University of Texas MD Anderson Cancer Center, this book shows how Bayesian designs for early-phase clinical trials can explore, refine, and optimize new experimental treatments. It emphasizes the importance of basing decisions on both efficacy and toxicity.

Clinical Trial Biostatistics and Biopharmaceutical Applications - Walter R. Young 2014-11-20

Since 1945, "The Annual Deming Conference on Applied Statistics" has been an important event in the statistics profession. In Clinical Trial Biostatistics and Biopharmaceutical Applications, prominent speakers from past Deming conferences present novel biostatistical methodologies in clinical trials as well as up-to-date biostatistical applications from the pharmaceutical industry. Divided into five sections, the book begins with emerging issues in clinical trial design and analysis, including the roles of modeling and simulation, the pros and cons of randomization procedures, the design of Phase II dose-ranging trials, thorough QT/QTc clinical trials, and assay sensitivity and the constancy assumption in noninferiority trials. The second section examines adaptive designs in drug development, discusses the consequences of group-sequential and adaptive designs, and illustrates group sequential design in R. The third section focuses on oncology clinical trials, covering competing risks, escalation with overdose control (EWOC) dose finding, and interval-censored time-to-event data. In the fourth section, the book describes multiple test problems with applications to adaptive designs, graphical approaches to multiple testing, the estimation of simultaneous confidence intervals for multiple comparisons, and weighted parametric multiple testing methods. The final section discusses the statistical analysis of biomarkers from omics technologies, biomarker strategies applicable to clinical development, and the statistical evaluation of surrogate endpoints. This book clarifies important issues when designing and analyzing clinical trials, including several misunderstood and unresolved challenges. It will help readers choose the right method for their biostatistical application. Each chapter is self-contained with references.

Introductory Adaptive Trial Designs - Mark Chang 2015-05-21

All the Essentials to Start Using Adaptive Designs in No TimeCompared to traditional clinical trial designs, adaptive designs often lead to increased success rates in drug development at reduced costs and time. Introductory Adaptive Trial Designs: A Practical Guide with R motivates newcomers to quickly and easily grasp the essence of adaptive desig

Adaptive Design Theory and Implementation Using SAS and R - Mark Chang 2014-12-01

Get Up to Speed on Many Types of Adaptive Designs Since the publication of the first edition, there have been remarkable advances in the methodology and application of adaptive trials. Incorporating many of these new developments, Adaptive Design Theory and Implementation Using SAS and R, Second Edition offers a detailed framework to understand the use of various adaptive design methods in clinical trials. New to the Second Edition Twelve new chapters covering blinded and semi-blinded sample size reestimation design, pick-the-winners design, biomarker-informed

adaptive design, Bayesian designs, adaptive multiregional trial design, SAS and R for group sequential design, and much more More analytical methods for K-stage adaptive designs, multiple-endpoint adaptive design, survival modeling, and adaptive treatment switching New material on sequential parallel designs with rerandomization and the skeleton approach in adaptive dose-escalation trials Twenty new SAS macros and R functions Enhanced end-of-chapter problems that give readers hands-on practice addressing issues encountered in designing real-life adaptive trials Covering even more adaptive designs, this book provides biostatisticians, clinical scientists, and regulatory reviewers with up-to-date details on this innovative area in pharmaceutical research and development. Practitioners will be able to improve the efficiency of their trial design, thereby reducing the time and cost of drug development.

A Comparison of Adaptive Designs in Clinical Trials - Sukyung Park 2014

In recent times, there has been an increasing interest in adaptive designs for clinical trials. As opposed to conventional designs, adaptive designs allow flexible design adaptation in the middle of a trial based on accumulated data. Although various models have been developed using both frequentist and Bayesian perspectives, relative statistical performances of adaptive designs are somewhat controversial and little is known about those of Bayesian adaptive designs. Most comparison studies also focused on single experimental treatment rather than multiple experimental treatments. In this report, both frequentist and Baysian adaptive designs were compared in terms of statistical power by a simulation study, assuming the situation when multiple experimental treatments are tested in multiple stages. The designs included in the current study are group sequential design (frequentist), adaptive design based on combination tests (frequentist), and Bayesian adaptive design (Bayesian). Based upon the results under multiple scenarios, the Bayesian adaptive design showed the highest power, and the design based on combination tests performed better than group sequential designs when proper interim adaptation could be conducted to increase power.

