Chapman & Hall/CRC

Handbooks of Modern Statistical Methods

Handbook of Methods for Designing, Monitoring, and Analyzing Dose-Finding Trials

Edited by

John O'Quigley

Alexia Iasonos

Björn Bornkamp

CRC Press
Taylor & Francis Group
A CHAPMAN & HALL BOOK

Handbook of Methods for Designing, Monitoring, and Analyzing Dose-Finding Trials

Chapman & Hall/CRC Handbooks of Modern Statistical Methods

Series Editor

Garrett Fitzmaurice
Department of Biostatistics
Harvard School of Public Health
Boston, MA, U.S.A.

Aims and Scope

The objective of the series is to provide high-quality volumes covering the state-of-the-art in the theory and applications of statistical methodology. The books in the series are thoroughly edited and present comprehensive, coherent, and unified summaries of specific methodological topics from statistics. The chapters are written by the leading researchers in the field, and present a good balance of theory and application through a synthesis of the key methodological developments and examples and case studies using real data.

The scope of the series is wide, covering topics of statistical methodology that are well developed and find application in a range of scientific disciplines. The volumes are primarily of interest to researchers and graduate students from statistics and biostatistics, but also appeal to scientists from fields where the methodology is applied to real problems, including medical research, epidemiology and public health, engineering, biological science, environmental science, and the social sciences.

Published Titles

Handbook of Mixed Membership Models and Their Applications
Edited by Edoardo M. Airoldi, David M. Blei,
Elena A. Erosheva, and Stephen E. Fienberg

Handbook of Statistical Methods and Analyses in Sports
Edited by Jim Albert, Mark E. Glickman, Tim B. Swartz, Ruud H. Koning

Handbook of Markov Chain Monte Carlo
Edited by Steve Brooks, Andrew Gelman,
Galin L. Jones, and Xiao-Li Meng

Handbook of Big Data
Edited by Peter Bühlmann, Petros Drineas,
Michael Kane, and Mark van der Laan

Published Titles Continued

Handbook of Discrete-Valued Time Series
Edited by Richard A. Davis, Scott H. Holan, Robert Lund, and Nalini Ravishanker

Handbook of Design and Analysis of Experiments
Edited by Angela Dean, Max Morris, John Stufken, and Derek Bingham

Longitudinal Data Analysis
Edited by Garrett Fitzmaurice, Marie Davidian, Geert Verbeke, and Geert Molenberghs

Handbook of Spatial Statistics
Edited by Alan E. Gelfand, Peter J. Diggle, Montserrat Fuentes, and Peter Guttorp

Handbook of Cluster Analysis
Edited by Christian Hennig, Marina Meila, Fionn Murtagh, and Roberto Rocci

Handbook of Survival Analysis
Edited by John P. Klein, Hans C. van Houwelingen, Joseph G. Ibrahim, and Thomas H. Scheike

Handbook of Quantile Regression
Edited by Roger Koenker, Victor Chernozhukov, Xuming He, and Limin Peng

Handbook of Spatial Epidemiology
Edited by Andrew B. Lawson, Sudipto Banerjee, Robert P. Haining, and María Dolores Ugarte

Handbook of Missing Data Methodology
Edited by Geert Molenberghs, Garrett Fitzmaurice, Michael G. Kenward, Anastasios Tsiatis, and Geert Verbeke

Handbook of Neuroimaging Data Analysis
Edited by Hernando Ombao, Martin Lindquist, Wesley Thompson, and John Aston

Handbook of Methods for Designing, Monitoring, and Analyzing Dose-Finding Trials
Edited by John O'Quigley, Alexia Iasonos, Björn Bornkamp

Chapman & Hall/CRC

Handbooks of Modern Statistical Methods

Handbook of Methods for Designing, Monitoring, and Analyzing Dose-Finding Trials

Edited by

John O'Quigley
French National Institute for Health and Medical Research
Faculty of Mathematics,
University Pierre and Marie Curie, Paris, France

Alexia Iasonos
Memorial Sloan Kettering Cancer Center
New York, USA

Björn Bornkamp
Novartis
Basel, Switzerland

CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

A CHAPMAN & HALL BOOK

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Printed on acid-free paper

International Standard Book Number-13: 978-1-4987-4610-6 (Hardback)

Contents

Editors

John O'Quigley is a professor of mathematics and research director at the French National Institute for Health and Medical Research based at the Faculty of Mathematics, University Pierre and Marie Curie, in Paris, France. He is author of the text *Proportional Hazards Regression* and has published extensively in the field of dose finding.

Alexia Iasonos is an associate attending biostatistician at the Memorial Sloan Kettering Cancer Center in New York. She has over one hundred publications in the leading statistical and clinical journals on the methodology and design of early-phase clinical trials. Dr. Iasonos has wide experience in the actual implementation of model-based, early-phase trials and has taught courses in international scientific meetings.

Björn Bornkamp is a statistical methodologist at Novartis in Basel, Switzerland, researching and implementing dose-finding designs in Phase II clinical trials. He is one of the co-developers of the MCP-Mod methodology for dose finding and main author of the DoseFinding R package. He has published numerous papers on dose finding, nonlinear models, and Bayesian statistics, and in 2013, he won the Royal Statistical Society award for statistical excellence in the pharmaceutical industry.

Preface

This volume covers recent developments in the design and analysis of dose-finding clinical trials. While the theory is closely examined, the unifying driving force is the clinical applications themselves. Given the high failure rate of Phase III confirmatory clinical trials, together with an increasing need to look at new agents in a timely manner, it has become apparent that poor accuracy in the early-phase trials can have significant consequences further down the line in the overall drug development. The aim of recent developments in early-phase trials is to greatly improve this accuracy and to achieve this while strictly respecting ethical requirements governing clinical trials in human subjects. In the long term, the end result will be a speedier and more reliable drug development process so that patients can more quickly see the real benefit from scientific advances in the laboratory.

In Phase I first-in-human trials, little is known on how the probability of encountering adverse events relates to dose when the drug is given to humans based on preclinical data. One objective of a trial is to learn more about this relationship, although we are severely hampered by the need to avoid overdosing. Further, underdosing is also a concern for oncology patients who participate in these trials, if there is no hope of benefit one should not offer to include patients in the trial. We need a trade-off between information gained via experimentation at various dose levels and the requirements of the treated patients themselves on a particular study. The statistical setting is thus unusual. This presents a considerable statistical challenge and has formed the basis of several of the model-based approaches that are discussed here. Challenges in Phase II dose-finding studies include the fact that efficacy information evaluated on the different dose levels is limited not only by a typically rather low sample size but also by the fact that biomarker, or short-term, endpoints are used compared to more definitive endpoints used in more extensive and longer-term Phase III clinical trials.

Explicitly characterizing the relation between the amount of a given drug and its effect, i.e., how the body reacts to given doses of the drug, has not traditionally been an objective of Phase I trials. Even some Phase II dose-finding trials do not aim to do this. As a result of this lack of precision, the goals of the older, or classical, standard dose-finding designs, such as the well-known 3 + 3, are not clear. In the absence of clear goals, it is not possible to say whether or not any proposed statistical methodology works well or is even fit for its purpose. In Phase II dose-finding clinical trials, a major focus has traditionally been statistical testing based on pairwise comparisons of the efficacy endpoint, which is not aligned with the goal of determining the efficacy dose–response curve. An aim in this current volume is to make very clear and explicit early on the goals of an early-phase study under different settings, and then to critically investigate how any statistical approach can meet these goals. In practice, the level of clinical complexity can increase rapidly, for example, studies in targeted therapies, combination therapies, bridging between different patient populations or several heterogeneous groups, and errors in recording adverse events. The several authors in this volume, through the many different approaches presented, never lose sight of the initial motivation and the study's objective. No statistical complexity, for

its own sake, is presented, and the methods described are being currently used to provide answers in applied clinical research. The material presented here, along with references to further work, provides an overview of various existing methods that can help a practicing statistician select an appropriate clinical trial design to match the objective of the study.

Contributors

Björn Bornkamp
Clinical Development and Analytics
Novartis Pharma AG
Basel, Switzerland

Frank Bretz
Clinical Development and Analytics
Novartis Pharma AG
Basel, Switzerland

Ying Kuen K. Cheung
Mailman School of Public Health
Columbia University
New York, New York

Mark R. Conaway
Department of Public Health Sciences
University of Virginia
Charlottesville, Virginia

Vladimir Dragalin
Quantitative Sciences
Janssen Research & Development
Beerse, Belgium

Emily V. Dressler
Division of Cancer Biostatistics
Markey Cancer Center
University of Kentucky
Lexington, Kentucky

Lei Gao
Research and Development
Sanofi US
Cambridge, Massachusetts

Sofia Friberg Hietala
Pharmetheus AB
Uppsala, Sweden

Alexia Iasonos
Department of Epidemiology and Biostatistics
Memorial Sloan Kettering Cancer Center
New York, New York

Franz König
Section of Medical Statistics
Medical University of Vienna
Vienna, Austria

Markus R. Lange
Clinical Development and Analytics
Novartis Pharma AG
Basel, Switzerland

Shing Lee
Mailman School of Public Health
Columbia University
New York, New York

Efthymios Manolis
European Medicines Agency
London, United Kingdom

Tobias Mielke
Innovation Center
ICON Clinical Research
Cologne, Germany

Arzu Onar-Thomas
Department of Biostatistics
St. Jude Childrens Research Hospital
Memphis, Tennessee

John O'Quigley
Laboratory of Theoretical and Applied Statistics
University Pierre and Marie Curie
Paris, France

José Pinheiro
Model-Based Drug Development
Janssen Research & Development
Raritan, New Jersey

Heinz Schmidli
Clinical Development and Analytics
Novartis Pharma AG
Basel, Switzerland

Oleksandr Sverdlov
Biostatistical Sciences and Pharmacometrics
Novartis Institutes for Biomedical Research
Cambridge, Massachusetts

Flora Musuamba Tshinanu
School of Pharmacy
University College London
London, United Kingdom

Fridtjof Thomas
Division of Biostatistics, Department of Preventive Medicine
University of Tennessee Health Science Center
Memphis, Tennessee

Nolan A. Wages
Department of Public Health Sciences
University of Virginia
Charlottesville, Virginia

Graham M. Wheeler
Cancer Research UK and UCL Cancer Trials Centre
University College London
London, United Kingdom

Xiaolei Xun
Clinical Development and Analytics
Novartis Pharma
Shanghai, China

Donglin Yan
College of Public Health, Department of Biostatistics
University of Kentucky
Lexington, Kentucky

Ying Yuan
Department of Biostatistics
The University of Texas MD Anderson Cancer Center
Houston, Texas

Liangcai Zhang
Department of Statistics
Rice University
Houston, Texas

Part I

Phase I Designs

1

Overview of Phase I Designs

Graham M. Wheeler

University College London

CONTENTS

Though many differing approaches for conducting phase I trials have been proposed over the past three decades, they all aim to target a specific dose level while minimizing the risk of patients in the trial experiencing intolerable toxicities. Here, we cover the two main types of phase I designs—rule-based and model-based—and provide an overview of the many designs available. We also discuss other design aspects, such as start-up rules and stopping rules, and summarize how clinical practice has changed over the years when it comes to designing a phase I trial.

1.1 Introduction

The primary objective of a phase I clinical trial is to investigate the safety profile of a novel drug or drug combination and identify a tolerable dose schedule that is likely to benefit patients (Chang and Chow, 2006). For cytotoxic therapies in oncology, such trials

are conducted using a small number of cancer patients for whom standard therapies have not worked (Horstmann et al., 2005). Due to the possibility of experimental treatments causing severe side effects, trials are conducted as *dose-escalation studies*. In general, patients are recruited into the trial and treated in small cohorts of one, two, or three, with the first cohort treated at an exceedingly low dose level considered safe in humans (Von Hoff et al., 1984; Eisenhauer et al., 2000). The number and severity of toxic reactions, as defined by the National Cancer Institute's Common Terminology Criteria for Adverse Events [NCI CTCAE (National Cancer Institute, 2009)], observed in patients undergoing treatment are recorded, and based on the results for the current cohort (and possibly previous cohorts), the next cohort of patients will be treated at either a higher dose level, a lower dose level, or the same dose level. The trial continues in this manner until all available patients have been treated, or some other stopping criterion is satisfied, such as a target number of patients have been consecutively dosed at one dose level, or the proportion of patients experiencing severe toxicity at a dose level exceeds a prespecified threshold (see Section 1.4.2).

Commonly, toxicity frequency and severity data are reduced to a single binary outcome known as *dose-limiting toxicity* (DLT) (Le Tourneau et al., 2009), and this response is used to determine whether dose escalation occurs or not. What constitutes a DLT will vary from trial to trial (Le Tourneau et al., 2011), but it is often the case that a DLT is said to have occurred in a patient if at least one severe toxicity [grade 3 or higher under the NCI CTCAE (NCI, 2009)] in a particular body system or organ of interest is observed in the first cycle of treatment (Babb and Rogatko, 2004).

The main objective of phase I trials is to identify the *maximum tolerated dose* (MTD) of the new drug. Although definitions of the MTD vary (Le Tourneau et al., 2009), it is often defined as the dose that, at the end of the trial, has an estimated probability of causing a DLT as close to some predetermined *target toxicity level* (TTL) as possible (Babb and Rogatko, 2004). In oncology, the TTL is fixed often at some probability between 0.20 and 0.35 (Neuenschwander et al., 2008; Le Tourneau et al., 2009). An alternative definition of the MTD is the dose with no more than a certain proportion (e.g., 33%) of patients at that dose experiencing DLT. If an MTD is successfully identified in a phase I trial, the drug is then taken forward into a phase II trial, with the MTD or a slightly lower dose designated as the recommended phase II dose (RP2D) (Le Tourneau et al., 2012).

The rationale for targeting a dose level that is potentially harmful with small probability is due to the belief that the higher the dose of a cytotoxic drug, the better the speed or extent of tumor response (Marshall, 2012). Therefore, the MTD of a cytotoxic drug is seen as a proxy for an efficacious dose level with limited toxicity potential. When considering molecularly targeted agents, which affect particular molecules required for cancer cells to mutate (carcinogenesis) rather than all cells, this may not necessarily be the case (Le Tourneau et al., 2009); in some cases, it has been observed that the dose–response relationship may be nonmonotonically increasing (Conolly and Lutz, 2004; Bretz et al., 2008). Most methods for phase I trials are based on the *assumption of monotonicity* (Box 1.1); that is, if a patient has a DLT at a given dose level, then the same patient would have had a DLT had they been given a higher dose level than the one they received. Conversely, had the patient not had a DLT at a given dose level, then the same patient would not have had a DLT had they been given a lower dose level than the one they received (O'Quigley and Zohar, 2006). This assumption can be summarized on a population level by saying that the probability of a DLT occurring in a patient is monotonically increasing with dose.

Box 1.1 The Assumption of Monotonicity

The probability of observing a dose-limiting toxicity (DLT) is monotonically increasing with dose.

Methods for conducting dose-escalation studies are usually dichotomized into two families: *rule-based designs*, where fixed rules applied to empirical counts of DLT/non-DLT responses govern the escalation and de-escalation of doses, and *model-based designs*, where statistical models are employed to describe the relationship between the dose given to a patient and the probability of DLT occurring (Rosenberger and Haines, 2002). O'Quigley and Zohar (2006) stated that any method considered for use in a phase I trial should aim to (1) minimize the number of patients treated at dose levels below the true MTD, (2) minimize the number of patients treated at dose levels above the true MTD, (3) minimize the number of patients used in the study in its entirety, and (4) be able to respond quickly to errors in initial guesses or incorrect dose allocations. In this chapter, we describe the main rule-based and model-based approaches for conducting phase I dose-escalation studies with a single binary DLT endpoint. We follow these up with discussions on modifications to these designs that have been used in clinical practice, the popularity of particular designs in clinical practice, and available software for various methods.

1.2 Rule-Based Designs

Rule-based designs have long been popular with clinicians in cytotoxic drug experimentation (Storer, 1989; Rogatko et al., 2007). The fundamental aspect of rule-based designs is that they do not require the dose–toxicity relationship to be modeled according to some function of dose level. Many of the methods proposed stem from the work on the *up-and-down design* by Dixon and Mood (1948), who sought to identify the mean or median height from which a weight may be dropped upon an explosive compound without detonation occurring. Over time, variations of the up-and-down design made their way into medical research.

1.2.1 The 3 + 3 design

The 3 + 3 design (Carter, 1973; Storer, 1989) is one of the first methods used to conduct dose-escalation studies in humans. The 3 + 3 design is the most commonly used design in phase I clinical trials (Rogatko et al., 2007; Penel et al., 2009; Le Tourneau et al., 2009, 2012) and has long been considered the routine method by clinicians for estimating the MTD of novel drugs in oncology (Penel et al., 2009).

For a trial of k dose levels of a new drug, denoted as $D = \{d_1, \ldots, d_k\}$, patients are treated in cohorts of three for the 3 + 3 design. The first cohort of patients are treated at d_1, the lowest dose level. If no patients in a cohort experience a DLT, then the next cohort is treated at the next highest dose level. If one out of the three patients experiences a DLT, then the next cohort is treated at the same dose level. If at dose level d_i at least two out of the three or six patients experience a DLT, the trial is terminated and d_{i-1} is deemed to be the MTD; if $d_{i-1} = d_0$, then no MTD is identified for safety reasons. The 3 + 3 design may be adapted so that excessive toxicity leads to dose de-escalation rather than trial termination (Storer, 1989; Dignam et al., 2006; Skolnik et al., 2008; Chow, 2011). That is, if d_i is deemed excessively toxic, and only three patients have received dose d_{i-1}, then another three patients are dosed at d_{i-1}. If at most one out of the six patients experiences a DLT, then the trial is terminated and d_{i-1} is the MTD; otherwise, the dose is de-escalated again under the same rules. If six patients had been treated at d_{i-1}, and d_i was deemed excessively toxic, then the trial would terminate and d_{i-1} would be recommended as the MTD. Figure 1.1 illustrates the trial schematic for the 3 + 3 design with dose de-escalation not permitted, and Figure 1.2 illustrates an example trial using data from a real

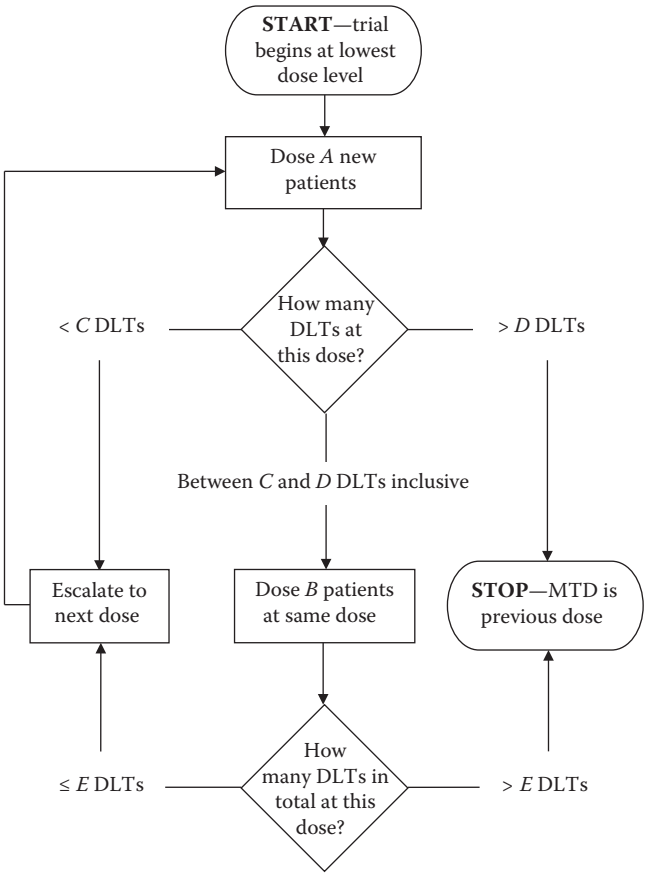

FIGURE 1.1
Design schematic of the $A + B$ design without dose de-escalation.

$3 + 3$ trial conducted by Park et al. (2005). The trial investigated the dose escalation of 5-fluorouracil (5-FU) in combination with a fixed dose of docetaxel in patients with advanced gastric cancer. Four dose levels were planned for experimentation: 250, 500, 750 and 1000 mg/m^2/day. In the first cohort, no patients experienced a DLT at the first dose level. The second cohort was given the dose level of 500 mg/m^2/day, at which one out of the three patients experienced a DLT. Therefore, the third cohort was also given the second dose level. No patients in the third cohort experienced a DLT, and so the fourth cohort was given the dose level of 750 mg/m^2/day. As two out of the three patients in the fourth cohort experienced a DLT, the trial was terminated after 12 patients and the MTD was identified as 500 mg/m^2/day.

There exist several variants of the traditional $3 + 3$ design, including generic $A + B$ trials where A and B are positive integers that denote cohort sizes to be used in the trial (Lin and Shih, 2001). For example, a $2 + 4$ trial would dose a cohort of two patients at a dose level and then add another four patients to that dose level if one of the initial two patients treated experienced a DLT. There are also $A + B + C$ designs where an extra cohort of C patients may be added onto a dose level if a predetermined number of DLTs are observed in $A + B$ patients. Examples include the $3 + 1 + 1$ design, which offers more aggressive dose escalation than the $3 + 3$ design (Storer, 2001), and the $3 + 3 + 3$ design (Hamberg

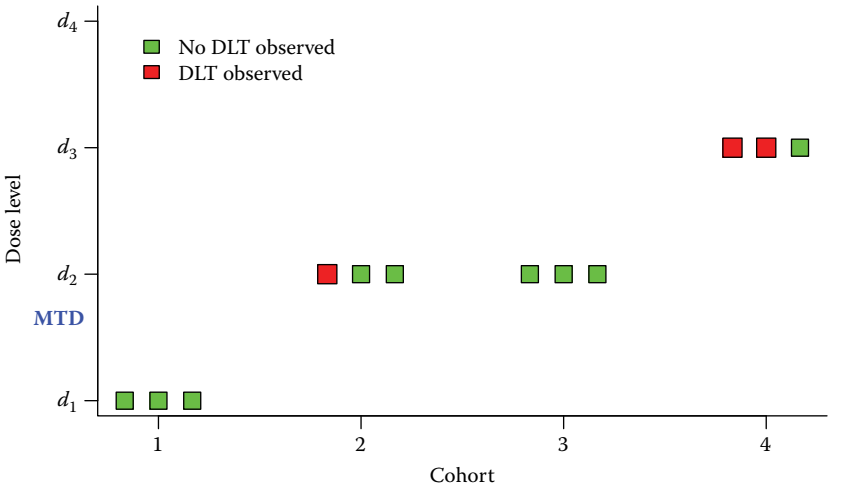

FIGURE 1.2
Example of dose-escalation pathway in a real 3 + 3 trial (Park et al., 2005). After observing one DLT in cohort 2 at dose level d_2, cohort 3 were dosed at dose level d_2 also. After escalating to dose level d_3, excessive toxicity leads to termination of the trial and dose level d_2 is the final MTD.

and Verweij, 2009), which after observing two DLTs in six patients, doses another cohort of three patients at the same dose level.

The main advantages of the 3 + 3 design are that neither a statistician nor highly technical computer software are required to help design or run the trial (Le Tourneau et al., 2009), and exact operating characteristics can be calculated (Lin and Shih, 2001; Wheeler et al., 2016). Additionally, the 3 + 3 design may be ideal for screening drugs very quickly to identify a dose level that exhibits very little toxicity in a small number of patients (Rosenberger and Haines, 2002). However, the pitfalls associated with the 3 + 3 design perhaps outweigh these benefits (Harrington et al., 2013). The 3 + 3 design is a *memoryless* design (Ratain et al., 1993; O'Quigley and Zohar, 2006), i.e., dose-escalation decisions are based on the observed results at the current dose, and the distribution of toxicities in previous cohorts is ignored (Zohar and O'Quigley, 2009). Furthermore, many of the trial participants are treated at subtherapeutic doses due to the slow dose-escalation process that the algorithm enforces (O'Quigley et al., 1990; Ratain et al., 1993), and a new cohort cannot be enrolled until toxicity outcomes have been observed for all patients in the current cohort. A common misconception is that the MTD determined in a 3 + 3 trial always has an expected toxicity rate of 33% since the dose selected as the MTD has an empirical toxicity rate of at most 33%. Large-scale simulation studies have shown that the expected toxicity rate at the estimated MTD depends on the number of doses under experimentation and is often much lower than 33% (Kang and Ahn, 2001, 2002; He et al., 2006; Chen et al., 2009). In fact, the 3 + 3 design does not have a TTL to target per se, meaning that the design is searching for an unknown dose with an unspecified toxicity probability.

1.2.2 Rolling-6 design

In order to shorten trial duration for the 3 + 3 design, Skolnik et al. (2008) proposed the *rolling-6 design*, in which dose-escalation/de-escalation decisions can be made for the next cohort of three patients, even when not all three patients in the previous cohort have a

definitive DLT/no-DLT response. These decisions depend on the number of patients currently enrolled in the cohort, the number of patients with DLTs, and the number of patients enrolled but not yet evaluable for DLT. The trial is run as a 3 + 3 design, but with several modifications: if DLT data are unavailable for one or more of the three patients at dose d_i, or if one DLT is observed at d_i, then the fourth patient (the first patient in the next cohort) is also dosed at d_i; if two or more DLTs have been observed, even if the third patient is not yet evaluable for DLT, then the fourth patient is given dose d_{i-1}. These rules also apply to the fifth and sixth patients (patients 2 and 3 of the next cohort). Several comparative simulation studies have shown that trials using the rolling-6 design are shorter in duration than those using the 3 + 3 design, but on average require more patients to identify an MTD and are more likely to result in excessive numbers of DLTs (at least three per dose) occurring (Onar-Thomas and Xiong, 2010; Sposto and Groshen, 2011; Doussau et al., 2012). The design has been implemented in practice, particularly in pediatric oncology trials (Mossé et al., 2013; Hoffman et al., 2015). However, it still possesses many of the pitfalls of the 3 + 3 design, and model-based alternatives have been shown to offer much better performance (Onar-Thomas and Xiong, 2010; Zhao et al., 2011).

1.2.3 Accelerated titration designs

An alternative class of rule-based methods to the traditional 3 + 3 design are accelerated titration designs (Simon et al., 1997), which permit intrapatient dose escalation in order to reduce the total sample size and the number of patients treated at subtherapeutic doses. Under accelerated titration designs, dose-escalation/de-escalation decisions are made within patients as well as between patients/cohorts and are based on the toxicity observed in the current treatment cycles and/or the largest toxicity in the first treatment cycle. A drawback of such designs is that intrapatient dose escalation may lead to difficulty in the analysis of trial data since cumulative or delayed toxicities may be masked (Hansen et al., 2014). Simon et al. found that the number of high-grade toxicities increased under accelerated titration compared to a design without intrapatient dose escalation. Although not exhaustive, the 3 + 3 design and accelerated titration designs are the primary rule-based designs used in phase I oncology trials (Rogatko et al., 2007).

1.2.4 Pharmacologically guided dose escalation

Another variation is pharmacologically guided dose escalation (PGDE) (Collins et al., 1990), which relies on *in vivo* data to predict DLT outcomes in humans. Dose escalation of one-patient cohorts is based on whether the area under the curve (AUC) of drug concentration over time is less than some target level. When such a level is exceeded, or when DLTs begin to occur, the design switches to the traditional 3 + 3 design. The PGDE method has had mixed results in clinical practice, in that reliable phase II doses have been recommended for some cytotoxic compounds that have high interpatient variability/heterogeneity (Graham and Workman, 1992; Hansen et al., 2014).

1.2.5 Improvements to conventional rule-based designs

Ivanova et al. (2003) proposed various up-and-down rules that incorporate more trial information than approaches based on the 3 + 3 design (i.e., the most recent cohort) in order to guide dose escalation. Among these is the Narayana rule, derived from the unpublished work of Narayana (1953), which recommends dose escalation or de-escalation from the current dose level based on the empirical proportions of DLTs observed and the k most recent dose–toxicity outcomes at the current level. The authors also considered different procedures

for estimating the MTD of a drug, including isotonic regression (Robertson et al., 1988), which adjusts the empirical DLT rates at different doses via the pooled adjacent violators algorithm (PAVA) to maintain monotonicity of toxicity in doses (Barlow et al., 1972).

The approaches discussed here aim to develop the early up-and-down design work of Dixon and Mood (1948) while keeping dose-escalation decisions dependent on the empirical DLT rates at each dose level. However, more statistical approaches for conducting dose-escalation studies have been proposed, which use mathematical models to quantify the relationship between the dose of a drug and the probability of a DLT occurring.

1.3 Model-Based Designs

Over the past two decades, there has been widespread interest in adaptive model-based designs for phase I clinical trials (Whitehead, 1997), particularly Bayesian designs, in order to overcome the shortcomings identified with the 3 + 3 design and other rule-based methods. Model-based designs use statistical models to estimate the underlying dose–toxicity relationship and can easily incorporate all trial data as well as *a priori* beliefs into the dose–toxicity relationship to help determine dose allocation and MTD recommendation.

1.3.1 The continual reassessment method

One of the first model-based designs for phase I clinical trials was the *continual reassessment method* (CRM) (O'Quigley et al., 1990). Under the CRM, the dose–toxicity curve is assumed to have some monotonically increasing functional form (Table 1.1), which is characterized by a single parameter a and dose level d or a transformed set of dose levels based on the initial dose–toxicity probability guesses, known as the *dose–toxicity skeleton*. The models presented in Table 1.1 are the two simplest and most commonly used; other model structures have been proposed, but under certain conditions, these are equivalent to either the power or logistic model (Cheung, 2011). The models are parameterized with respect to $\exp(a)$ to ensure that the dose–toxicity function is increasing in dose. Transformed dose levels are used to ensure that the chosen model is a sensible fit for the dose–toxicity skeleton (the prior guesses for the dose–toxicity probabilities at each dose level) and can easily be computed by backward substitution (Cheung, 2011).

In a Bayesian setting, a prior belief about the shape of the dose–toxicity curve, along with any surrounding uncertainty, is expressed as a prior distribution on parameter a; this information may be elicited from clinical opinion and data from previous studies if available and calibrated so that it does not dominate over the data that are accrued during the trial (Legedza and Ibrahim, 2001; Rosenberger et al., 2005; Cheung, 2011). As the trial progresses, patient data are used to update the prior distribution on a to obtain a posterior belief about the shape of the dose–toxicity curve. Let $D = \{d_1, \ldots, d_k\}$ be the set of k dose

TABLE 1.1
Common models for one-parameter CRM.

Model	$\psi(d, a)$	Restrictions
Power	$d^{\exp(a)}$	$0 < d < 1$
Logistic	$\frac{\exp(a_1+\exp(a)d)}{1+\exp(a_1+\exp(a)d)}$	a_1 fixed $-\infty < d < \infty$

labels, obtained from the dose–toxicity skeleton of a new drug under experimentation. Let $x_j \in D$ be the dose level that patient j receives and Y_j be the binary DLT outcome for patient j, i.e.,

$$Y_j = \begin{cases} 1 & \text{if patient } j \text{ experiences a DLT} \\ 0 & \text{otherwise} \end{cases} \tag{1.1}$$

Let $\Omega_j = \{x_1, y_1, \ldots, x_j, y_j\}$ denote the set of trial data (doses given and DLT outcomes) for the first j patients and $g(a)$ denote the prior distribution of a, which is defined on the set $\mathcal{A} = (-\infty, \infty)$. Then using Bayes' theorem (Bayes, 1763), we may obtain the posterior distribution of a, denoted as $f(a \mid \Omega_j)$:

$$f(a \mid \Omega_j) = \frac{g(a)L(a \mid \Omega_j)}{\int_{a \in \mathcal{A}} g(a)L(a \mid \Omega_j)\, da}, \tag{1.2}$$

where the likelihood $L(a \mid \Omega_j)$ is of the form

$$L(a \mid \Omega_j) = \prod_{l=1}^{j} \psi(x_l, a)^{y_l} \left[1 - \psi(x_l, a)\right]^{1-y_l}. \tag{1.3}$$

The posterior belief about the shape of the dose–toxicity curve, derived from the posterior distribution of a, allows us to select a dose level that has an estimated probability of DLT as close to the desired TTL as possible; we denote the TTL as θ here. O'Quigley et al. (1990) propose two different, but closely related, estimators. One obtains the posterior mean of a, denoted as $\hat{a}$, and uses this plug-in estimate to find x_{j+1}, the dose for the next patient, i.e.,

$$\hat{a} = \int_{a \in \mathcal{A}} a\, f(a \mid \Omega_j)\, da, \tag{1.4}$$

$$x_{j+1} = \arg\min_{d_i \in D} \left(\psi\left(d_i, \hat{a}\right) - \theta\right)^2. \tag{1.5}$$

The other approach integrates over the distribution of a to obtain a posterior mean estimate of $\psi(d_i, a)$ for $i = 1, \ldots, k$ and finds the dose with mean probability of DLT closest to θ:

$$x_{j+1} = \arg\min_{d_i \in D} \left(\int_{a \in \mathcal{A}} \psi(d_i, a)\, f(a \mid \Omega_j)\, da - \theta\right)^2. \tag{1.6}$$

Once the dose has been chosen for patient $j + 1$, the trial repeats the above computation based on the trial data set Ω_{j+1}, which is formed by the union of Ω_j and $\{x_{j+1}, y_{j+1}\}$, the dose and DLT outcome of patient $j + 1$. The trial is either stopped after an MTD estimate has been reached with a sufficient level of certainty or when a maximum number of patients have been treated (see Section 1.4.2). The CRM may also be used using maximum likelihood estimation to update the parameter a and determine dose escalation for future patients (O'Quigley and Shen, 1996). Rather than using a prior distribution $g(a)$ for a, the $3 + 3$ design is used as a start-up rule until the first DLT response is observed (estimation of $\hat{a}$ requires at least one DLT response and one non-DLT response). After this, maximum likelihood estimation is used to estimate a, with dose escalation and MTD selection conducted as shown in Equation 1.5. An example of how the shape of the dose–toxicity curve changes with more data is shown in Figure 1.3.

There are several advantages to using the CRM instead of the $3 + 3$ design. First, the CRM incorporates all trial information into the dose-escalation decision-making process, rather than just the current cohort as in the $3 + 3$ design. Furthermore, an explicit TTL θ can be stated, which means that the MTD identified at the end of the trial has a meaning

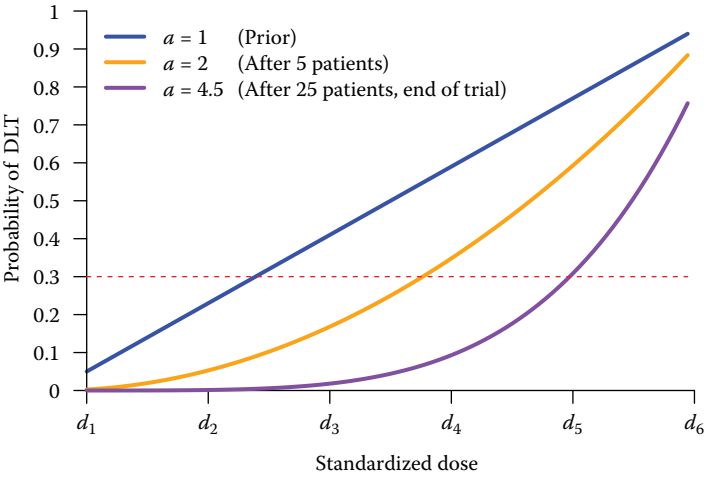

FIGURE 1.3
Example of how dose–toxicity curve changes with patient data, assuming a power model for the CRM design. Here, at the end of the trial seeking a dose with probability of DLT as close to $\theta = 0.30$ as possible, dose level d_5 is selected as the MTD.

to both statisticians and clinicians. The CRM provides faster dose escalation and more accurate convergence to the true MTD than the 3 + 3 design (O'Quigley et al., 1990; Le Tourneau et al., 2009), as shown in numerous simulation studies (O'Quigley, 1999; Thall and Lee, 2003; Iasonos et al., 2008; Onar et al., 2009; Onar-Thomas and Xiong, 2010). In its original form, the faster dose-escalation had the potential to lead to patients being assigned to high dose levels. The model and dose-escalation schematic of the CRM are easily adaptable to circumvent this problem, and several papers have proposed various changes to aspects of the original CRM design. In particular, it is now common practice to start the trial at the lowest dose under experimentation and to not escalate more than one dose level per patient (O'Quigley and Chevret, 1991; Faries, 1994; Goodman et al., 1995; Møller, 1995). There have also been investigations into how the prior distribution and dose–toxicity skeleton should be chosen (Cheung, 2011; Lee and Cheung, 2011; Iasonos and O'Quigley, 2012), as well as appropriate stopping rules for trials using the CRM (O'Quigley and Reiner, 1998; Zohar and Chevret, 2001) (Section 1.4.2) and how the CRM performs under model misspecification. While one can never truly know if they have chosen the correct model for the dose–toxicity curve, several studies have shown that while operating characteristics may be different under different model choices, a simple one-parameter CRM is likely to be more robust in targeting the correct MTD (Paoletti and Kramar, 2009; Iasonos et al., 2016).