Modern Adaptive Randomized Clinical Trials - Oleksandr Sverdlov 2015-06-30

Is adaptive randomization always better than traditional fixed-schedule randomization? Which procedures should be used and under which circumstances? What special considerations are required for adaptive randomized trials? What kind of statistical inference should be used to achieve valid and unbiased treatment comparisons following adaptive random

Covariates in Adaptive Designs for Clinical Trials - Margarida Cristina Geraldes 1999

Modern Approaches to Clinical Trials Using SAS - Sandeep Menon 2015-12-09

Get the tools you need to use SAS® in clinical trial design! Unique and multifaceted, Modern Approaches to Clinical Trials Using SAS: Classical, Adaptive, and Bayesian Methods, edited by Sandeep M. Menon and Richard C. Zink, thoroughly covers several domains of modern clinical trial design: classical, group sequential, adaptive, and Bayesian methods that are applicable to and widely used in various phases of pharmaceutical development. Written for biostatisticians, pharmacometricians, clinical developers, and statistical programmers involved in the design, analysis, and interpretation of clinical trials, as well as students in graduate and postgraduate programs in statistics or biostatistics, the book touches on a wide variety of topics, including dose-response and dose-escalation designs; sequential methods to stop trials early for overwhelming efficacy, safety, or futility; Bayesian designs that incorporate historical data; adaptive sample size re-estimation; adaptive randomization to allocate subjects to more effective treatments; and population enrichment designs. Methods are illustrated using clinical trials from diverse therapeutic areas, including

dermatology, endocrinology, infectious disease, neurology, oncology, and rheumatology. Individual chapters are authored by renowned contributors, experts, and key opinion leaders from the pharmaceutical/medical device industry or academia. Numerous real-world examples and sample SAS code enable users to readily apply novel clinical trial design and analysis methodologies in practice.

Clinical Trial Methodology - Karl E. Peace 2010-07-20

Now viewed as its own scientific discipline, clinical trial methodology encompasses the methods required for the protection of participants in a clinical trial and the methods necessary to provide a valid inference about the objective of the trial. Drawing from the authors' courses on the subject as well as the first author's more than 30 years working in the pharmaceutical industry, Clinical Trial Methodology emphasizes the importance of statistical thinking in clinical research and presents the methodology as a key component of clinical research. From ethical issues and sample size considerations to adaptive design procedures and statistical analysis, the book first covers the methodology that spans every clinical trial regardless of the area of application. Crucial to the generic drug industry, bioequivalence clinical trials are then discussed. The authors describe a parallel bioequivalence clinical trial of six formulations incorporating group sequential procedures that permit sample size re-estimation. The final chapters incorporate real-world case studies of clinical trials from the authors' own experiences. These examples include a landmark Phase III clinical trial involving the treatment of duodenal ulcers and Phase III clinical trials that contributed to the first drug approved for the treatment of Alzheimer's disease. Aided by the U.S. FDA, the U.S. National Institutes of Health, the pharmaceutical industry, and academia, the area of clinical trial methodology has evolved over the last six decades into a scientific discipline. This guide explores the processes essential for developing and conducting a quality clinical trial protocol and providing quality data collection, biostatistical analyses, and a clinical study report, all while maintaining the highest standards of ethics and excellence.

Sequential Experimentation in Clinical Trials - Jay Bartroff 2012-12-12

Sequential Experimentation in Clinical Trials: Design and Analysis is developed from decades of work in research groups, statistical pedagogy, and workshop participation. Different parts of the book can be used for short courses on clinical trials, translational medical research, and sequential experimentation. The authors have successfully used the book to teach innovative clinical trial designs and statistical methods for Statistics Ph.D. students at Stanford University. There are additional online supplements for the book that include chapter-specific exercises and information. Sequential Experimentation in Clinical Trials: Design and Analysis covers the much broader subject of sequential experimentation that includes group sequential and adaptive designs of Phase II and III clinical trials, which have attracted much attention in the past three decades. In particular, the broad scope of design and analysis problems in sequential experimentation clearly requires a wide range of statistical methods and models from nonlinear regression analysis, experimental design, dynamic programming, survival analysis, resampling, and likelihood and Bayesian inference. The background material in these building blocks is summarized in Chapter 2 and Chapter 3 and certain sections in Chapter 6 and Chapter 7. Besides group sequential tests and adaptive designs, the book also introduces sequential change-point detection methods in Chapter 5 in connection with pharmacovigilance and public health surveillance. Together with dynamic programming and approximate dynamic programming in Chapter 3, the book therefore covers all basic topics for a graduate course in sequential analysis designs.