1.3.2 Escalation with overdose control (EWOC)

In order to overcome concerns about quickly escalating doses and overdosing patients under the CRM, Babb et al. (1998) proposed the *escalation with overdose control* (EWOC) design. Under the EWOC design, the posterior distribution of the MTD is updated after each patient, and a chosen percentile of the MTD distribution is used to select doses for future patients. This percentile, denoted as α, is known as the *feasibility bound* and reflects how conservative investigators are in escalating dose levels between patients. The feasibility bound can be interpreted via a decision-theoretic loss function, which describes the relative

preference of underdosing a patient compared to overdosing a patient. For some dose level d and MTD μ, the loss function for feasibility bound α is

$$\text{Loss}(d, \mu) = \begin{cases} \alpha(\mu - d) & \text{if } d \text{ is an underdose, i.e., } d \leq \mu \\ (1-\alpha)(d - \mu) & \text{if } d \text{ is an overdose, i.e., } d \geq \mu. \end{cases} \tag{1.7}$$

In words, for any $\delta > 0$, the loss incurred by overdosing a patient (with respect to the MTD μ) by δ units is $\frac{1-\alpha}{\alpha}$ times greater than underdosing a patient by δ units (Babb et al., 1998; Babb and Rogatko, 2001). For $\alpha < 0.50$, the loss function in Equation 1.7 places a higher penalty on overdosing, whereas if $\alpha = 0.50$, one is indifferent between overdosing and underdosing patients. In order to conduct dose escalation, Babb et al. (1998) proposed a two-parameter logistic function to model the probability of DLT, given dose level d_i:

$$\psi(d_i, a_1, a_2) = \frac{\exp(a_1 + \exp(a_2)d_i)}{1 + \exp(a_1 + \exp(a_2)d_i)}, \tag{1.8}$$

where a_1 and a_2 are model parameters. If for MTD μ, we denote $\psi(\mu, a_1, a_2) = \theta$ and for the lowest dose level d_1, we denote $\psi(d_1, a_1, a_2) = \rho_0$ for some probability $\rho_0 \in (0, 1)$, one can transform these expressions and rewrite a_1 and a_2 as

$$a_1 = \frac{\mu \,\text{logit}(\rho_0) - d_1 \,\text{logit}(\theta)}{\mu - d_1} \quad \text{and} \quad a_2 = \log\left(\frac{\text{logit}(\theta) - \text{logit}(\rho_0)}{\mu - d_1}\right). \tag{1.9}$$

So, a_1 and a_2 can be expressed in terms of μ, the MTD, and ρ_0, the probability of toxicity at dose d_1. These parameters are more meaningful to clinicians and can be used in the Bayesian updating procedure by placing prior distributions upon μ and ρ_0 (Kadane et al., 1980; Babb et al., 1998). For prior distributions on μ and ρ_0, Babb et al. (1998) suggest a uniform distribution over the interval $[d_1, d_k]$ for μ and a uniform distribution over the interval $[0, \theta]$ for ρ_0, though others have been proposed (Tighiouart et al., 2005). Similar to Equation 1.2, the joint posterior distribution for μ and ρ_0 given trial data Ω_j and prior distribution $g(\mu, \rho_0)$, denoted as $f(\mu, \rho_0 \,|\, \Omega_j)$, can be obtained. With this, the marginal cumulative distribution function of μ, $H_j(\mu')$ is

$$H_j(\mu') = \mathbb{P}(\mu \leq \mu' \,|\, \Omega_j) = \int_{x_1}^{\mu'} \int_0^{\theta} f(\mu, \rho_0 \,|\, \Omega_j)\, d\rho_0\, d\mu, \tag{1.10}$$

and the dose for patient $j+1$, x_{j+1} is chosen as

$$x_{j+1} = \arg\min_{d_i \in D} \left\{ \left(H_j\left(d_i\right) - \alpha \right)^2 \right\}. \tag{1.11}$$

Figure 1.4 illustrates how dose is chosen based on the cumulative distribution function of the MTD; in this instance with $\alpha = 0.25$ (i.e., overdosing is three times worse than underdosing), d_2 is the closest dose level and so would be chosen as the dose for the next patient.

The EWOC model is more conservative in dose escalation relative to the CRM. However, in some cases, the MTD estimated at the end of the trial may be a dose level not used for any patient throughout the trial (Berry et al., 2010). To overcome this, several trials have let the feasibility bound α increase as more patients are accrued (Babb and Rogatko, 2001, 2004; Cheng et al., 2004; Chu et al., 2009; Tighiouart and Rogatko, 2010). As information accrues during the trial, one can afford to be less conservative and escalate more quickly in order to identify the MTD. This can be achieved by letting α increase toward some upper limit, say 0.50, at which point the EWOC approach with $\alpha = 0.50$ is equivalent to a CRM model that uses the posterior median of the MTD distribution to select the next dose level [see Appendix B.3.1 of Carlin and Louis (2009)]. However, the mechanism by which α changes during the trial requires careful consideration (Wheeler, 2016).

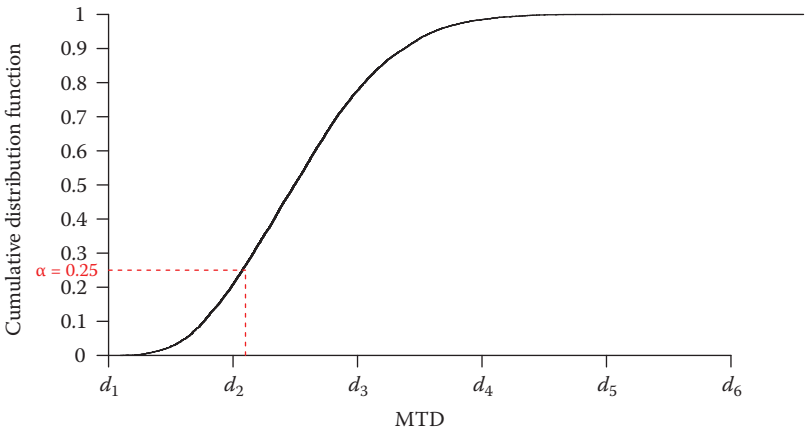

FIGURE 1.4
Example of dose selection for the EWOC approach with feasibility bound $\alpha = 0.25$.

1.3.3 Toxicity probability interval designs

The toxicity probability interval (TPI) (Ji et al., 2007) and modified TPI (mTPI) (Ji et al., 2010) designs are model-based alternatives to the 3 + 3 design where posterior probabilities for the risk of DLT belonging to each of three intervals determine whether the dose for the next cohort is escalated, held at the current dose, or de-escalated. Each dose level's probability of causing a DLT is assigned a vague prior distribution (Ji et al., 2007, 2010, use beta distributions), and the number of patients and the number of DLTs at each dose are used to update these prior distributions, using what is known as a beta-binomial model. Three intervals, $U = [0, \theta - \epsilon_1)$, known as the underdosing interval, $P = [\theta - \epsilon_1, \theta + \epsilon_2]$, the proper dosing interval, and $O = (\theta + \epsilon_2, 1]$, the overdosing interval, are specified; the cutoffs ϵ_1 and ϵ_2 can be elicited from clinicians. Under the mTPI design at current dose level d_i, with the probability of DLT parameter p_i, the ratio between the area of the distribution p_i within each interval and its width is calculated. If the ratio is maximized for interval U, then the dose is escalated; if the ratio is maximized for interval P, then the dose stays at the same level; if the ratio is maximized for interval O, then the dose is de-escalated. The use of a beta-binomial model means that calculations to obtain the posterior probability distribution of DLT at each dose are computationally fast and simple. Furthermore, the simple escalate/stay/de-escalate rules are analogous to the 3 + 3 design, which many clinicians are familiar with, except that under the mTPI design, a TTL can be explicitly targeted and estimates of p_i at the end of the trial (using isotonic regression, for example) can be used to choose the MTD. Ji and Wang (2013) conducted a simulation study that showed the mTPI design recommended the correct MTD more often and overdoses less often than the 3 + 3 design, and the mTPI design can even be run using Microsoft Excel, making it accessible to those without advanced statistical programs.

1.3.4 Curve-free methods

Several approaches exist for dose-finding studies where an explicit model relating dose level to the probability of DLT is not required. Gasparini and Eisele (2000, 2001) proposed the use of a *product of beta prior* (PBP) approach, which induces a monotonic relationship between dose and probability of toxicity without specifying a particular model form. Given dose and toxicity outcome data for current patients in the trial, the dose for the next cohort

of patients is that with a posterior probability of DLT closest to the TTL θ. A potential problem with the curve-free approach of Gasparini and Eisele (2000) is that it becomes stuck at a dose level and is unable to escalate even after observing many non-DLT responses (Cheung, 2002, 2011). Whitehead et al. (2010) also proposed a curve-free approach, where decisions to escalate are based on maximizing the probability of the risk of toxicity being equal to θ. In essence, discrete risks of toxicity are specified at the start of trial (say, 0.05, 0.10, 0.20, 0.30, and 0.60), and after observing dose and toxicity data, the posterior probability that the risk of toxicity is equal to each of the discrete risks is calculated. This form of design has been adapted for a trial of two agents in combination (Whitehead et al., 2012), including an extension with both toxicity and efficacy outcomes (Whitehead et al., 2011) (see Section 1.4.3). While curve-free methods do not assume a specific form for the relationship between dose and toxicity, separate assumptions are required to be made on the prior probabilities of DLT at each dose to be considered in the trial. O'Quigley (2002) provides a discussion on the equivalence of the CRM and the curve-free approach of Gasparini and Eisele (2000), in the sense that identical operating characteristics can be obtained from each method by specifying appropriate design quantities for each design.

1.3.5 Optimal design theory approaches

Haines et al. (2003) proposed the use of optimal design theory for dose-escalation decision making. In particular, Bayesian D-optimality was proposed, which chooses the dose level that minimizes the global variance of the model parameters, or equivalently, maximizes the information that can be obtained about the shape of the dose–toxicity relationship, subject to additional toxicity constraints. Other optimal design theoretic approaches for phase I trials have been proposed, particularly for trials with multiple outcomes and for combination therapies, though they require additional constraints or penalization in order to prevent unethical dose recommendations (Mats et al., 1998; Dragalin and Fedorov, 2006; Dragalin et al., 2008; Roy et al., 2009; Pronzato, 2010; Fedorov and Leonov, 2013; Azriel, 2014; Haines and Clark, 2014).

1.4 Modifications to Proposed Designs

The designs in Sections 1.2 and 1.3 are not necessarily fixed in how they are conducted. Methodologists and clinicians have proposed several modifications to these approaches in order to overcome potential design pitfalls, or because of specific requirements/constraints in their trials.

1.4.1 Start-up rules

A clinician may deem it problematic to immediately use a statistical model to determine dose escalation for the first few patients, especially if very little is known about how a novel drug behaves in human patients. For example, when using a Bayesian model, if the prior distributions for the model parameters are highly variable, one may not be comfortable in using these distributions to determine dose-escalation decisions until some data are obtained. Similarly, if one wishes to use maximum likelihood estimation methods to estimate parameters, we will not be able to obtain maximum likelihood estimates of the parameters until we observe heterogeneous DLT responses, i.e., at least one non-DLT response and at least one DLT response. Therefore, an initial dose-escalation rule may be used in order to

obtain preliminary toxicity data before the statistical model is implemented. For example, the likelihood approach of the CRM (O'Quigley and Shen, 1996) uses the 3 + 3 design as a start-up rule until the first DLT outcome is observed, before then reverting to the CRM modeling approach described in Section 1.3.1. Iasonos and O'Quigley (2012) recommend using data from the first stage of the design to inform the structure of the skeleton to be used for the CRM in the second stage. Ivanova et al. (2003) proposed an alternative start-up rule that depends on the TTL, primarily aiming to conserve patient resources and enable the first dose given under the main design to be closer to the MTD. For optimal design approaches, Haines et al. (2003) constructed a constrained optimal design in the first stage, i.e., allocated a small number of patients across the dose levels so that information about the dose–toxicity curve was maximized, yet patients were not placed at toxic doses. After data on these patients were obtained, they proceeded with their sequential dose-escalation approach.

1.4.2 Stopping rules

As well as considerations for how to start a trial, the criteria for stopping a dose-escalation trial need to be stated. Stopping a trial before a maximum number of patients have been treated is considered for two reasons; either the MTD is judged to be outside of the planned set of doses to be experimented on (i.e., all doses are too toxic, or all doses have a probability of DLT well below the TTL), or the addition of more patients into the trial is unlikely to yield any more information that would change the current MTD estimate. There exist several different approaches for determining when it is suitable to stop a phase I trial. For example, Thall and Russell (1998) recommend terminating a trial if the posterior probability of all dose levels having a DLT rate above (or below) the TTL is at least 0.90, and this has been implemented as a safety constraint in many other dose-escalation designs (Yin et al., 2006). With respect to stopping a trial early when a suitably accurate MTD estimate has been obtained, several rules have been proposed, particularly for the CRM. These include stopping a trial when a fixed number of patients have been consecutively dosed at one dose level (Korn et al., 1994), when the width of the confidence interval for the MTD reaches a particular level (O'Quigley et al., 1990), or stopping when the probability that the next m patients to be dosed in the trial are given the same dose level exceeds some level (e.g., 0.90) (O'Quigley and Reiner, 1998; Zohar and Chevret, 2001; O'Quigley, 2002). The choice of one or more stopping rules for a trial is ultimately dependent on the number of patients available, as well as the statistical expertise at hand, the prior knowledge of the dose–toxicity relationship, and the number of dose levels under consideration.

1.4.3 Choice of endpoints

The methods discussed so far all use a single binary outcome for the occurrence of DLT. While conveniently simple, there are pitfalls to using such an endpoint. First, one has to wait for DLT outcomes to be recorded before making dose recommendations for the next cohort, thus potentially leading to long trial durations. Using a time-to-event (TITE) endpoint (see Chapter 3) can help to reduce trial duration, while still providing informed dose-escalation decision making. Also, toxicity outcomes are graded from 0 (no toxicity) to 5 (death), as per the NCI CTCAE (NCI, 2009), with intermediate gradings relating to the severity of a side effect. Rather than using a binary endpoint for DLT, a categorical endpoint for toxicity could be used so that recording of low-grade toxicities can provide information as to how toxic other doses might be; this can be done throughout the trial, or in the first stage of a two-stage design (Iasonos et al., 2011). Approaches incorporating toxicity gradings are discussed in Chapter 3. Furthermore, toxicities occurring in different

body systems may be more or less important to clinicians, and one may wish to reduce the number of different DLTs or high-grade toxicities a patient might receive on treatment; approaches using multiple toxicity constraints have been developed to this end (Bekele and Thall, 2004; Lee et al., 2011).

In addition to using toxicity information, efficacy outcomes may also be used to inform dose-escalation and end-of-trial dose recommendation; it may be the case that a biologically optimal dose (BOD) is sought, rather than an MTD. Several joint-outcome models have been proposed, using binary, categorical, and continuous efficacy outcomes, and these are explored in Chapter 5.

1.4.4 Combination therapies and schedules

Combination therapies are used frequently in the treatment of cancer, and many designs for escalating two or more drugs together have been proposed, though not necessarily implemented (Harrington et al., 2013). Combination dose-escalation studies can present difficulties not observed in single-agent trials, such as modeling interactive treatment/toxicity effects between drugs, deciding on the escalation strategy, attributing toxicity to one specific drug or a combination of several, and in order to explore several combinations, more patients are likely to be required. Furthermore, it is possible to recommend multiple MTDs to take forward to phase II trials. Nevertheless, the aforementioned designs and modifications discussed in this chapter have all motivated the design of dose-escalation studies with multiple drugs, some of which include graded outcomes, efficacy endpoints, and attributing toxicity to specific agents; these are explored in Chapter 6. Furthermore, approaches for conducting dual-agent dose-escalation studies can be used for single-agent trials to optimize both dose and schedule of treatment administration; these designs are discussed in Chapter 7.

1.5 Usage of Different Designs in Clinical Practice

Several reviews have shown that model-based designs have been used rarely for conducting phase I dose-escalation studies. One review of 1,235 phase I dose-escalation studies testing new anticancer agents between 1991 and 2006 found that 1,215 (98.4%) of such trials used the traditional $3+3$ design or some variant, with only 17 trials (1.4%) using the CRM method and 3 trials using the EWOC design (Rogatko et al., 2007). Further, Le Tourneau et al. (2009) found that of 181 phase I clinical trials conducted between January 2007 and December 2008, 168 trials used the traditional $3+3$ design (1 of which featured intrapatient dose escalation) and 7 used the accelerated titration design. Of the remaining six trials, five used the modified CRM and one used the CRM design with a TITE endpoint (TITE-CRM) (see Chapter 3). In a review of single-agent phase I trials of molecularly targeted agents published between 2000 and 2010, Le Tourneau et al. (2012) found 6 (7.1%) out of 84 trials used a model-based design (specifically the modified CRM approach), and Rivoirard et al. (2016) assessed 228 radiochemotherapy phase I trials published between 1990 and 2015, finding 3 (1.3%) that used a model-based design (all TITE-CRM). With respect to planned phase I trials, a survey of 35 clinical trial units (CTUs) registered with the UK Clinical Research Collaboration showed that in the 7 CTUs involved in phase I trials, all ongoing studies were implementing the $3+3$ design, with only 1 study being planned with the CRM (Jaki, 2013). While these reviews generally indicate few phase I trials have used model-based designs, there is a growing movement for changes in clinical practice. In particular, Iasonos and O'Quigley (2014) found 53 trials published between 2003 and 2013 that implemented

either the CRM, EWOC, or TITE-CRM designs, and recent papers have called for more early-phase cancer trials to use novel adaptive designs in practice (Petroni et al., 2017; Wong et al., 2016).

1.5.1 Barriers to adopting novel designs

The reluctance to use adaptive model-based designs for phase I dose-escalation studies has been attributed to numerous reasons, including lack of understanding of statistical methods, fears of lending control to statistical models, concerns about obtaining regulatory approval, lack of user-friendly software, or even just reluctance to break from traditional methods (Bailey et al., 2009; Gönen, 2009; Mandrekar et al., 2010; Harrington et al., 2013; Jaki, 2013). However, Bailey et al. (2009) described how in a phase I trial of nilotinib and imatinib in patients with imatinib-resistant gastrointestinal stromal tumors (GISTs), a close working relationship between the trial statisticians and clinicians with nontechnical training in related statistical concepts allowed all parties to be clear on interpreting trial findings and making dose-escalation decisions based on the model's recommendations. With respect to obtaining regulatory approval, the American Society of Clinical Oncology (ASCO), the US Food and Drug Administration (FDA), and the European Medicines Agency (EMA) have introduced guidance to encourage the use of Bayesian adaptive designs in oncology trials (Gaydos et al., 2006, 2012).