NEJM Clinical Problem Solving - Sanjay Saint 2006-05-09

Expert clinical problem-solving methods and guidance—from the editors and contributors of the New England Journal of Medicine This invaluable resource from the New England Journal of Medicine expertly addresses methods and challenges in clinical diagnosis. Including the peer-reviewed content of the NEJM's renowned "Clinical Problem Solving" feature, this powerful resource is packed with case discussions from both ambulatory and hospital practice. Each Case Presentation reveals thought-provoking clinical and laboratory clues as the diagnostic considerations begin to emerge. Subsequent clinical detail and discussion and expert analysis add to the diagnostic picture until a final clinical diagnosis is reached. New England Journal of Medicine: Clinical Problem-Solving features: Published cases drawn from the New England Journal of Medicine reflecting actual patient-management situations that physicians experience in their everyday clinical practice Two brand new, never-before-published chapters on medical decision-making skills and methods Wide-ranging coverage of the major considerations in each case, from underlying pathophysiology to signs from the physical examination to lab testing strategies More than 100 full-color illustrations, tables, and algorithms Meticulously selected references that open up avenues for further study And much more! From cover to cover, New England Journal of Medicine: Clinical Problem-Solving presents the best case analysis, diagnostic thought processes, and problem-solving-- direct from master clinicians.

Adaptive Design Methods in Clinical Trials - Shein-Chung Chow 2006-11-16

Although adaptive design methods are flexible and useful in clinical research, little or no regulatory guidelines are available. One of the first books on the topic, Adaptive Design Methods in Clinical Trials presents the principles and methodologies in adaptive design and analysis that pertain to adaptations made to trial or statistical procedures that are based on accrued data of ongoing clinical trials. The book also offers a well-balanced summary of current regulatory perspectives and recently developed statistical methods in this area. After an introduction to basic concepts and statistical considerations of adaptive design methods, the book questions the impact on target patient populations as the result of protocol amendments and discusses the generalization of statistical inference. The authors also present various adaptive design methods, including where hypotheses are modified during the conduct of clinical trials, for dose selection, and commonly used adaptive group sequential design methods in clinical trials. Following a discussion of blind procedures for sample size re-estimation, the book describes statistical tests for seamless phase II/III adaptive designs and statistical inference for switching adaptively from one treatment to another. The book concludes with computer simulations and various case studies of clinical trials. By providing theoretical and computer simulation results, method comparisons, and practical guidelines for choosing an optimal design, Adaptive Design Methods in Clinical Trials fills the need for a unified, comprehensive, and updated resource in the clinical research and development of adaptive design and analysis.

Design and Analysis of Clinical Trials - Shein-Chung Chow 2013-09-30

Praise for the Second Edition: "...a grand feast for biostatisticians. It stands readyto satisfy the appetite of any pharmaceutical scientist with arespectable statistical appetite." —Journal of ClinicalResearch Best Practices The Third Edition of Design and Analysis of ClinicalTrials provides complete, comprehensive, and expanded coverageof recent health treatments and interventions. Featuring a unifiedpresentation, the book provides a well-balanced summary of currentregulatory requirements and recently developed statistical methodsas well as an overview of the various designs

and analyses that areutilized at different stages of clinical research and development.Additional features of this Third Edition include: • New chapters on biomarker development and targetclinical trials, adaptive design, trials for evaluating diagnosticdevices, statistical methods for translational medicine, andtraditional Chinese medicine • A balanced overview of current and emerging clinicalissues as well as newly developed statistical methodologies • Practical examples of clinical trials that demonstrateeveryday applicability, with illustrations and examples to explainkey concepts • New sections on bridging studies and global trials, QTstudies, multinational trials, comparative effectiveness trials,and the analysis of QT/QTc prolongation • A complete and balanced presentation of clinical andscientific issues, statistical concepts, and methodologies forbridging clinical and statistical disciplines • An update of each chapter that reflects changes inregulatory requirements for the drug review and approval processand recent developments in statistical design and methodology forclinical research and development Design and Analysis of Clinical Trials, Third Editioncontinues to be an ideal clinical research reference for academic,pharmaceutical, medical, and regulatory scientists/researchers,statisticians, and graduate-level students.