One of the more technical barriers to implementing adaptive model-based designs that Gönen (2009) highlighted was the specification of prior distributions for model parameters. However, for phase I trials, prior distributions can be obtained by working closely with clinical experts to elicit opinions about dose–toxicity relationships, by using information from past dose-escalation studies and other trials, and conducting sensitivity analyses and fine-tuning prior distributions so that unrealistic and unwanted model behavior is avoided (Legedza and Ibrahim, 2001; Geller, 2004; Rosenberger et al., 2005; Adamina et al., 2009; Cheung, 2011).

Perhaps the main reason for the infrequent use of novel adaptive designs in phase I trials is that an investigator insists on using a particular method (Jaki, 2013), either because the investigator has used it in past work or because previous studies in that disease area have used the same method. For phase I oncology trials, this means that the ubiquity of published trials using the $3 + 3$ design will likely influence other investigators to use the $3 + 3$ design also. Gönen (2009) also mentioned the challenge of motivating investigators to consider novel methods. While extensive simulation studies have shown several model-based designs to have much better operating characteristics than the standard $3 + 3$ design (see Section 1.3.1), motivating investigators to consider new methods for future trials is dependent on overcoming all of the above barriers. Therefore, establishing good collaborative relationships between clinical and statistical experts [as discussed in the example trial of Bailey et al. (2009)] is likely to be fundamental to overcoming practical, technical, and motivational barriers (Harrington et al., 2013).

1.5.2 Available tools and software

Increases in computational power mean that advanced simulation studies to investigate model characteristics such as dose-escalation behavior and MTD recommendation can be conducted quickly with free, user-friendly software (Berry et al., 2010; Sweeting et al., 2013). Examples include the open software library of the MD Anderson Cancer Center*

* Division of Quantitative Sciences—Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Software Download Site: https://biostatistics.mdanderson.org/SoftwareDownload

and the Comprehensive R Archive Network (CRAN) library[†], which provide open-source programs for, among many other things, conducting and simulating dose-escalation studies. More information on available software for designing and assisting with phase I dose-finding studies is presented in Chapter 10.

1.6 Summary

Over the past three decades, many approaches have been proposed for conducting phase I dose-escalation studies. These include both rule-based and model-based approaches that, as this chapter and the rest of this handbook will show, can be tailored to suit a wide range of trials defined by the disease and treatments under study, the endpoints of interest, the patient population, as well as the clinical, statistical, and computational expertise available. The uptake of novel designs that exhibit vast improvements upon the traditional up-and-down methods, such as the $3 + 3$ design, has long been hindered by several barriers, but there is a growing movement to design new trials using these methods and for more widespread changes to be made to clinical practice. A collaborative effort between clinicians and statisticians can help to overcome the barriers documented, leading to well-designed trials that will benefit trial participants and future patients.

References

M. Adamina, G. Tomlinson, and U. Guller. Bayesian statistics in oncology: A guide for the clinical investigator. *Cancer*, 115(23):5371–5381, 2009. doi:10.1002/cncr.24628.

D. Azriel. Optimal sequential designs in phase I studies. *Computational Statistics and Data Analysis*, 71:288–297, 2014. doi:10.1016/j.csda.2013.05.010.

J. S. Babb and A. Rogatko. Bayesian methods for phase I cancer clinical trials. In N. L. Geller, editor, *Advances in Clinical Trial Biostatistics*, pp. 1–40. Marcel Dekker, New York, 2004.

J. S. Babb and A. Rogatko. Patient specific dosing in a cancer phase I clinical trial. *Statistics in Medicine*, 20(14):2079–2090, 2001. doi:10.1002/sim.848.

J. S. Babb, A. Rogatko, and S. Zacks. Cancer phase I clinical trials: Efficient dose escalation with overdose control. *Statistics in Medicine*, 17(10):1103–1120, 1998.

S. M. Bailey, B. Neuenschwander, G. Laird, and M. Branson. A Bayesian case study in oncology phase I combination dose-finding using logistic regression with covariates. *Journal of Biopharmaceutical Statistics*, 19(3):469–484, 2009. doi:10.1080/10543400902802409.

R. E. Barlow, D. J. Bartholomew, J. M. Bremner, and H. D. Brunk. *Statistical Inference under Order Restrictions*. Wiley, New York, 1972.

T. Bayes. An essay towards solving a problem in the doctrine of chances. *Philosophical Transactions of the Royal Society of London*, 53:370–418, 1763. doi:10.1098/rstl.1763.0053.

[†] Available at https://cran.r-project.org

B. N. Bekele and P. F. Thall. Dose-finding based on multiple toxicities in a soft tissue sarcoma trial. *Journal of the American Statistical Association*, 99(465):26–35, 2004. doi:10.1198/016214504000000043.

S. M. Berry, B. P. Carlin, J. J. Lee, and P. Mueller. *Bayesian Adaptive Methods for Clinical Trials*. Chapman & Hall/CRC Biostatistics Series, Taylor and Francis, Boca Raton, FL, 2010.

F. Bretz, J. Hsu, J. Pinheiro, and Y. Liu. Dose finding—A challenge in statistics. *Biometrical Journal*, 50(4):480–504, 2008. doi:10.1002/bimj.200810438.

B. P. Carlin and T. A. Louis. *Bayesian Methods for Data Analysis*, 3rd edn. Chapman & Hall/CRC, Boca Raton, FL, 2009.

S. K. Carter. Study design principles for the clinical evaluation of new drugs as developed by the chemotherapy programme of the National Cancer Institute. In M. Staquet, editor, *The Design of Clinical Trials in Cancer Therapy*, pp. 242–289. Éditions Scientifiques Europeenes, Brussels, Belgium, 1973.

M. Chang and S.-C. Chow. Power and sample size for dose response studies. In N. Ting, editor, *Dose Finding in Drug Development*, Chapter 14, pp. 220–242. Springer, New York, 2006.

Z. Chen, M. D. Krailo, J. Sun, and S. P. Azen. Range and trend of expected toxicity level (ETL) in standard A + B designs: A report from the Children's Oncology Group. *Contemporary Clinical Trials*, 30(2):123–128, 2009. doi:10.1016/j.cct.2008.10.006.

J. D. Cheng, J. S. Babb, C. Langer, S. Aamdal, F. Robert, L. R. Engelhardt, O. Fernberg, J. Schiller, G. Forsberg, and R. K. Alpaugh. Individualized patient dosing in phase I clinical trials: The role of escalation with overdose control in PNU214936. *Journal of Clinical Oncology*, 22(4):602–609, 2004. doi:10.1200/JCO.2004.12.034.

Y. K. Cheung. *Dose Finding by the Continual Reassessment Method*. Chapman & Hall/CRC Biostatistics Series, Taylor and Francis, Boca Raton, FL, 2011.

Y. K. Cheung. On the use of nonparametric curves in phase I trials with low toxicity tolerance. *Biometrics*, 58(1):237–240, 2002.

S.-C. Chow. *Controversial Statistical Issues in Clinical Trials*. Taylor and Francis, Boca Raton, FL, 2011.

P.-L. Chu, Y. Lin, and W. J. Shih. Unifying CRM and EWOC designs for phase I cancer clinical trials. *Journal of Statistical Planning and Inference*, 139(3):1146–1163, 2009. doi:10.1016/j.jspi.2008.07.005.

J. M. Collins, C. K. Grieshaber, and B. A. Chabner. Pharmacologically guided phase I clinical trials based upon preclinical drug development. *Journal of the National Cancer Institute*, 82(16):1321–1326, 1990. doi:10.1093/jnci/82.16.1321.

R. B. Conolly and W. K. Lutz. Nonmonotonic dose-response relationships: Mechanistic basis, kinetic modeling, and implications for risk assessment. *Toxicological Sciences*, 77(1):151–157, 2004. doi:10.1093/toxsci/kfh007.

J. Dignam, T. Karrison, and G. Bryant. Design and analysis of oncology clinical trials. In A. Chang, P. Ganz, D. Hayes, T. Kinsella, H. Pass, J. Schiller, R. Stone, and V. Strecher, editors, *Oncology: An Evidence-Based Approach*, pp. 112–126. Springer, New York, 2006.

W. Dixon and A. Mood. A method for obtaining and analyzing sensitivity data. *Journal of the American Statistical Association*, 43(241):109–126, 1948.

A. Doussau, B. Asselain, M. Le Deley, B. Geoerger, F. Doz, G. Vassal, and X. Paoletti. Dose-finding designs in pediatric phase I clinical trials: Comparison by simulations in a realistic timeline framework. *Contemporary Clinical Trials*, 33(4):657–665, 2012. 10.1016/j.cct.2011.11.015.

V. Dragalin and V. Fedorov. Adaptive designs for dose-finding based on efficacy-toxicity response. *Journal of Statistical Planning and Inference*, 136(6):1800–1823, 2006. 10.1016/j.jspi.2005.08.005.

V. Dragalin, V. Fedorov, and Y. Wu. Adaptive designs for selecting drug combinations based on efficacy-toxicity response. *Journal of Statistical Planning and Inference*, 138(2): 352–373, 2008. doi:10.1016/j.jspi.2007.06.017.

E. A. Eisenhauer, P. J. O'Dwyer, M. Christian, and J. S. Humphrey. Phase I clinical trial design in cancer drug development. *Journal of Clinical Oncology*, 18(3):684–692, 2000.

D. Faries. Practical modifications of the continual reassessment method for phase I cancer clinical trials. *Journal of Biopharmaceutical Statistics*, 4(2):147–64, 1994. doi:10.1080/10543409408835079.

V. V. Fedorov and S. L. Leonov. *Optimal Design for Nonlinear Response Models*. CRC Press, Boca Raton, FL, 2013.

M. Gasparini and J. Eisele. Correction: A curve-free method for phase I clinical trials. *Biometrics*, 57(2):659–660, 2001.

M. Gasparini and J. Eisele. A curve-free method for phase I clinical trials. *Biometrics*, 56 (2):609–615, 2000.

B. Gaydos, A. Koch, F. Miller, M. Posch, M. Vandemeulebroecke, and S. J. Wang. Perspective on adaptive designs: 4 years European Medicines Agency reflection paper, 1 year draft US FDA guidance—Where are we now? *Clinical Investigation*, 2(3):235–240, 2012. doi:10.4155/cli.12.5.

B. Gaydos, M. Krams, I. Perevozskaya, F. Bretz, Q. Liu, P. Gallo, D. Berry, C. Chuangstein, J. Pinheiro, and A. Bedding. Adaptive dose-response studies. *Drug Information Journal*, 40:451–461, 2006.

N. L. Geller. *Advances in Clinical Trial Biostatistics*. Marcel Dekker, New York, 2004.

M. Gönen. Bayesian clinical trials: No more excuses. *Clinical Trials*, 6(3):203–204, 2009. doi:10.1177/1740774509105374.

S. N. Goodman, M. L. Zahurak, and S. Piantadosi. Some practical improvements in the continual reassessment method for phase I studies. *Statistics in Medicine*, 14(11):1149–1161, 1995. doi:10.1002/sim.4780141102.

M. A. Graham and P. Workman. The impact of pharmacokinetically guided dose escalation strategies in phase I clinical trials: Critical evaluation and recommendations for future studies. *Annals of Oncology*, 3(5):339–347, 1992.

L. M. Haines and A. E. Clark. The construction of optimal designs for dose-escalation studies. *Statistics and Computing*, 24:101–109, 2014. doi:10.1007/s11222-012-9356-2.

L. M. Haines, I. Perevozskaya, and W. F. Rosenberger. Bayesian optimal designs for phase I clinical trials. *Biometrics*, 59(3):591–600, 2003.

P. Hamberg and J. Verweij. Phase I drug combination trial design: Walking the tightrope. *Journal of Clinical Oncology*, 27(27):4441–4443, 2009. doi:10.1200/JCO.2009.23.6703.

A. R. Hansen, D. M. Graham, G. R. Pond, and L. L. Siu. Phase 1 trial design: Is 3 + 3 the best? *Cancer Control*, 21(3):200–208, 2014.

J. A. Harrington, G. M. Wheeler, M. J. Sweeting, A. P. Mander, and D. I. Jodrell. Adaptive designs for dual-agent phase I dose-escalation studies. *Nature Reviews Clinical Oncology*, 10(5):277–288, 2013. doi:10.1038/nrclinonc.2013.35.

W. He, J. Liu, B. Binkowitz, and H. Quan. A model-based approach in the estimation of the maximum tolerated dose in phase I cancer clinical trials. *Statistics in Medicine*, 25(12): 2027–2042, 2006. doi:10.1002/sim.2334.

L. M. Hoffman, M. Fouladi, J. Olson, V. M. Daryani, C. F. Stewart, C. Wetmore, M. Kocak, A. Onar-Thomas, L. Wagner, S. Gururangan, et al. Phase I trial of weekly MK-0752 in children with refractory central nervous system malignancies: A pediatric brain tumor consortium study. *Child's Nervous System*, 31(8):1283–1289, 2015. doi:10.1007/s00381-015-2725-3.

E. Horstmann, M. S. McCabe, L. Grochow, S. Yamamoto, L. Rubinstein, T. Budd, D. Shoemaker, E. J. Emanuel, and C. Grady. Risks and benefits of phase 1 oncology trials, 1991 through 2002. *The New England Journal of Medicine*, 352(9):895–904, 2005. doi:10.1056/NEJMsa042220.

A. Iasonos and J. O'Quigley. Adaptive dose-finding studies: A review of model-guided phase I clinical trials. *Journal of Clinical Oncology*, 32(23):2505–2511, 2014. doi:10.1200/JCO.2013.54.6051.

A. Iasonos and J. O'Quigley. Interplay of priors and skeletons in two-stage continual reassessment method. *Statistics in Medicine*, 31(30):4321–4336, 2012. doi:10.1002/sim.5559.

A. Iasonos, N. A. Wages, M. R. Conaway, K. Cheung, Y. Yuan, and J. O'Quigley. Dimension of model parameter space and operating characteristics in adaptive dose-finding studies. *Statistics in Medicine*, 35(21):3760–3775, 2016. doi:10.1002/sim.6966.

A. Iasonos, A. S. Wilton, E. R. Riedel, V. E. Seshan, and D. R. Spriggs. A comprehensive comparison of the continual reassessment method to the standard 3 + 3 dose escalation scheme in phase I dose-finding studies. *Clinical Trials*, 5(5):465–477, 2008. doi:10.1177/1740774508096474.

A. Iasonos, S. Zohar, and J. O'Quigley. Incorporating lower grade toxicity information into dose finding designs. *Clinical Trials*, 8(4):370–379, 2011. doi:10.1177/1740774511410732..

A. Ivanova, A. Montazer-Haghighi, S. G. Mohanty, and S. D. Durham. Improved up-and-down designs for phase I trials. *Statistics in Medicine*, 22(1):69–82, 2003. doi:10.1002/sim.1336.

T. Jaki. Uptake of novel statistical methods for early-phase clinical studies in the UK public sector. *Clinical Trials*, 10(2):344–346, 2013. doi:10.1177/1740774512474375.

Y. Ji, Y. Li, and B. N. Bekele. Dose-finding in phase I clinical trials based on toxicity probability intervals. *Clinical Trials*, 4(3):235–244, 2007. doi:10.1177/1740774507079442.

Y. Ji, P. Liu, Y. Li, and B. N. Bekele. A modified toxicity probability interval method for dose-finding trials. *Clinical Trials*, 7(6):653–663, 2010. doi:10.1177/1740774510382799.

Y. Ji and S.-J. Wang. Modified toxicity probability interval design: A safer and more reliable method than the 3 + 3 design for practical phase I trials. *Journal of Clinical Oncology*, 31(14):1785–1791, 2013. doi:10.1200/JCO.2012.45.7903.

J. B. Kadane, J. M. Dickey, R. L. Winkler, W. S. Smith, C. Peters, M. Dickey, L. Winkler, and S. C. Peters. Interactive elicitation of opinion for a normal linear model. *Journal of the American Statistical Association*, 75(372):845–854, 1980.

S.-H. Kang and C. W. Ahn. The expected toxicity rate at the maximum tolerated dose in the standard phase I cancer clinical trial design. *Drug Information Journal*, 35(8): 1189–1199, 2001.

S.-H. Kang and C. W. Ahn. An investigation of the traditional algorithm-based designs for phase 1 cancer clinical trials. *Drug Information Journal*, 36:865–873, 2002.

E. L. Korn, D. Midthune, T. T. Chen, L. V. Rubinstein, M. C. Christian, and R. M. Simon. A comparison of two phase I trial designs. *Statistics in Medicine*, 13(18):1799–1806, 1994. doi:10.1002/sim.4780131802.

C. Le Tourneau, H. K. Gan, A. R. A. Razak, and X. Paoletti. Efficiency of new dose escalation designs in dose-finding phase I trials of molecularly targeted agents. *PlOS One*, 7(12):e51039, 2012. doi:10.1371/journal.pone.0051039.

C. Le Tourneau, J. J. Lee, and L. L. Siu. Dose escalation methods in phase I cancer clinical trials. *Journal of the National Cancer Institute*, 101(10):708–720, 2009. doi:10.1093/jnci/djp079.

C. Le Tourneau, A. R. A. Razak, H. K. Gan, S. Pop, V. Diéras, P. Tresca, and X. Paoletti. Heterogeneity in the definition of dose-limiting toxicity in phase I cancer clinical trials of molecularly targeted agents: A review of the literature. *European Journal of Cancer*, 47(10):1468–1475, 2011. doi:10.1016/j.ejca.2011.03.016.

S. M. Lee, B. Cheng, and Y. K. Cheung. Continual reassessment method with multiple toxicity constraints. *Biostatistics*, 12(2):386–398, 2011. doi:10.1093/biostatistics/kxq062.

S. M. Lee and Y. K. Cheung. Calibration of prior variance in the Bayesian continual reassessment method. *Statistics in Medicine*, 30(17):2081–2089, 2011. doi:10.1002/sim.4139.

A. T. R. Legedza and J. G. Ibrahim. Heterogeneity in phase I clinical trials: Prior elicitation and computation using the continual reassessment method. *Statistics in Medicine*, 20(6): 867–882, 2001.

Y. Lin and W. J. Shih. Statistical properties of the traditional algorithm-based designs for phase I cancer clinical trials. *Biostatistics*, 2(2):203–215, 2001. doi:10.1093/biostatistics/2.2.203.

S. J. Mandrekar, R. Qin, and D. J. Sargent. Model-based phase I designs incorporating toxicity and efficacy for single and dual agent drug combinations: Methods and challenges. *Statistics in Medicine*, 29(10):1077–1083, 2010. doi:10.1002/sim.3706.

J. L. Marshall. Maximum-tolerated dose, optimum biologic dose, or optimum clinical value: Dosing determination of cancer therapies. *Journal of Clinical Oncology*, 30(23):2815–2816, 2012. doi:10.1200/JCO.2012.43.4233.

V. A. Mats, W. F. Rosenberger, and N. Flournoy. Restricted optimality for phase I clinical trials. In N. Flournoy, W. F. Rosenberger, W. K. Wong, editors, *New Developments and Applications in Experimental Design*, IMS Lecture Notes—Monograph Series, Volume 34, pp. 50–61, 1998.

S. Møller. An extension of the continual reassessment methods using a preliminary up-and-down design in a dose finding study in cancer patients, in order to investigate a greater range of doses. *Statistics in Medicine*, 14(9):911–922, 1995.

Y. P. Mossé, M. S. Lim, S. D. Voss, K. Wilner, K. Ruffner, J.-F. Laliberté, D. Rolland, F. M. Balis, J. M. Maris, B. J. Weigel, et al. Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: A Children's Oncology Group phase 1 consortium study. *The Lancet Oncology*, 14(6):472–480, 2013. doi:10.1016/S1470-2045(13)70095-0.

T. V. Narayana. Sequential procedures in probit analysis. Ph.D Thesis, University of North Carolina, 1953. http://www.stat.ncsu.edu/information/library/mimeo.archive/isms_1953_82.pdf.

National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events v4.0, 2009. http://evs.nci.nih.gov/ftp1/CTCAE/.

B. Neuenschwander, M. Branson, and T. Gsponer. Critical aspects of the Bayesian approach to phase I cancer trials. *Statistics in Medicine*, 27(13):2420–2439, 2008. doi:10.1002/sim.3230.

A. Onar, M. Kocak, and J. M. Boyett. Continual reassessment method vs. traditional empirically based design: Modifications motivated by phase I trials in pediatric oncology by the Pediatric Brain Tumor Consortium. *Journal of Biopharmaceutical Statistics*, 19(3):437–455, 2009. doi:10.1080/10543400902800486.

A. Onar-Thomas and Z. Xiong. A simulation-based comparison of the traditional method, Rolling-6 design and a frequentist version of the continual reassessment method with special attention to trial duration in pediatric phase I oncology trials. *Contemporary Clinical Trials*, 31(3):259–270, 2010. doi:10.1016/j.cct.2010.03.006.

J. O'Quigley. Another look at two phase I clinical trial designs. *Statistics in Medicine*, 18 (20):2683–2690, 1999.

J. O'Quigley. Continual reassessment designs with early termination. *Biostatistics*, 3(1): 87–99, 2002.

J. O'Quigley and S. Chevret. Methods for dose finding studies in cancer clinical trials: A review and results of a Monte Carlo study. *Statistics in Medicine*, 10(11):1647–64, 1991. doi:10.1002/sim.4780101104.

J. O'Quigley, M. Pepe, and L. Fisher. Continual reassessment method: A practical design for phase 1 clinical trials in cancer. *Biometrics*, 46(1):33–48, 1990.

J. O'Quigley and E. Reiner. Miscellanea: A stopping rule for the continual reassessment method. *Biometrika*, 85(3):741–748, 1998.

J. O'Quigley and L. Z. Shen. Continual reassessment method: A likelihood approach. *Biometrics*, 52(2):673–684, 1996.

J. O'Quigley and S. Zohar. Experimental designs for phase I and phase I/II dose-finding studies. *British Journal of Cancer*, 94(5):609–13, 2006. doi:10.1038/sj.bjc.6602969.

X. Paoletti and A. Kramar. A comparison of model choices for the continual reassessment method in phase I cancer trials. *Statistics in Medicine*, 28(24):3012–3028, 2009. doi:10.1002/sim.3682.

S. H. Park, S.-M. Bang, E. K. Cho, D. B. Shin, J. H. Lee, W. K. Lee, and M. Chung. Phase I dose-escalating study of docetaxel in combination with 5-day continuous infusion of 5-fluorouracil in patients with advanced gastric cancer. *BMC Cancer*, 5(87):1–5, 2005. doi:10.1186/1471-2407-5-87.

N. Penel, N. Isambert, P. Leblond, C. Ferte, A. Duhamel, and J. Bonneterre. "Classical 3 + 3 design" versus "accelerated titration designs": Analysis of 270 phase 1 trials investigating anti-cancer agents. *Investigational New Drugs*, 27(6):552–556, 2009. 10.1007/s10637-008-9213-5.

G. R. Petroni, N. A. Wages, G. Paux, and F. Dubois. Implementation of adaptive methods in early-phase clinical trials. *Statistics in Medicine*, 36(2):215–224, 2017. doi:10.1002/sim.6910.

L. Pronzato. Penalized optimal designs for dose-finding. *Journal of Statistical Planning and Inference*, 140:283–296, 2010. doi:10.1016/j.jspi.2009.07.012.

M. J. Ratain, R. Mick, R. L. Schilsky, and M. Siegler. Statistical and ethical issues in the design and conduct of phase I and II clinical trials of new anticancer agents. *Journal of the National Cancer Institute*, 85(20):1637–1643, 1993.

R. Rivoirard, A. Vallard, J. Langrand-Escure, M. Ben Mrad, G. Wang, J.-B. Guy, P. Diao, A. Dubanchet, E. Deutsch, C. Rancoule, and N. Magne. Thirty years of phase I radiochemotherapy trials: Latest development. *European Journal of Cancer*, 58:1–7, 2016. doi:10.1016/j.ejca.2016.01.012.

T. Robertson, F. T. Wright, and R. L. Dykstra. *Ordered Restricted Statistical Inference*. John Wiley & Sons, New York, 1988.

A. Rogatko, D. Schoeneck, W. Jonas, M. Tighiouart, F. R. Khuri, and A. Porter. Translation of innovative designs into phase I trials. *Journal of Clinical Oncology*, 25(31):4982–4986, 2007. doi:10.1200/JCO.2007.12.1012.

W. F. Rosenberger, G. C. Canfield, I. Perevozskaya, L. M. Haines, and P. Hausner. Development of interactive software for Bayesian optimal phase 1 clinical trial design. *Drug Information Journal*, 39:89–98, 2005.

W. F. Rosenberger and L. M. Haines. Competing designs for phase I clinical trials: A review. *Statistics in Medicine*, 21(18):2757–2770, 2002. doi:10.1002/sim.1229.

A. Roy, S. Ghosal, and W. F. Rosenberger. Convergence properties of sequential Bayesian D-optimal designs. *Journal of Statistical Planning and Inference*, 139(2):425–440, 2009. doi:10.1016/j.jspi.2008.04.025.

R. Simon, B. Freidlin, L. Rubinstein, S. G. Arbuck, J. Collins, and M. C. Christian. Accelerated titration designs for phase I clinical trials in oncology. *Journal of the National Cancer Institute*, 89(15):1138–1147, 1997.

J. M. Skolnik, J. S. Barrett, B. Jayaraman, D. Patel, and P. C. Adamson. Shortening the timeline of pediatric phase I trials: The rolling six design. *Journal of Clinical Oncology*, 26(2):190–195, 2008. doi:10.1200/JCO.2007.12.7712.

R. Sposto and S. Groshen. A wide-spectrum paired comparison of the properties of the rolling 6 and 3 + 3 phase I study designs. *Contemporary Clinical Trials*, 32(5):694–703, 2011. doi:10.1016/j.cct.2011.04.009.

B. E. Storer. Design and analysis of phase I clinical trials. *Biometrics*, 45(3):925–937, 1989.

B. E. Storer. An evaluation of phase I clinical trial designs in the continuous dose-response setting. *Statistics in Medicine*, 20(16):2399–2408, 2001. doi:10.1002/sim.903.

M. J. Sweeting, A. P. Mander, and T. Sabin. BCRM: Bayesian continual reassessment method designs for phase I dose-finding trials. *Journal of Statistical Software*, 54(13): 1–26, 2013.

P. F. Thall and S. Lee. Practical model-based dose-finding in phase I clinical trials: Methods based on toxicity. *International Journal of Gynecological Cancer*, 13:251–261, 2003.

P. F. Thall and K. E. Russell. A strategy for dose-finding and safety monitoring based on efficacy and adverse outcomes in phase I/II clinical trials. *Biometrics*, 54(1):251–264, 1998.

M. Tighiouart and A. Rogatko. Dose finding with escalation with overdose control (EWOC) in cancer clinical trials. *Statistical Science*, 25(2):217–226, 2010.

M. Tighiouart, A. Rogatko, and J. S. Babb. Flexible Bayesian methods for cancer phase I clinical trials. Dose escalation with overdose control. *Statistics in Medicine*, 24(14): 2183–2196, 2005. doi:10.1002/sim.2106.

D. D. Von Hoff, J. Kuhn, and G. M. Clark. Design and conduct of phase I trials. In M. E. Buyse, M. J. Staquet, R. J. Sylvester, editors, *Cancer Clinical Trials: Methods and Practice*, pp. 210–220. Oxford University Press, Oxford, 1984.

G. M. Wheeler, M. J. Sweeting, and A. P. Mander. AplusB: A web application for investigating A + B designs for phase I cancer clinical trials. *PLoS One*, 11(7):e0159026, 2016. doi:10.1371/journal.pone.0159026.

G. M. Wheeler. Incoherent dose-escalation in phase I trials using the escalation with overdose control approach. *Statistical Papers*, 1–11, 2016. doi:10.1007/s00362-016-0790-7.

J. Whitehead. Bayesian decision procedures with application to dose-finding studies. *International Journal of Pharmaceutical Medicine*, 11:201–208, 1997.

J. Whitehead, H. Thygesen, and A. Whitehead. A Bayesian dose-finding procedure for phase I clinical trials based only on the assumption of monotonicity. *Statistics in Medicine*, 29(17):1808–1824, 2010. doi:10.1002/sim.3963.

J. Whitehead, H. Thygesen, and A. Whitehead. Bayesian procedures for phase I/II clinical trials investigating the safety and efficacy of drug combinations. *Statistics in Medicine*, 30(16):1952–1970, 2011. doi:10.1002/sim.4267.

J. Whitehead, H. Thygesen, T. Jaki, S. Davies, S. Halford, H. Turner, N. Cook, and D. Jodrell. A novel Phase I/IIa design for early phase oncology studies and its application in the evaluation of MK-0752 in pancreatic cancer. *Statistics in Medicine*, 31(18): 1931–43, 2012. doi:10.1002/sim.5331.

K. M. Wong, A. Capasso, and S. G. Eckhardt. The changing landscape of phase I trials in oncology. *Nature Reviews Clinical Oncology*, 13(2):106–117, 2016. doi:10.1038/nrclinonc.2015.194.

G. Yin, Y. Li, and Y. Ji. Bayesian dose-finding in phase I/II clinical trials using toxicity and efficacy odds ratios. *Biometrics*, 62(3):777–784, 2006. doi:10.1111/j.1541-0420.2006.00534.x.

L. Zhao, J. Lee, R. Mody, and T. M. Braun. The superiority of the time-to-event continual reassessment method to the rolling six design in pediatric oncology phase I trials. *Clinical Trials*, 8(4):361–369, 2011. doi:10.1177/1740774511407533.

S. Zohar and S. Chevret. The continual reassessment method: Comparison of Bayesian stopping rules for dose-ranging studies. *Statistics in Medicine*, 20(19):2827–2843, 2001. doi:10.1002/sim.920.

S. Zohar and J. O'Quigley. Re: Dose escalation methods in phase I cancer clinical trials. *Journal of the National Cancer Institute*, 101(24):1732–1733; author reply 1733–1735, 2009. doi:10.1093/jnci/djp400.

Overview of Phase I Designs

M. Adamina , G. Tomlinson , and U. Guller . Bayesian statistics in oncology: A guide for the clinical investigator. Cancer, 115(23):5371–5381, 2009. doi:10.1002/cncr.24628.

D. Azriel . Optimal sequential designs in phase I studies. Computational Statistics and Data Analysis, 71:288–297, 2014. doi:10.1016/j.csda.2013.05.010.

J. S. Babb and A. Rogatko . Bayesian methods for phase I cancer clinical trials. In N.L. Geller , editor, Advances in Clinical Trial Biostatistics, pp. 1–40. Marcel Dekker, New York, 2004.

J. S. Babb and A. Rogatko . Patient specific dosing in a cancer phase I clinical trial. Statistics in Medicine, 20(14):2079–2090, 2001. doi:10.1002/sim.848.

J. S. Babb , A. Rogatko , and S. Zacks . Cancer phase I clinical trials: Efficient dose escalation with overdose control. Statistics in Medicine, 17(10):1103–1120, 1998.

S. M. Bailey , B. Neuenschwander , G. Laird , and M. Branson . A Bayesian case study in oncology phase I combination dose-finding using logistic regression with covariates. Journal of Biopharmaceutical Statistics, 19(3):469–484, 2009. doi:10.1080/10543400902802409.

R. E. Barlow , D.J. Bartholomew , J.M. Bremner , and H.D. Brunk . Statistical Inference under Order Restrictions. Wiley, New York, 1972.

T. Bayes . An essay towards solving a problem in the doctrine of chances. Philosophical Transactions of the Royal Society of London, 53:370–418, 1763. doi:10.1098/rstl.1763.0053.

B. N. Bekele and P.F. Thall . Dose-finding based on multiple toxicities in a soft tissue sarcoma trial. Journal of the American Statistical Association, 99(465):26–35, 2004. doi:10.1198/016214504000000043.

S. M. Berry , B.P. Carlin , J.J. Lee , and P. Mueller . Bayesian Adaptive Methods for Clinical Trials. Chapman & Hall/CRC Biostatistics Series, Taylor and Francis, Boca Raton, FL, 2010.

F. Bretz , J. Hsu , J. Pinheiro , and Y. Liu . Dose finding—A challenge in statistics. Biometrical Journal, 50(4):480–504, 2008. doi:10.1002/bimj.200810438.

B. P. Carlin and T.A. Louis . Bayesian Methods for Data Analysis, 3rd edn. Chapman & Hall/CRC, Boca Raton, FL, 2009.

S. K. Carter . Study design principles for the clinical evaluation of new drugs as developed by the chemotherapy programme of the National Cancer Institute. In M. Staquet , editor, The Design of Clinical Trials in Cancer Therapy, pp. 242–289. Éditions Scientifiques Europeenes, Brussels, Belgium, 1973.

M. Chang and S.C. Chow . Power and sample size for dose response studies. In N. Ting , editor, Dose Finding in Drug Development, Chapter 14, pp. 220–242. Springer, New York, 2006.

Z. Chen , M.D. Krailo , J. Sun , and S.P. Azen . Range and trend of expected toxicity level (ETL) in standard A + B designs: A report from the Children's Oncology Group. Contemporary Clinical Trials, 30(2):123–128, 2009. doi:10.1016/j.cct.2008.10.006.

J. D. Cheng , J.S. Babb , C. Langer , S. Aamdal , F. Robert , L.R. Engelhardt , O. Fernberg , J. Schiller , G. Forsberg , and R.K. Alpaugh . Individualized patient dosing in phase I clinical trials: The role of escalation with overdose control in PNU214936. Journal of Clinical Oncology, 22(4):602–609, 2004. doi:10.1200/JCO.2004.12.034.

Y. K. Cheung . Dose Finding by the Continual Reassessment Method. Chapman & Hall/CRC Biostatistics Series, Taylor and Francis, Boca Raton, FL, 2011.

Y. K. Cheung . On the use of nonparametric curves in phase I trials with low toxicity tolerance. Biometrics, 58(1):237–240, 2002.

S.C. Chow . Controversial Statistical Issues in Clinical Trials. Taylor and Francis, Boca Raton, FL, 2011.

P.L. Chu , Y. Lin , and W.J. Shih . Unifying CRM and EWOC designs for phase I cancer clinical trials. Journal of Statistical Planning and Inference, 139(3):1146–1163, 2009. doi:10.1016/j.jspi.2008.07.005.

J. M. Collins , C.K. Grieshaber , and B.A. Chabner . Pharmacologically guided phase I clinical trials based upon preclinical drug development. Journal of the National Cancer Institute, 82(16):1321–1326, 1990. doi:10.1093/jnci/82.16.1321.

R. B. Conolly and W.K. Lutz . Nonmonotonic dose-response relationships: Mechanistic basis, kinetic modeling, and implications for risk assessment. Toxicological Sciences, 77(1):151–157, 2004. doi:10.1093/toxsci/kfh007.

J. Dignam , T. Karrison , and G. Bryant . Design and analysis of oncology clinical trials. In A. Chang , P. Ganz , D. Hayes , T. Kinsella , H. Pass , J. Schiller , R. Stone , and V. Strecher , editors, Oncology: An Evidence-Based Approach, pp. 112–126. Springer, New York, 2006.

W. Dixon and A. Mood . A method for obtaining and analyzing sensitivity data. Journal of the American Statistical Association, 43(241):109–126, 1948.

A. Doussau , B. Asselain , M. Le Deley, B. Geoerger , F. Doz , G. Vassal , and X. Paoletti . Dose-finding designs in pediatric phase I clinical trials: Comparison by simulations in a realistic timeline framework. Contemporary Clinical Trials, 33(4):657–665, 2012. 10.1016/j.cct.2011.11.015.

V. Dragalin and V. Fedorov . Adaptive designs for dose-finding based on efficacy-toxicity response. Journal of Statistical Planning and Inference, 136(6):1800–1823, 2006. 10.1016/j.jspi.2005.08.005.

V. Dragalin , V. Fedorov , and Y. Wu . Adaptive designs for selecting drug combinations based on efficacy-toxicity response. Journal of Statistical Planning and Inference, 138(2): 352–373, 2008. doi:10.1016/j.jspi.2007.06.017.

E. A. Eisenhauer , P.J. O'Dwyer , M. Christian , and J.S. Humphrey . Phase I clinical trial design in cancer drug development. Journal of Clinical Oncology, 18(3):684–692, 2000.

D. Faries . Practical modifications of the continual reassessment method for phase I cancer clinical trials. Journal of Biopharmaceutical Statistics, 4(2):147–164, 1994. doi:10.1080/10543409408835079.