Clinical Trial Design - Guosheng Yin 2013-06-07

A balanced treatment of the theories, methodologies, and designissues involved in clinical trials using statisticalmethods There has been enormous interest and development in Bayesianadaptive designs, especially for early phases of clinical trials.However, for phase III trials, frequentist methods still play adominant role through controlling type I and type II errors in thehypothesis testing framework. From practical perspectives, ClinicalTrial Design: Bayesian and Frequentist Adaptive Methods providescomprehensive coverage of both Bayesian and frequentist approachesto all phases of clinical trial design. Before underpinning variousadaptive methods, the book establishes an overview of thefundamentals of clinical trials as well as a comparison of Bayesianand frequentist statistics. Recognizing that clinical trial design is one of the mostimportant and useful skills in the pharmaceutical industry, thisbook provides detailed discussions on a variety of statisticaldesigns, their properties, and operating characteristics for phaseI, II, and III clinical trials as well as an introduction to phaseIV trials. Many practical issues and challenges arising in clinicaltrials are addressed. Additional topics of coverage include: Risk and benefit analysis for toxicity and efficacytrade-offs Bayesian predictive probability trial monitoring Bayesian adaptive randomization Late onset toxicity and response Dose finding in drug combination trials Targeted therapy designs The author utilizes cutting-edge clinical trial designs andstatistical methods that have been employed at the world's leadingmedical centers as well as in the pharmaceutical industry. Thesoftware used throughout the book is freely available on the book'srelated website, equipping readers with the necessary tools fordesigning clinical trials. Clinical Trial Design is an excellent book for courses on thetopic at the graduate level. The book also serves as a valuablereference for statisticians and biostatisticians in thepharmaceutical industry as well as for researchers andpractitioners who design, conduct, and monitor clinical trials intheir everyday work.

The Theory of Response-Adaptive Randomization in Clinical Trials - Feifang Hu 2006-09-29

Presents a firm mathematical basis for the use of response-adaptive randomization procedures in practice The Theory of Response-Adaptive Randomization in Clinical Trials is the result of the authors' ten-year collaboration as well as their collaborations with other researchers in investigating the important questions regarding response-adaptive randomization

in a rigorous mathematical framework. Response-adaptive allocation has a long history in biostatistics literature; however, largely due to the disastrous ECMO trial in the early 1980s, there is a general reluctance to use these procedures. This timely book represents a mathematically rigorous subdiscipline of experimental design involving randomization and answers fundamental questions, including: How does response-adaptive randomization affect power? Can standard inferential tests be applied following response-adaptive randomization? What is the effect of delayed response? Which procedure is most appropriate and how can "most appropriate" be quantified? How can heterogeneity of the patient population be incorporated? Can response-adaptive randomization be performed with more than two treatments or with continuous responses? The answers to these questions communicate a thorough understanding of the asymptotic properties of each procedure discussed, including asymptotic normality, consistency, and asymptotic variance of the induced allocation. Topical coverage includes: The relationship between power and response-adaptive randomization The general result for determining asymptotically best procedures Procedures based on urn models Procedures based on sequential estimation Implications for the practice of clinical trials Useful for graduate students in mathematics, statistics, and biostatistics as well as researchers and industrial and academic biostatisticians, this book offers a rigorous treatment of the subject in order to find the optimal procedure to use in practice.

Randomised Response-Adaptive Designs in Clinical Trials - Anthony C Atkinson 2013-12-26

Randomised Response-Adaptive Designs in Clinical Trials presents methods for the randomised allocation of treatments to patients in sequential clinical trials. Emphasizing the practical application of clinical trial designs, the book is designed for medical and applied statisticians, clinicians, and statisticians in training. After introducing clinical trials in drug development, the authors assess a simple adaptive design for binary responses without covariates. They discuss randomisation and covariate balance in normally distributed responses and cover many important response-adaptive designs for binary responses. The book then develops response-adaptive designs for continuous and longitudinal responses, optimum designs with covariates, and response-adaptive designs with covariates. It also covers response-adaptive designs that are derived by optimising an objective function subject to constraints on the variance of estimated parametric functions. The concluding chapter explores future directions in the development of adaptive designs.