V. V. Fedorov and S.L. Leonov . Optimal Design for Nonlinear Response Models. CRC Press, Boca Raton, FL, 2013.

M. Gasparini and J. Eisele . Correction: A curve-free method for phase I clinical trials. Biometrics, 57(2):659–660, 2001.

M. Gasparini and J. Eisele . A curve-free method for phase I clinical trials. Biometrics, 56 (2):609–615, 2000.

B. Gaydos , A. Koch , F. Miller , M. Posch , M. Vandemeulebroecke , and S.J. Wang . Perspective on adaptive designs: 4 years European Medicines Agency reflection paper, 1 year draft US FDA guidance—Where are we now? Clinical Investigation, 2(3):235–240, 2012. doi:10.4155/cli.12.5.

B. Gaydos , M. Krams , I. Perevozskaya , F. Bretz , Q. Liu , P. Gallo , D. Berry , C. Chuangstein , J. Pinheiro , and A. Bedding . Adaptive dose-response studies. Drug Information Journal, 40:451–461, 2006.

N. L. Geller . Advances in Clinical Trial Biostatistics. Marcel Dekker, New York, 2004.

M. Gönen . Bayesian clinical trials: No more excuses. Clinical Trials, 6(3):203–204, 2009. doi:10.1177/1740774509105374.

S. N. Goodman , M.L. Zahurak , and S. Piantadosi . Some practical improvements in the continual reassessment method for phase I studies. Statistics in Medicine, 14(11):1149–1161, 1995. doi:10.1002/sim.4780141102.
M. A. Graham and P. Workman . The impact of pharmacokinetically guided dose escalation strategies in phase I clinical trials: Critical evaluation and recommendations for future studies. Annals of Oncology, 3(5):339–347, 1992.
L. M. Haines and A.E. Clark . The construction of optimal designs for dose-escalation studies. Statistics and Computing, 24:101–109, 2014. doi:10.1007/s11222-012-9356-2.
L. M. Haines , I. Perevozskaya , and W.F. Rosenberger . Bayesian optimal designs for phase I clinical trials. Biometrics, 59(3):591–600, 2003.
P. Hamberg and J. Verweij . Phase I drug combination trial design: Walking the tightrope. Journal of Clinical Oncology, 27(27):4441–4443, 2009. doi:10.1200/JCO.2009.23.6703.
A. R. Hansen , D.M. Graham , G.R. Pond , and L.L. Siu . Phase 1 trial design: Is 3 + 3 the best? Cancer Control, 21(3):200–208, 2014.
J. A. Harrington , G.M. Wheeler , M.J. Sweeting , A.P. Mander , and D.I. Jodrell . Adaptive designs for dual-agent phase I dose-escalation studies. Nature Reviews Clinical Oncology, 10(5):277–288, 2013. doi:10.1038/nrclinonc.2013.35.
W. He , J. Liu , B. Binkowitz , and H. Quan . A model-based approach in the estimation of the maximum tolerated dose in phase I cancer clinical trials. Statistics in Medicine, 25(12): 2027–2042, 2006. doi:10.1002/sim.2334.
L. M. Hoffman , M. Fouladi , J. Olson , V.M. Daryani , C.F. Stewart , C. Wetmore , M. Kocak , A. Onar-Thomas , L. Wagner , S. Gururangan , et al. Phase I trial of weekly MK-0752 in children with refractory central nervous system malignancies: A pediatric brain tumor consortium study. Child's Nervous System, 31(8):1283–1289, 2015. doi:10.1007/s00381-015-2725-3.
E. Horstmann , M.S. McCabe , L. Grochow , S. Yamamoto , L. Rubinstein , T. Budd , D. Shoemaker , E.J. Emanuel , and C. Grady . Risks and benefits of phase 1 oncology trials, 1991 through 2002. The New England Journal of Medicine, 352(9):895–904, 2005. doi:10.1056/NEJMsa042220.
A. Iasonos and J. O'Quigley . Adaptive dose-finding studies: A review of model-guided phase I clinical trials. Journal of Clinical Oncology, 32(23):2505–2511, 2014. doi:10.1200/JCO.2013.54.6051.
A. Iasonos and J. O'Quigley . Interplay of priors and skeletons in two-stage continual reassessment method. Statistics in Medicine, 31(30):4321–4336, 2012. doi:10.1002/sim.5559.
A. Iasonos , N.A. Wages , M.R. Conaway , K. Cheung , Y. Yuan , and J. O'Quigley . Dimension of model parameter space and operating characteristics in adaptive dose-finding studies. Statistics in Medicine, 35(21):3760–3775, 2016. doi:10.1002/sim.6966.
A. Iasonos , A.S. Wilton , E.R. Riedel , V.E. Seshan , and D.R. Spriggs . A comprehensive comparison of the continual reassessment method to the standard 3 + 3 dose escalation scheme in phase I dose-finding studies. Clinical Trials, 5(5):465–477, 2008. doi:10.1177/1740774508096474.
A. Iasonos , S. Zohar , and J. O'Quigley . Incorporating lower grade toxicity information into dose finding designs. Clinical Trials, 8(4):370–379, 2011. doi:10.1177/1740774511410732.
A. Ivanova , A. Montazer-Haghighi , S.G. Mohanty , and S.D. Durham . Improved up-and-down designs for phase I trials. Statistics in Medicine, 22(1):69–82, 2003. doi:10.1002/sim.1336.
T. Jaki . Uptake of novel statistical methods for early-phase clinical studies in the UK public sector. Clinical Trials, 10(2):344–346, 2013. doi:10.1177/1740774512474375.
Y. Ji , Y. Li , and B.N. Bekele . Dose-finding in phase I clinical trials based on toxicity probability intervals. Clinical Trials, 4(3):235–244, 2007. doi:10.1177/1740774507079442.
Y. Ji , P. Liu , Y. Li , and B.N. Bekele . A modified toxicity probability interval method for dose-finding trials. Clinical Trials, 7(6):653–663, 2010. doi:10.1177/1740774510382799.
Y. Ji and S.J. Wang . Modified toxicity probability interval design: A safer and more reliable method than the 3 + 3 design for practical phase I trials. Journal of Clinical Oncology, 31(14):1785–1791, 2013. doi:10.1200/JCO.2012.45.7903.
J. B. Kadane , J.M. Dickey , R.L. Winkler , W.S. Smith , C. Peters , M. Dickey , L. Winkler , and S.C. Peters . Interactive elicitation of opinion for a normal linear model. Journal of the American Statistical Association, 75(372):845–854, 1980.
S.H. Kang and C.W. Ahn . The expected toxicity rate at the maximum tolerated dose in the standard phase I cancer clinical trial design. Drug Information Journal, 35(8): 1189–1199, 2001.
S.H. Kang and C.W. Ahn . An investigation of the traditional algorithm-based designs for phase 1 cancer clinical trials. Drug Information Journal, 36:865–873, 2002.
E. L. Korn , D. Midthune , T.T. Chen , L.V. Rubinstein , M.C. Christian , and R.M. Simon . A comparison of two phase I trial designs. Statistics in Medicine, 13(18):1799–1806, 1994. doi:10.1002/sim.4780131802.
C. Le Tourneau, H.K. Gan , A.R. A. Razak , and X. Paoletti . Efficiency of new dose escalation designs in dose-finding phase I trials of molecularly targeted agents. PlOS One, 7(12):e51039, 2012. doi:10.1371/journal.pone.0051039.
C. Le Tourneau, J.J. Lee , and L.L. Siu . Dose escalation methods in phase I cancer clinical trials. Journal of the National Cancer Institute, 101(10):708–720, 2009. doi:10.1093/jnci/djp079.
C. Le Tourneau, A.R. A. Razak , H.K. Gan , S. Pop , V. Di éras, P. Tresca , and X. Paoletti . Heterogeneity in the definition of dose-limiting toxicity in phase I cancer clinical trials of molecularly targeted agents: A review of the literature. European Journal of Cancer, 47(10):1468–1475, 2011. doi:10.1016/j.ejca.2011.03.016.
S. M. Lee , B. Cheng , and Y.K. Cheung . Continual reassessment method with multiple toxicity constraints. Biostatistics, 12(2):386–398, 2011. doi:10.1093/biostatistics/kxq062.
S. M. Lee and Y.K. Cheung . Calibration of prior variance in the Bayesian continual reassessment method. Statistics in Medicine, 30(17):2081–2089, 2011. doi:10.1002/sim.4139.
A. T.R. Legedza and J.G. Ibrahim . Heterogeneity in phase I clinical trials: Prior elicitation and computation using the continual reassessment method. Statistics in Medicine, 20(6): 867–882, 2001.
Y. Lin and W.J. Shih . Statistical properties of the traditional algorithm-based designs for phase I cancer clinical trials. Biostatistics, 2(2):203–215, 2001. doi:10.1093/biostatistics/2.2.203.
S. J. Mandrekar , R. Qin , and D.J. Sargent . Model-based phase I designs incorporating toxicity and efficacy for single and dual agent drug combinations: Methods and challenges. Statistics in Medicine, 29(10):1077–1083, 2010. doi:10.1002/sim.3706.
J. L. Marshall . Maximum-tolerated dose, optimum biologic dose, or optimum clinical value: Dosing determination of cancer therapies. Journal of Clinical Oncology, 30(23):2815–2816, 2012. doi:10.1200/JCO.2012.43.4233.

V. A. Mats , W.F. Rosenberger , and N. Flournoy . Restricted optimality for phase I clinical trials. In N. Flournoy , W.F. Rosenberger , W.K. Wong , editors, New Developments and Applications in Experimental Design, IMS Lecture Notes—Monograph Series, Volume 34, pp. 50–61, 1998.

S. Møller . An extension of the continual reassessment methods using a preliminary up-and-down design in a dose finding study in cancer patients, in order to investigate a greater range of doses. Statistics in Medicine, 14(9):911–922, 1995.

Y. P. Mossé , M.S. Lim , S.D. Voss , K. Wilner , K. Ruffner , J.F. Laliberté , D. Rolland , F.M. Balis , J.M. Maris , B.J. Weigel , et al. Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: A Children's Oncology Group phase 1 consortium study. The Lancet Oncology, 14(6):472–480, 2013. doi:10.1016/S1470-2045(13)70095-0.

T. V. Narayana . Sequential procedures in probit analysis. Ph.D Thesis, University of North Carolina, 1953. http://www.stat.ncsu.edu/information/library/mimeo.archive/isms_1953_82.pdf.

National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events v4.0 , 2009. http://evs.nci.nih.gov/ftp1/CTCAE/.

B. Neuenschwander , M. Branson , and T. Gsponer . Critical aspects of the Bayesian approach to phase I cancer trials. Statistics in Medicine, 27(13):2420–2439, 2008. doi:10.1002/sim.3230.

A. Onar , M. Kocak , and J.M. Boyett . Continual reassessment method vs. traditional empirically based design: Modifications motivated by phase I trials in pediatric oncology by the Pediatric Brain Tumor Consortium. Journal of Biopharmaceutical Statistics, 19(3):437–455, 2009. doi:10.1080/10543400902800486.

A. Onar-Thomas and Z. Xiong . A simulation-based comparison of the traditional method, Rolling-6 design and a frequentist version of the continual reassessment method with special attention to trial duration in pediatric phase I oncology trials. Contemporary Clinical Trials, 31(3):259–270, 2010. doi:10.1016/j.cct.2010.03.006.

J. O'Quigley . Another look at two phase I clinical trial designs. Statistics in Medicine, 18 (20):2683–2690, 1999.

J. O'Quigley . Continual reassessment designs with early termination. Biostatistics, 3(1): 87–99, 2002.

J. O'Quigley and S. Chevret . Methods for dose finding studies in cancer clinical trials: A review and results of a Monte Carlo study. Statistics in Medicine, 10(11):1647–1664, 1991. doi:10.1002/sim.4780101104.

J. O'Quigley , M. Pepe , and L. Fisher . Continual reassessment method: A practical design for phase 1 clinical trials in cancer. Biometrics, 46(1):33–48, 1990.

J. O'Quigley and E. Reiner . Miscellanea: A stopping rule for the continual reassessment method. Biometrika, 85(3):741–748, 1998.

J. O'Quigley and L.Z. Shen . Continual reassessment method: A likelihood approach. Bio-metrics, 52(2):673–684, 1996.

J. O'Quigley and S. Zohar . Experimental designs for phase I and phase I/II dose-finding studies. British Journal of Cancer, 94(5):609–613, 2006. doi:10.1038/sj.bjc.6602969.

X. Paoletti and A. Kramar . A comparison of model choices for the continual reassessment method in phase I cancer trials. Statistics in Medicine, 28(24):3012–3028, 2009. doi:10.1002/sim.3682.

S. H. Park , S.M. Bang , E.K. Cho , D.B. Shin , J.H. Lee , W.K. Lee , and M. Chung . Phase I dose-escalating study of docetaxel in combination with 5-day continuous infusion of 5-fluorouracil in patients with advanced gastric cancer. BMC Cancer, 5(87):1–5, 2005. doi:10.1186/1471-2407-5-87.

N. Penel , N. Isambert , P. Leblond , C. Ferte , A. Duhamel , and J. Bonneterre . "Classical 3 + 3 design" versus "accelerated titration designs": Analysis of 270 phase 1 trials investigating anti-cancer agents. Investigational New Drugs, 27(6):552–556, 2009. 10.1007/s10637-008-9213-5.

G. R. Petroni , N.A. Wages , G. Paux , and F. Dubois . Implementation of adaptive methods in early-phase clinical trials. Statistics in Medicine, 36(2):215–224, 2017. doi:10.1002/sim.6910.

L. Pronzato . Penalized optimal designs for dose-finding. Journal of Statistical Planning and Inference, 140:283–296, 2010. doi:10.1016/j.jspi.2009.07.012.

M. J. Ratain , R. Mick , R.L. Schilsky , and M. Siegler . Statistical and ethical issues in the design and conduct of phase I and II clinical trials of new anticancer agents. Journal of the National Cancer Institute, 85(20):1637–1643, 1993.

R. Rivoirard , A. Vallard , J. Langrand-Escure , M. Ben Mrad, G. Wang , J.B. Guy , P. Diao , A. Dubanchet , E. Deutsch , C. Rancoule , and N. Magne . Thirty years of phase I radiochemotherapy trials: Latest development. European Journal of Cancer, 58:1–7, 2016. doi:10.1016/j.ejca.2016.01.012.

T. Robertson , F.T. Wright , and R.L. Dykstra . Ordered Restricted Statistical Inference. John Wiley & Sons, New York, 1988.

A. Rogatko , D. Schoeneck , W. Jonas , M. Tighiouart , F.R. Khuri , and A. Porter . Translation of innovative designs into phase I trials. Journal of Clinical Oncology, 25(31):4982–4986, 2007. doi:10.1200/JCO.2007.12.1012.

W. F. Rosenberger , G.C. Canfield , I. Perevozskaya , L.M. Haines , and P. Hausner . Development of interactive software for Bayesian optimal phase 1 clinical trial design. Drug Information Journal, 39:89–98, 2005.

W. F. Rosenberger and L.M. Haines . Competing designs for phase I clinical trials: A review. Statistics in Medicine, 21(18):2757–2770, 2002. doi:10.1002/sim.1229.

A. Roy , S. Ghosal , and W.F. Rosenberger . Convergence properties of sequential Bayesian D-optimal designs. Journal of Statistical Planning and Inference, 139(2):425–440, 2009. doi:10.1016/j.jspi.2008.04.025.

R. Simon , B. Freidlin , L. Rubinstein , S.G. Arbuck , J. Collins , and M.C. Christian . Accelerated titration designs for phase I clinical trials in oncology. Journal of the National Cancer Institute, 89(15):1138–1147, 1997.

J. M. Skolnik , J.S. Barrett , B. Jayaraman , D. Patel , and P.C. Adamson . Shortening the timeline of pediatric phase I trials: The rolling six design. Journal of Clinical Oncology, 26(2):190–195, 2008. doi:10.1200/JCO.2007.12.7712.

R. Sposto and S. Groshen . A wide-spectrum paired comparison of the properties of the rolling 6 and 3 + 3 phase I study designs. Contemporary Clinical Trials, 32(5):694–703, 2011. doi:10.1016/j.cct.2011.04.009.

B. E. Storer . Design and analysis of phase I clinical trials. Biometrics, 45(3):925–937, 1989.

B. E. Storer . An evaluation of phase I clinical trial designs in the continuous dose-response setting. Statistics in Medicine, 20(16):2399–2408, 2001. doi:10.1002/sim.903.

M. J. Sweeting , A.P. Mander , and T. Sabin . BCRM: Bayesian continual reassessment method designs for phase I dose-finding trials. Journal of Statistical Software, 54(13): 1–26, 2013.

P. F. Thall and S. Lee . Practical model-based dose-finding in phase I clinical trials: Methods based on toxicity. International Journal of Gynecological Cancer, 13:251–261, 2003.

P. F. Thall and K.E. Russell . A strategy for dose-finding and safety monitoring based on efficacy and adverse outcomes in phase I/II clinical trials. Biometrics, 54(1):251–264, 1998.

M. Tighiouart and A. Rogatko . Dose finding with escalation with overdose control (EWOC) in cancer clinical trials. Statistical Science, 25(2):217–226, 2010.
M. Tighiouart , A. Rogatko , and J.S. Babb . Flexible Bayesian methods for cancer phase I clinical trials. Dose escalation with overdose control. Statistics in Medicine, 24(14): 2183–2196, 2005. doi:10.1002/sim.2106.
D. D. Von Hoff , J. Kuhn , and G.M. Clark . Design and conduct of phase I trials. In M.E. Buyse , M.J. Staquet , R.J. Sylvester , editors, Cancer Clinical Trials: Methods and Practice, pp. 210–220. Oxford University Press, Oxford, 1984.
G. M. Wheeler , M.J. Sweeting , and A.P. Mander . AplusB: A web application for investigating A + B designs for phase I cancer clinical trials. PLoS One, 11(7):e0159026, 2016. doi:10.1371/journal.pone.0159026.
G. M. Wheeler . Incoherent dose-escalation in phase I trials using the escalation with overdose control approach. Statistical Papers, 1–11, 2016. doi:10.1007/s00362-016-0790-7.
J. Whitehead . Bayesian decision procedures with application to dose-finding studies. International Journal of Pharmaceutical Medicine, 11:201–208, 1997.
J. Whitehead , H. Thygesen , and A. Whitehead . A Bayesian dose-finding procedure for phase I clinical trials based only on the assumption of monotonicity. Statistics in Medicine, 29(17):1808–1824, 2010. doi:10.1002/sim.3963.
J. Whitehead , H. Thygesen , and A. Whitehead . Bayesian procedures for phase I/II clinical trials investigating the safety and efficacy of drug combinations. Statistics in Medicine, 30(16):1952–1970, 2011. doi:10.1002/sim.4267.
J. Whitehead , H. Thygesen , T. Jaki , S. Davies , S. Halford , H. Turner , N. Cook , and D. Jodrell . A novel Phase I/IIa design for early phase oncology studies and its application in the evaluation of MK-0752 in pancreatic cancer. Statistics in Medicine, 31(18): 1931–1943, 2012. doi:10.1002/sim.5331.
K. M. Wong , A. Capasso , and S.G. Eckhardt . The changing landscape of phase I trials in oncology. Nature Reviews Clinical Oncology, 13(2):106–117, 2016. doi:10.1038/nrclinonc.2015.194.
G. Yin , Y. Li , and Y. Ji . Bayesian dose-finding in phase I/II clinical trials using toxicity and efficacy odds ratios. Biometrics, 62(3):777–784, 2006. doi:10.1111/j.1541-0420.2006.00534.x.
L. Zhao , J. Lee , R. Mody , and T.M. Braun . The superiority of the time-to-event continual reassessment method to the rolling six design in pediatric oncology phase I trials. Clinical Trials, 8(4):361–369, 2011. doi:10.1177/1740774511407533.
S. Zohar and S. Chevret . The continual reassessment method: Comparison of Bayesian stopping rules for dose-ranging studies. Statistics in Medicine, 20(19):2827–2843, 2001. doi:10.1002/sim.920.
S. Zohar and J. O'Quigley . Re: Dose escalation methods in phase I cancer clinical trials. Journal of the National Cancer Institute, 101(24):1732–1733; author reply 1733–1735, 2009. doi:10.1093/jnci/djp400.

Model-Based Designs for Safety

J. Babb , A. Rogatko , and S. Zacks . Cancer phase I clinical trials: Efficient dose escalation with overdose control. Statistics in Medicine, 17(10):1103–1120, 1998. doi:10.1002/(SICI) 1097-0258(19980530)17:101103::AID-SIM7933.0.CO;2-9.
B. N. Bekele and P. F. Thall . Dose-finding based on multiple toxicities in a soft tissue sarcoma trial. Journal of the American Statistical Association, 99(465):26–35, 2004. doi:10.1198/016214504000000043.
E. V. Dressler and Z. Huang . ordcrm: Likelihood-Based Continual Reassessment (CRM) Dose Finding Designs. R package version 1.0.0, https://cran.r-project.org/package=ordcrm, 2016.
A. Ivanova . Escalation, group and A + B designs for dose-finding trials. Statistics in Medicine, 25(21):3668–3678, 2006. doi:10.1002/sim.2470.
S. M. Lee , B. Cheng , and Y. K. Cheung . Continual reassessment method with multiple toxicity constraints. Biostatistics, 12(2):386–398, 2011. doi:10.1093/biostatistics/kxq062.
S. M. Lee and Y. K. Cheung . Model calibration in the continual reassessment method. Clinical Trials, 6(3):227–238, 2009. doi:10.1177/1740774509105076.
S. M. Lee , D. L. Hershman , P. Martin , J. P. Leonard , and Y. K. Cheung . Toxicity burden score: A novel approach to summarize multiple toxic effects. Annals of Oncology, 23(2): 537–541, 2012. doi:10.1093/annonc/mdr146.
Y. Lin and W. J. Shih . Statistical properties of the traditional algorithm-based designs for phase I cancer clinical trials. Biostatistics, 2(2):203–215, 2001. doi:10.1093/biostatistics/2.2.203.
National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0, 2009 .
E. Reiner , X. Paoletti , and J. O'Quigley . Operating characteristics of the standard phase I clinical trial design. Computational Statistics and Data Analysis, 30(3):303–315, 1999. doi:10.1016/S0167-9473(98)00095-4.
A. Rogatko , J. S. Babb , H. Wang , M. J. Slifker , and G. R. Hudes . Patient characteristics compete with dose as predictors of acute treatment toxicity in early phase clinical trials. Clinical Cancer Research, 10(14):4645–4651, 2004. doi:10.1158/1078-0432.ccr-03-0535.
J. Ruan , P. Martin , R. R. Furman , S. M. Lee , K. Cheung , J. M. Vose , A. LaCasce , J. Morrison , R. Elstrom , S. Ely , et al. Bortezomib plus CHOP-rituximab for previously untreated diffuse large B-cell lymphoma and mantle cell lymphoma. Journal of Clinical Oncology, 29(6):690–697, 2011. doi:10.1200/jco.2010.31.1142.
M. Tighiouart , G. Cook-Wiens , and A. Rogatko . Escalation with overdose control using ordinal toxicity grades for cancer phase I clinical trials. Journal of Probability and Statistics, 2012:18, 2012. doi:10.1155/2012/317634.
A. Trotti , T. F. Pajak , C. K. Gwede , R. Paulus , J. Cooper , A. Forastiere , J. A. Ridge , D. Watkins-Bruner , A. S. Garden , K. K. Ang , et al. TAME: Development of a new method for summarising adverse events of cancer treatment by the Radiation Therapy Oncology Group. Lancet Oncology, 8(7):613–624, 2007. doi:10.1016/s1470-2045(07)70144-4.
E. M. Van Meter , E. Garrett-Mayer , and D. Bandyopadhyay . Dose-finding clinical trial design for ordinal toxicity grades using the continuation ratio model: An extension of the continual reassessment method. Clinical Trials, 9(3):303–313, 2012. doi:10.1177/1740774512443593.
E. M. Van Meter , E. Garrett-Mayer , and D. Bandyopadhyay . Proportional odds model for dose-finding clinical trial designs with ordinal toxicity grading. Statistics in Medicine, 30 (17):2070–2080, 2011. doi:10.1002/sim.4069.

Dose-Finding Methods for Nonbinary Outcomes

B. N. Bekele and P. F. Thall . Dose-finding based on multiple toxicities in a soft tissue sarcoma trial. Journal of the American Statistical Association, 99(465):26–35, 2004.

B. Cheng and S. M. Lee . On the consistency of the continual reassessment method with multiple toxicity constraints. Journal of Statistical Planning and Inference, 164:1–9, 2015.

S. M. Lee , B. Cheng , and Y. K. Cheung . Continual reassessment method with multiple toxicity constraints. Biostatistics, 12(2):386–398, 2011.

Z. Yuan , R. Chappell , and H. Bailey . The continual reassessment method for multiple toxicity grades: A Bayesian quasi-likelihood approach. Biometrics, 63(1):173–179, 2007.

M. Ezzalfani , S. Zohar , R. Qin , S. J. Mandrekar , and M. C. Deley . Dose-finding designs using a novel quasi-continuous endpoint for multiple toxicities. Statistics in Medicine, 32(16):2728–2746, 2013.

A. Ivanova and S. H. Kim . Dose finding for continuous and ordinal outcomes with a monotone objective function: A unified approach. Biometrics, 65(1):307–315, 2009.

S. M. Lee , D. Backenroth , Y. K. Cheung , D. Vulih , B. Anderson , P. Ivy , and L. Minasian . Case example of dose optimization using data from bortezomib dose-finding trials. Journal of Clinical Oncology, 34:1395–1401, 2016.

Y. K. Cheung and R. Chappell . Sequential designs for phase I clinical trials with late-onset toxicities. Biometrics, 56(4):1177–1182, 2000.

Y. K. Cheung and M. S. V. Elkind . Stochastic approximation with virtual observations for dose finding on discrete levels. Biometrika, 97:109–121, 2010.

E. M. Van Meter , E. Garret-Mayer , and D. Bandyopadhyay . Proportional odds model for dose-finding clinical trial desings with ordinal toxicity grading. Statistics in Medicine, 30(17):2070–2080, 2011.

E. M. Van Meter , E. Garret-Mayer , and D. Bandyopadhyay . Dose-finding clinical trial design for ordinal toxicity grades using the continuation ratio model: An extension of the continual reassessment method. Clinical Trials, 9(3):303–313, 2012.

C. Wang , T. Chen , and I. Tyan . Designs for phase I cancer clinical trials with differentiation of graded toxicity. Communications in Statistics: Theory and Method, 29:975–987, 2000.

A. Iasonos , S. Zohar , and J. O'Quigley . Incorporating lower grade toxicity information into dose finding desings. Clinical Trials, 8(4):370–379, 2011.

A. Rogatko , J. S. Babb , H. Wang , M. J. Slifker , and G. R. Hudes . Patient characteristics compete with dose as predictors of acute treatment toxicity in early phase clinical trials. Clinical Cancer Research, 10:4645–4651, 2004.

A. Trotti , T. Pajak , C. Gwede , R. Paulus , J. Cooper , A. Forastiere , J. Ridge , D. Watkins-Bruner , A. Garden , K. Ang , and W. Curran . TAME: Development of a new method for summarising adverse events of cancer treatment by the Radiation Therapy Oncology Group. Lancet Oncology, 8(7):613–624, 2007.

S. M. Lee , D. L. Hershman , P. Martin , J. P. Leonard , and Y. K. Cheung . Toxicity burden score: A novel approach to summarize multiple toxic effects. Annals of Oncology, 23(2):537–541, 2012.

S. M. Lee and Y. K. Cheung . Model calibration in the continual reassessment method. Clinical Trials, 6(3):227–238, 2009.

J. P. Leornard , R. R. Furman , and Y. K. Cheung , et al. Phase I/II trial of bortezomib plus CHOP-rituximab in diffuse large B cell and mantle cell lymphoma: Phase I results. Blood, 106(11):147A, 2005.

S. M. Lee and Y. K. Cheung . Calibration of prior variance in the Bayesian continual reassessment method. Statistics in Medicine, 30:2081–2089, 2011.

A. Jia , S. M. Lee , and Y. K. Cheung . Characterisation of the likelihood continual reassessment method. Biometrika, 101:599–612, 2014.

Dose-Finding Trials in Pediatric Oncology

American Cancer Society. Cancer facts & figures 2014—special section: Childhood & adolescent cancers . http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-042151.pdf, 2014. Accessed: November 24, 2015 .

J. Boklan . Little patients, losing patience: Pediatric cancer drug development. Molecular Cancer Therapeutics, 5(8):1905–1908, 2006.

K.E. Deffenbacher , J. Iqbal , W. Sanger , Y. Shen , C. Lachel , Z. Liu , Y. Liu , M.S. Lim , S.L. Perkins , K. Fu , et al . Molecular distinctions between pediatric and adult mature B-cell non-Hodgkin lymphomas identified through genomic profiling. Blood, 119(16):3757–3766, 2012.

J.R. Downing , R.K. Wilson , J. Zhang , E.R. Mardis , C.H. Pui , L. Ding , T.J. Ley , and W.E. Evans . The pediatric cancer genome project. Nature Genetics, 44(6):619–622, 2012. doi: 10.1038/ng.2287.

C. Jones , L. Perryman , and D. Hargrave . Paediatric and adult malignant glioma: Close relatives or distant cousins? Nature Reviews Clinical Oncolgy, 9(7):400–413, 2012. doi: 10.1038/nrclinonc.2012.87.

D.W. Parsons , M. Li , X. Zhang , S. Jones , R.J. Leary , J.C.H. Lin , S.M. Boca , H. Carter , J. Samayoa , C. Bettegowda , et al . The genetic landscape of the childhood cancer medulloblastoma. Science 331(6016):435–439, 2011.

Tufts Center for the Study of Drug Development. How the Tufts Center for the Study of Drug Development pegged the cost of a new drug at $2.6 billion . http://csdd.tufts.edu/files/uploads/coststudybackgrounder.pdf, November 18, 2014. Accessed: November 24, 2015 .

J. Avorn . The $2.6 billion pill—Methodologic and policy considerations. New England Journal of Medicine, 372(20):1877–1879, 2015.

N. Aumock , J. Smith , and S. Townsend . Do incentives drive pediatric research? McKinsey Center for Government, October 2013.

Federal Drug Administration (FDA). Pediatric exclusivity granted: Drugs to which FDA has granted pediatric exclusivity for pediatric studies under Section 505A of the Federal Food, Drug, and Cosmetic Act . http://www.fda.gov/Drugs/DevelopmentApproval-Process/DevelopmentResources/ucm050005.htm, October 2015. Accessed: November 19, 2015 .

M.E. Ceja , A.M. Christensen , and S.P. Yang . Dosing considerations in pediatric oncology. U.S. Pharmacist, 38(Oncology suppl):8–11, 2013.

V. Ivanovska , C.M. A. Rademaker , L. van Dijk , and A.K. Mantel-Teeuwisse . Pediatric drug formulations: A review of challenges and progress. Pediatrics, 134(2):361–372, 2014.

M. Smith , M. Bernstein , W.A. Bleyer , J.D. Borsi , P. Ho , I.J. Lewis , A. Pearson , F. Pein , C. Pratt , G. Reaman , et al . Conduct of phase I trials in children with cancer. Journal of Clinical Oncology, 16(3):966–978, 1998.

V.M. Piñeiro-Carrero and E.O. Piñeiro . Liver. Pediatrics, 113(4 Suppl):1097–1106, 2004.
D.P. Lee , J.M. Skolnik , and P.C. Adamson . Pediatric phase I trials in oncology: An analysis of study conduct efficiency. Journal of Clinical Oncology, 23(33):8431–8441, 2005.
J.S. Weber , L.A. Levit , P.C. Adamson , S. Bruinooge , H.A. Burris , M.A. Carducci , A.P. Dicker , M. Gönen, S.M. Keefe , M.A. Postow , et al . American society of clinical oncology policy statement update: The critical role of phase I trials in cancer research and treatment. Journal of Clinical Oncology, 33(3):278–284, 2015.
17 J.M. Skolnik , J.S. Barrett , B. Jayaraman , D. Patel , and P.C. Adamson . Shortening the timeline of pediatric phase I trials: The rolling six design. Journal of Clinical Oncology, 26(2):190–195, 2008.
J. O'Quigley , M. Pepe , and L. Fisher . Continual reassessment method: A practical design for phase I clinical trials in cancer. Biometrics, 46(1):33–48, 1990.
A. Gajjar , C.F. Stewart , D.W. Ellison , S. Kaste , L.E. Kun , R.J. Packer , S. Goldman , M. Chintagumpala , D. Wallace , N. Takebe , et al . Phase I study of vismodegib in children with recurrent or refractory medulloblastoma: A pediatric brain tumor consortium study. Clinical Cancer Research, 19(22):6305–6312, 2013.
M.W. Kieran , R.J. Packer , A. Onar , S.M. Blaney , P. Phillips , I.F. Pollack , J.R. Geyer , S. Gururangan , A. Banerjee , S. Goldman , et al . Phase I and pharmacokinetic study of the oral farnesyltransferase inhibitor lonafarnib administered twice daily to pediatric patients with advanced central nervous system tumors using a modified continuous reassessment method: A pediatric brain tumor consortium study. Journal of Clinical Oncology, 25(21):3137–3143, 2007.
J.G. Villablanca , M.D. Krailo , M.M. Ames , J.M. Reid , G.H. Reaman , and C.P. Reynolds . Phase I trial of oral fenretinide in children with high-risk solid tumors: A report from the Children's Oncology Group (CCG 09709). Journal of Clinical Oncology, 24(21):3423–3430, 2006.
B.C. Widemann , W.L. Salzer , R.J. Arceci , S.M. Blaney , E. Fox , D. End, A. Gillespie , P. Whitcomb , J.S. Palumbo , A. Pitney , et al . Phase I trial and pharmacokinetic study of the farnesyltransferase inhibitor tipifarnib in children with refractory solid tumors or neurofibromatosis type I and plexiform neurofibromas. Journal of Clinical Oncology, 24(3):507–516, 2006.
A. Broniscer , S.D. Baker , C. Wetmore , A.S. Pai Panandiker, J. Huang , A.M. Davidoff , A. Onar-Thomas, J.C. Panetta , T.K. Chin , T.E. Merchant , et al . Phase I trial, pharmacokinetics, and pharmacodynamics of vandetanib and dasatinib in children with newly diagnosed diffuse intrinsic pontine glioma. Clinical Cancer Research, 19(11):3050–3058, 2013.
D.D. Von Hoff, P.M. LoRusso , C.M. Rudin , J.C. Reddy , R.L. Yauch , R. Tibes , G.J. Weiss , M.J. Borad , C.L. Hann , J.R. Brahmer , et al . Inhibition of the hedgehog pathway in advanced basal-cell carcinoma. New England Journal of Medicine, 361(12):1164–1172, 2009.
C.M. Rudin , C.L. Hann , J. Laterra , R.L. Yauch , C.A. Callahan , L. Fu , T. Holcomb , J. Stinson , S.E. Gould , B. Coleman , et al . Treatment of medulloblastoma with hedgehog pathway inhibitor GDC-0449. New England Journal of Medicine, 361(12):1173–1178, 2009.
K.D. Robarge , S.A. Brunton , G.M. Castanedo , Y. Cui , M.S. Dina , R. Goldsmith , S.E. Gould , O. Guichert , J.L. Gunzner , J. Halladay , et al . GDC-0449—A potent inhibitor of the hedgehog pathway. Bioorganic & Medicinal Chemistry Letters, 19(19):5576–5581, 2009.
J.T. Romer , H. Kimura , S. Magdaleno , K. Sasai , C. Fuller , H. Baines , M. Connelly , C.F. Stewart , S. Gould , L.L. Rubin et al . Suppression of the Shh pathway using a small molecule inhibitor eliminates medulloblastoma in P tc1+/−p53−/− mice. Cancer Cell, 6(3):229–240, 2004.
28 H. Kimura , J.M. Y. Ng , and T. Curran . Transient inhibition of the hedgehog pathway in young mice causes permanent defects in bone structure. Cancer Cell, 13(3):249–260, 2008.
K. Seidel , C.P. Ahn , D. Lyons , A. Nee , K. Ting , I. Brownell , T. Cao , R.A. D. Carano , T. Curran , M. Schober , et al . Hedgehog signaling regulates the generation of ameloblast progenitors in the continuously growing mouse incisor. Development, 137(22):3753–3761, 2010.
G.W. Robinson , B.A. Orr , G. Wu , S. Gururangan , T. Lin , I. Qaddoumi , R.J. Packer , S. Goldman , M.D. Prados , A. Desjardins , et al . Vismodegib exerts targeted efficacy against recurrent sonic hedgehog-subgroup medulloblastoma: Results from phase II pediatric brain tumor consortium studies PBTC-025b and PBTC-032. Journal of Clinical Oncology, 33(24):2646–2654, 2015.
A. Onar-Thomas and Z. Xiong . A simulation-based comparison of the traditional method, Rolling-6 design and a frequentist version of the continual reassessment method with special attention to trial duration in pediatric phase I oncology trials. Contemporary Clinical Trials, 31(3):259–270, 2010.
R. Sposto and S. Groshen . A wide-spectrum paired comparison of the properties of the Rolling 6 and 3 + 3 phase I study designs. Contemporary Clinical Trials, 32(5):694–703, 2011.
Y.K. Cheung and R. Chappell . Sequential designs for phase I clinical trials with late-onset toxicities. Biometrics, 56(4):1177–1182, 2000.
T.M. Braun . Generalizing the TITE-CRM to adapt for early- and late-onset toxicities. Statistics in Medicine, 25(12):2071–2083, 2006.
A. Iasonos , A.S. Wilton , E.R. Riedel , V.E. Seshan , and D.R. Spriggs . A comprehensive comparison of the continual reassessment method to the standard 3 + 3 dose escalation scheme in phase I dose-finding studies. Clinical Trials, 5(5):465–477, 2008.
A. Onar , M. Kocak , and J.M. Boyett . Continual reassessment method vs. traditional empirically-based design: Modifications motivated by phase I trials in pediatric oncology by the pediatric brain tumor consortium. Journal of Biopharmaceutical Statistics, 19(3):437–455, 2009.
N.A. Wages , M.R. Conaway , and J. O'Quigley . Performance of two-stage continual reassessment method relative to an optimal benchmark. Clinical Trials, 10(6):862–875, 2013.
J. O'Quigley , M.D. Hughes , and T. Fenton . Dose-finding designs for HIV studies. Biometrics, 57(4):1018–1029, 2001.
J. O'Quigley and A. Iasonos . Bridging solutions in dose finding problems. Statistics in Biopharmaceutical Research, 6(2):185–197, 2014.
Institute of Medicine (US). Clinical trials in cancer . Forum on Drug Discovery, Development, and Translation. Transforming Clinical Research in the United States: Challenges and Opportunities, Chapter 6. Workshop Summary. Washington, DC: National Academies Press. http://www.ncbi.nlm.nih.gov/books/NBK50895/, 2010. Accessed: November 30, 2015 .
41 S.B. Bavdekar . Pediatric clinical trials. Perspectives in Clinical Research, 4(1):89–99, 2013.
National Cancer Institute (NCI). An analysis of the National Cancer institute's investment in pediatric cancer research . http://www.cancer.gov/types/childhood-cancers/research/pediatric-analysis.pdf, September 2013. Accessed: August 22, 2016 .