Statistical Design, Monitoring, and Analysis of Clinical Trials - Weichung Joe Shih 2021-10-26

Statistical Design, Monitoring, and Analysis of Clinical Trials, Second Edition concentrates on the biostatistics component of clinical trials. This new edition is updated throughout and includes five new chapters. Developed from the authors' courses taught to public health and medical students, residents, and fellows during the past 20 years, the text shows how biostatistics in clinical trials is an integration of many fundamental scientific principles and statistical methods. The book begins with ethical and safety principles, core trial design concepts, the principles and methods of sample size and power calculation, and analysis of covariance and stratified analysis. It then focuses on sequential designs and methods for two-stage Phase II cancer trials to Phase III group sequential trials, covering monitoring safety, futility, and efficacy. The authors also discuss the development of sample size reestimation and adaptive group sequential procedures, phase 2/3 seamless design and trials with predictive biomarkers, exploit multiple testing procedures, and explain the concept of estimand, intercurrent events, and different missing data processes, and

describe how to analyze incomplete data by proper multiple imputations. This text reflects the academic research, commercial development, and public health aspects of clinical trials. It gives students and practitioners a multidisciplinary understanding of the concepts and techniques involved in designing, monitoring, and analyzing various types of trials. The book's balanced set of homework assignments and in-class exercises are appropriate for students and researchers in (bio)statistics, epidemiology, medicine, pharmacy, and public health.

Handbook of Adaptive Designs in Pharmaceutical and Clinical Development - Annpey Pong 2016-04-19

In response to the US FDA's Critical Path Initiative, innovative adaptive designs are being used more and more in clinical trials due to their flexibility and efficiency, especially during early phase development. Handbook of Adaptive Designs in Pharmaceutical and Clinical Development provides a comprehensive and unified presentation of the princip

Adaptive Design Methods in Clinical Trials, Second Edition - Shein-Chung Chow 2011-12-01

With new statistical and scientific issues arising in adaptive clinical trial design, including the U.S. FDA's recent draft guidance, a new edition of one of the first books on the topic is needed. Adaptive Design Methods in Clinical Trials, Second Edition reflects recent developments and regulatory positions on the use of adaptive designs in clinical trials. It unifies the vast and continuously growing literature and research activities on regulatory requirements, scientific and practical issues, and statistical methodology. New to the Second Edition Along with revisions throughout the text, this edition significantly updates the chapters on protocol amendment and clinical trial simulation to incorporate the latest changes. It also includes five entirely new chapters on two-stage adaptive design, biomarker adaptive trials, target clinical trials, sample size and power estimation, and regulatory perspectives. Following in the tradition of its acclaimed predecessor, this second edition continues to offer an up-to-date resource for clinical scientists and researchers in academia, regulatory agencies, and the pharmaceutical industry. Written in an intuitive style at a basic mathematical and statistical level, the book maintains its practical approach with an emphasis on concepts via numerous examples and illustrations.

Clinical Trial Design Challenges in Mood Disorders - Mauricio Tohen 2015-01-24

Poor clinical trial designs result in failed studies wasting research funds and limiting the advancement of cures for disorders. Clinical Trial Design Challenges in Mood Disorders outlines classic problems researchers face in designing clinical trials and discusses how best to address them for the most definitive and generalizable results. Traditional trial designs are included as well as novel analytic techniques. The book examines information on high placebo response, the generalizability of studies conducted in the developing world, the duration of maintenance studies, and the application of findings into clinical practice. With representation from contributors throughout the world and from academia, industry, regulatory agencies, and advocacy groups, this book will contribute toward improved clinical trial design and valid, precise, and reliable answers about what works better and faster for patients. Summarizes common trial design problems and their solutions Encompasses funding, subject selection, regulatory issues and more Identifies best practices for definitive and generalizable results Includes traditional trial designs and novel analytic techniques Represents academia, industry, regulatory agencies, and advocacy groups

Adaptive Design in Clinical Trials - Vladimir Dragalin 2007

Adaptive Design Theory and Implementation Using SAS and R -

Sequential Experimentation in Clinical

Trials - Jay Bartroff 2012-12-12
Sequential Experimentation in Clinical Trials: Design and Analysis is developed from decades of work in research groups, statistical pedagogy, and workshop participation. Different parts of the book can be used for short courses on clinical trials, translational medical research, and sequential experimentation. The authors have successfully used the book to teach innovative clinical trial designs and statistical methods for Statistics Ph.D. students at Stanford University. There are additional online supplements for the book that include chapter-specific exercises and information. Sequential Experimentation in Clinical Trials: Design and Analysis covers the much broader subject of sequential experimentation that includes group sequential and adaptive designs of Phase II and III clinical trials, which have attracted much attention in the past three decades. In particular, the broad scope of design and analysis problems in sequential experimentation clearly requires a wide range of statistical methods and models from nonlinear regression analysis, experimental design, dynamic programming, survival analysis, resampling, and likelihood and Bayesian inference. The background material in these building blocks is summarized in Chapter 2 and Chapter 3 and certain sections in Chapter 6 and Chapter 7. Besides group sequential tests and adaptive designs, the book also introduces sequential change-point detection methods in Chapter 5 in connection with pharmacovigilance and public health surveillance. Together with dynamic programming and approximate dynamic programming in Chapter 3, the book therefore covers all basic topics for a graduate course in sequential analysis designs.

Adaptive Design of Clinical Trials with Interim Selection of Treatment Arms - Yueh-Wen Liao 2012
When developing new drugs, Phase I and II trials are commonly conducted to determine the dose of the new treatment in preparation for the subsequent confirmatory Phase III trial. However, because these early-phase trials usually do not have large enough sample sizes to decide which dosage level or treatment regimen is the best, several of them may arise as candidates for the confirmatory Phase III trial. Conventional fixed sample size designs that carry out all the treatment arms of interest are obviously expensive. Therefore, the pharmaceutical industry is increasingly interested in adaptive designs that can use information acquired during the course of the trial to update certain of the design features. In this thesis we explore several existing designs and discuss their pros and cons. We then propose one that shares the flexibility of Bayesian adaptive designs, while still being able to maintain the frequentist type I error probability. We develop an asymptotic theory for efficient outcome-adaptive randomization schemes and optimal stopping rules. Our approach consists of developing asymptotic lower bounds for the expected sample sizes from the treatment arms and the control arm, and using generalized sequential likelihood ratio procedures to achieve these bounds. These allow us to allocate patients and study resources efficiently by using outcome-adaptive randomization schemes, or by arm suspension/selection if fixed randomization is used. We also derive an adaptive test with a p-value that can be evaluated by Monte Carlo simulation based on an ordering scheme of the sample space. We then show that the approach can also be applied to the closely related problem of multi-stage testing of multiple hypotheses.

Adaptive Design Theory and Implementation Using SAS and R, Second Edition - Mark Chang 2014-12-01
Get Up to Speed on Many Types of Adaptive Designs Since the publication of the first edition, there have been remarkable advances in the methodology and application of adaptive trials. Incorporating many of these new developments, Adaptive Design Theory and Implementation Using SAS and R, Second Edition offers a detailed framework to understand the use of various

adaptive design methods in clinical trials. New to the Second Edition Twelve new chapters covering blinded and semi-blinded sample size reestimation design, pick-the-winners design, biomarker-informed adaptive design, Bayesian designs, adaptive multiregional trial design, SAS and R for group sequential design, and much more More analytical methods for K-stage adaptive designs, multiple-endpoint adaptive design, survival modeling, and adaptive treatment switching New material on sequential parallel designs with rerandomization and the skeleton approach in adaptive dose-escalation trials Twenty new SAS macros and R functions Enhanced end-of-chapter problems that give readers hands-on practice addressing issues encountered in designing real-life adaptive trials Covering even more adaptive designs, this book provides biostatisticians, clinical scientists, and regulatory reviewers with up-to-date details on this innovative area in pharmaceutical research and development. Practitioners will be able to improve the efficiency of their trial design, thereby reducing the time and cost of drug development.

An Introduction to Adaptive Designs With Applications to Clinical Trials Using R - Michael R. Chernick 2015-04-01 This book presents an up-to-date, accessible, and authoritative look into the rapidly emerging study of statistical adaptive design. Employing the R language throughout, it emphasizes the usefulness of adaptive design methods and technology in public health and research settings through practical examples and plentiful exercises. Special focus is on adaptive late-stage clinical trial designs as extensions of the highly successful group sequential methods that have been applied for more than two decades. It is the first elementary text on the subject matter that is aimed at clinicians, investigators, credit rating analysts, medical writers, regulatory affairs specialists, and applied statisticians.

Neuroscience Trials of the Future - National Academies of Sciences, Engineering, and Medicine 2016-12-07 On March 3-4, 2016, the National Academies of Sciences, Engineering, and Medicine's Forum on Neuroscience and Nervous System Disorders held a workshop in Washington, DC, bringing together key stakeholders to discuss opportunities for improving the integrity, efficiency, and validity of clinical trials for nervous system disorders. Participants in the workshop represented a range of diverse perspectives, including individuals not normally associated with traditional clinical trials. The purpose of this workshop was to generate discussion about not only what is feasible now, but what may be possible with the implementation of cutting-edge technologies in the future.

Biopharmaceutical Applied Statistics Symposium - Karl E. Peace 2018-08-20 This BASS book Series publishes selected high-quality papers reflecting recent advances in the design and biostatistical analysis of biopharmaceutical experiments – particularly biopharmaceutical clinical trials. The papers were selected from invited presentations at the Biopharmaceutical Applied Statistics Symposium (BASS), which was founded by the first Editor in 1994 and has since become the premier international conference in biopharmaceutical statistics. The primary aims of the BASS are: 1) to raise funding to support graduate students in biostatistics programs, and 2) to provide an opportunity for professionals engaged in pharmaceutical drug research and development to share insights into solving the problems they encounter.The BASS book series is initially divided into three volumes addressing: 1) Design of Clinical Trials; 2) Biostatistical Analysis of Clinical Trials; and 3) Pharmaceutical Applications. This book is the first of the 3-volume book series. The topics covered include: A Statistical Approach to Clinical Trial Simulations, Comparison of Statistical Analysis Methods Using Modeling and Simulation for Optimal Protocol Design, Adaptive Trial Design in Clinical Research, Best Practices and Recommendations for Trial Simulations in the Context of

Designing Adaptive Clinical Trials, Designing and Analyzing Recurrent Event Data Trials, Bayesian Methodologies for Response-Adaptive Allocation, Addressing High Placebo Response in Neuroscience Clinical Trials, Phase I Cancer Clinical Trial Design: Single and Combination Agents, Sample Size and Power for the Mixed Linear Model, Crossover Designs in Clinical Trials, Data Monitoring: Structure for Clinical Trials and Sequential Monitoring Procedures, Design and Data Analysis for Multiregional Clinical Trials – Theory and Practice, Adaptive Group-Sequential Multi-regional Outcome Studies in Vaccines, Development and Validation of Patient-reported Outcomes, Interim Analysis of Survival Trials: Group Sequential Analyses, and Conditional Power – A Non-proportional Hazards Perspective.

Adaptive and Flexible Clinical Trials - Richard Chin 2016-04-19

Adaptive clinical trial designs, unlike traditional fixed clinical trial designs, enable modification of studies in response to the data generated in the course of the trial. This often results in studies that are substantially faster, more efficient, and more powerful. Recent developments in web-based real-time data entry and advances in statistical methods have made adaptive clinical trials much more popular because they have become both more practical and attractive. However, there is paucity of resources that explain the mathematical framework and the practical considerations for adaptive designs without the use of highly technical statistical jargon. Suitable for readers in academia, industry, and government involved in drug development, Adaptive and Flexible Clinical Trials is the first book that comprehensively explains all essential aspects of adaptive clinical trials. Written in an easy-to-understand style aimed at clinicians and other non-statisticians, this book focuses not on the statistical details, but rather on the application of statistical concepts for adaptive clinical trials. Utilizing concrete examples, the book thoroughly explains the design, conduct, and analysis of adaptive and flexible clinical trials, allowing readers to select and design the appropriate trial designs from a conceptual perspective. From basic theory to real-life practical issues, it covers all aspects of adaptive and flexible clinical trials, including regulatory issues, interim analysis, adaptive dosing, and sequential designs.