Phase I/II Dose-Finding Designs with Efficacy and Safety Endpoints

Asakawa, T. , Hamada, C. (2013). A pragmatic dose-finding approach using short-term surrogate efficacy outcomes to evaluate binary efficacy and toxicity outcomes in phase I cancer clinical trials. Pharmaceutical Statistics 12(5), 315–327.

Asakawa, T. , Hirakawa, A. , Hamada, C. (2013). Bayesian model averaging continual reassessment method for bivariate binary efficacy and toxicity outcomes in phase I oncology trials. Journal of Biopharmaceutical Statistics 24(2), 310–325.

Atkinson, A. C. , Donev, A. N. , Tobias, R. (2007). Optimum Experimental Designs, with SAS. Oxford University Press, Oxford, UK.

Babb, J. , Rogatko, A. , Zacks, S. (1998). Cancer phase I clinical trials: Efficient dose escalation with overdose control. Statistics in Medicine 17, 1103–1120.

Bekele, B. N. , Shen, Y. (2005). A Bayesian approach to jointly modeling toxicity and biomarker expression in a phase I/II dose-finding trial. Biometrics 61, 344–354.

Braun, T. M. (2002). The bivariate continual reassessment method: extending the CRM to phase I trials of two competing outcomes. Controlled Clinical Trials 23, 240–256.

Chen, Z. , Yuan, Y. , Li, Z. , Kutner, M. , Owonikoko, T. , Curran, W. J. , Khuri, F. , Kowalski, J. (2015). Dose escalation with over-dose and under-dose controls in phase I/II clinical trials. Contemporary Clinical Trials 43, 133–141.

Cook, R. D. , Fedorov, V. V. , (1995). Constrained optimization of experimental design. Statistics 26, 129–178.

Cunanan, K. , Koopmeiners, J. S. (2014). Evaluating the performance of copula models in phase I–II clinical trials under model misspecification. BMC Medical Research Methodology 14, 51. doi:10.1186/1471-2288-14-51.

Dragalin, V. (2010). Seamless phase I/II designs. In A. Pong and S.C. Chow (eds.), Handbook of Adaptive Designs in Pharmaceutical and Clinical Development, pp. 12.1–12.23, Chapman & Hall, Boca Raton, FL.

Dragalin, V. , Fedorov, V. V. (2006). Adaptive designs for dose-finding based on efficacytoxicity response. Journal of Statistical Planning and Inference 136, 1800–1823.

Dragalin, V. , Fedorov, V. V. , Wu, Y. (2008). Two-stage design for dose-finding that accounts for both efficacy and safety. Statistics in Medicine 27, 5156–5176.

Durham, S. D. , Flournoy, N. , Li, W. (1998). A sequential design for maximizing the probability of a favourable response. Canadian Journal of Statistics 26(3), 479–495.

Fan, S. K. , Chaloner, K. (2004). Optimal designs and limiting optimal designs for a trinomial response. Journal of Statistical Planning and Inference 126, 347–360.

Fan, S. K. , Chaloner, K. (2001). Optimal designs for a continuation-ratio model. In A. Atkinson , P. Hackl , W. G. Müller (eds.), mODa 6—Advances in Model-Oriented Design and Analysis, pp. 77–85, Springer-Verlag, Berlin and Heidelberg GmbH.

Fedorov, V. V. (1972). Theory of Optimal Experiments. Academic Press, New York and London.

Fedorov, V. V. , Flournoy, N. , Wu, Y. , Zhang, R. (2011). Best Intention Designs in Dose Finding Studies. Isaac Newton Institute for Mathematical Sciences, Cambridge, UK.

Fedorov, V. V. , Hackl, P. (1997). Model-Oriented Design of Experiments. Springer Science + Business Media, New York.

Fedorov, V. V. , Leonov, S. L. (2014). Optimal Design for Nonlinear Response Models. CRC Press, Boca Raton, FL.

Fedorov, V. V. , Wu, Y. (2007). Dose finding designs for continuous responses and binary utility. Journal of Biopharmaceutical Statistics 17(6), 1085–1096.

Gao, L. , Rosenberger, W. F. (2013). Adaptive Bayesian design with penalty based on toxicity-efficacy response. In D. Uciński , A. C. Atkinson , M. Patan (eds.), mODa 10— Advances in Model-Oriented Design and Analysis, pp. 91–98, Springer International Publishing, Basel, Switzerland.

Gooley, T. A. , Martin, P. J. , Fisher, L. D. , Pettinger, M. (1994). Simulation as a design tool for phase I/II clinical trials: An example from bone marrow transplantation. Controlled Clinical Trials 15, 450–462.

Guo, B. , Yuan, Y. (2015). A Bayesian dose-finding design for phase I/II clinical trials with nonignorable dropouts. Statistics in Medicine 34(10), 1721–1732.

Haines, L. , Perevozskaya, I. , Rosenberger, W. F. (2003). Bayesian optimal designs for phase I clinical trials. Biometrics 59, 591–600.

Hardwick, J. , Mayer, M. C. , Stout, V. (2003). Directed walk designs for dose-response problems with competing failure modes. Biometrics 59, 229–236.

Hardwick, J. , Stout, V. (2001). Optimizing a unimodal response function for binary variables. In A. Atkinson , B. Bogacka , A. Zhigljavsky (eds.), Optimum Design 2000, pp. 195–208, Springer-Verlag, US.

Hirakawa, A. (2012). An adaptive dose finding approach for correlated bivariate binary and continuous outcomes in phase I oncology trials. Statistics in Medicine 31, 516–532.

Hoering, A. , LeBlanc, M. , Crowley, J. (2011). Seamless phase I/II trial design for assessing toxicity and efficacy for targeted agents. Clinical Cancer Research 17(4), 640–646.

Hoering, A. , Mitchell, A. , LeBlanc, M. , Crowley, J. (2013). Early phase trial design for assessing several dose levels for toxicity and efficacy for targeted agents. Clinical Trials 10(2), 422–429.

Hu, F. , Rosenberger, W. F. (2006). The Theory of Response-Adaptive Randomization in Clinical Trials. John Wiley & Sons, New York.

Hunsberger, S. , Rubinstein, L. V. , Dancey, J. , Korn, E. L. (2005). Dose escalation trial designs based on molecularly targeted endpoint. Statistics in Medicine 24, 2171–2181.

Iasonos, A. , O'Quigley, J. (2016). Dose expansion cohorts in phase I trials. Statistics in Biopharmaceutical Research 8(2), 161–170.

Iasonos, A. , Wages, N. A. , Conaway, M. R. , Cheung, K. , Yuan, Y. , O'Quigley, J. (2016). Dimension of model parameter space and operating characteristics in adaptive dose-finding studies. Statistics in Medicine 35, 3760–3775.

Ivanova, A. V. (2003). A new dose-finding design for bivariate outcomes. Biometrics 59, 1001–1007.

Ji, Y. , Bekele, N. (2009). Adaptive randomization for multiarm comparative clinical trials based on joint efficacy/toxicity outcomes. Biometrics 65, 876–884.

Jin, I. H. , Liu, S. , Thall, P. F. , Yuan, Y. (2014). Using data augmentation to facilitate conduct of phase I–II clinical trials with delayed outcomes. Journal of the American Statistical Association 109, 525–536.

Kiefer, J. , Wolfowitz, J. (1960). The equivalence of two extremum problems. Canadian Journal of Mathematics 12, 363–366.

Kiefer, J. , Wolfowitz, J. (1952). Stochastic estimation of the maximum of regression function. Annals of Mathematical Statistics 25, 529–532.

Koopmeiners, J. S. , Modiano, J. (2014). A Bayesian adaptive phase I-II clinical trial for evaluating efficacy and toxicity with delayed outcomes. Clinical Trials 11, 38–48.
Kpamegan, E. E. , Flournoy, N. (2001). An optimizing up-and-down design. In A. Atkinson , B. Bogacka , A. Zhigljavsky (eds), Optimum Design 2000, pp. 211–223, Springer-Verlag, US.
Kpamegan, E. E. , Flournoy, N. (2008). Up-and-down designs for selecting the dose with maximum success probability. Sequential Analysis 27, 78–96.
Li, W. , Durham, S. D. , Flournoy, N. (1995). An adaptive design for maximization of a contingent binary response. In N. Flournoy , W. F. Rosenberger (eds.), Adaptive Designs, pp. 179–196, IMS Lecture Notes Monograph Series 25, Hayward, CA.
Lei, X. , Yuan, Y. , Yin, G. (2011). Bayesian phase II adaptive randomization by jointly modeling time-to-event efficacy and binary toxicity. Lifetime Data Analysis 17(1), 156–174.
Loke, Y. C. , Tan, S. B. , Cai, Y. Y. , Machin, D. (2006). A Bayesian dose finding design for dual endpoint phase I trials. Statistics in Medicine 25, 3–22.
O'Quigley, J. , Hughes, M. D. , Fenton, T. (2001). Dose-finding designs for HIV studies. Biometrics 57, 1018–1029.
O'Quigley, J. , Pepe, M. , Fisher, L. (1990). Continual reassessment method: A practical design for phase I clinical studies in cancer. Biometrics 46, 33–48.
Padmanabhan, S. K. , Hsuan, F. , Dragalin, V. (2010). Adaptive penalized *D*-optimal designs for dose finding based on continuous efficacy and toxicity. Statistics in Biopharmaceutical Research 2(2), 182–198.
Pronzato, L. (2008). Asymptotic properties of adaptive penalized optimal designs with application to dose finding. Technical Report ISRN I3S/RR-2008-19-FR, University Nice Sophia Antipolis, 33 pp.
Pronzato, L. (2010). Asymptotic properties of adaptive penalized optimal designs over a finite space. In A. Giovagnoli , A. C. Atkinson , B. Torsney (eds) and C. May (co-ed.) mODa 9—Advances in Model-Oriented Design and Analysis, pp. 165–172, Springer-Verlag, Berlin and Heidelberg.
Pronzato, L. (2010). Penalized optimal adaptive designs for dose finding. Journal of Statistical Planning and Inference 140, 283–296.
Seegers, V. , Chevret, S. , Resche-Rigon, M. (2011). Dose-finding design driven by efficacy in onco-hematology phase I/II trials. Statistics in Medicine 30, 1574–1583.
Sverdlov, O. , Wong, W. K. (2014). Novel statistical designs for phase I/II and phase II clinical trials with dose-finding objectives. Therapeutic Innovation and Regulatory Science 48(5), 601–615.
Sverdlov, O. , Wong, W. K. , Ryeznik, Y. (2014). Adaptive clinical trial designs for phase I cancer studies. Statistics Surveys 8, 2–44.
Thall, P. F. (2010). Bayesian models and decision algorithms for complex early phase clinical trials. Statistical Science 25(2), 227–244.
Thall, P. F. , Cook, J. D. (2004). Dose-finding based on efficacy-toxicity trade-offs. Bio-metrics 60, 684–693.
Thall, P. F. , Estey, E. H. , Sung, H. G. (1999). A new statistical method for dose-finding based on efficacy and toxicity in early phase clinical trials. Investigational New Drugs 17, 155–167.
Thall, P. F. , Inoue, L. Y. T. , Martin, T. G. (2002). Adaptive decision making in a lymphocyte infusion trial. Biometrics 58, 560–568.
Thall, P. F. , Nguyen, H. Q. , Estey, E. H. (2008). Patient-specific dose finding based on bivariate outcomes and covariates. Biometrics 64, 1126–1136.
Thall, P. F. , Russell, K. T. (1998). A strategy for dose finding and safety monitoring based on efficacy and adverse outcomes in phase I/II clinical trials. Biometrics 54, 532–540.
Wang, M. , Day, R. (2010). Adaptive Bayesian design for phase I dose-finding trials using a joint model of response and toxicity. Journal of Biopharmaceutical Statistics 20(1), 125–144.
Whitehead, J. , Brunier, H. (1995). Bayesian decision procedures for dose determining experiments. Statistics in Medicine 14, 885–893.
Whitehead, J. , Williamson, D. (1998). Bayesian decision procedures based on logistic regression models for dose-finding studies. Journal of Biopharmaceutical Statistics 8(3), 445–467.
Whitehead, J. , Zhou, Y. , Stevens, J. , Blakey, G. (2004). An evaluation of a Bayesian method of dose escalation based on bivariate binary responses. Journal of Biopharmaceutical Statistics 14(4), 969–983.
Whitehead, J. , Zhou, Y. , Stevens, J. , Blakey, G. , Price, J. , Leadbetter, J. (2006). Bayesian decision procedures for dose-escalation based on evidence of undesirable events and therapeutic benefit. Statistics in Medicine 25, 37–53.
World Medical Association (WMA) General Assembly . (1964). Declaration of Helsinki—Ethical principles for medical research involving human subjects. http://www.wma.net/en/30publications/10policies/b3/ (Accessed on July 23, 2016).
Yin, G. , Li, Y. , Ji, Y. (2006). Bayesian dose-finding in phase I/II clinical trials using toxicity and efficacy odds ratios. Biometrics 62, 777–787.
Yin, G. , Yuan, Y. (2009). Bayesian model averaging continual reassessment method in phase I clinical trials. Journal of the American Statistical Association 104(487), 954–968.
Yin, G. , Zheng, S. , Xu, J. (2013). Two-stage dose finding for cytostatic agents in phase I oncology trials. Statistics in Medicine 32, 644–660.
Yuan, Y. , Nguyen, H. Q. , Thall, P. F. (2016). Bayesian Designs for Phase I/II Clinical Trials. CRC Press, Boca Raton, FL.
Yuan, Y. , Yin, G. (2009). Bayesian dose finding by jointly modeling toxicity and efficacy as time-to-event outcomes. Applied Statistics 58(5), 719–736.
Zang, Y. , Lee, J. J. , Yuan, Y. (2014). Adaptive designs for identifying optimal biologic dose for molecularly targeted agents. Clinical Trials 11(3), 319–327.
Zhang, W. , Sargent, D. J. , Mandrekar, S. (2006) An adaptive dose-finding design incorporating both toxicity and efficacy. Statistics in Medicine 25, 2365–2383.
Zhong, W. , Carlin, B. P. , Koopmeiners, J. S. (2013). Flexible link continual reassessment methods for trivariate binary outcome phase I/II trials. Journal of Statistical Theory and Practice 7, 442–455.
Zhong, W. , Koopmeiners, J. S. , Carlin, B. P. (2012). A trivariate continual reassessment method for phase I/II trials of toxicity, efficacy, and surrogate efficacy. Statistics in Medicine 30, 3885–3895.
Zhou, Y. , Whitehead, J. , Bonvini, E. , Stevens, J. W. (2006). Bayesian decision procedures for binary and continuous bivariate dose-escalation studies. Pharmaceutical Statistics 5, 125–133.
Zohar, S. , Chevret, S. (2007). Recent developments in adaptive designs for phase I/II dose-finding studies. Journal of Biopharmaceutical Statistics 17, 1071–1083.

Zohar, S. , O'Quigley, J. (2006). Identifying the most successful dose (MSD) in dose-finding studies in cancer. Pharmaceutical Statistics 5, 187–199.
Zohar, S. , O'Quigley, J. (2006). Optimal designs for estimating the most successful dose. Statistics in Medicine 25, 4311–4320.

Designing Early-Phase Drug Combination Trials

M. K. Riviere , F. Dubois , and S. Zohar . Competing designs for drug combination in phase I dose-finding clinical trials. Statistics in Medicine, 34(1):1–12, 2015.
M. R. Conaway , S. Dunbar , and S. D. Peddada . Designs for single- or multiple-agent phase I trials. Biometrics, 60(3):661–669, 2004.
G. Yin and Y. Yuan . A latent contingency table approach to dose finding for combinations of two agents. Biometrics, 65(3):866–875, 2009.
G. Yin and Y. Yuan . Bayesian dose finding in oncology for drug combinations by copula regression. Journal of the Royal Statistical Society: Series C (Applied Statistics), 58(2):211–224, 2009.
T. M. Braun and S. F. Wang . A hierarchical Bayesian design for phase I trials of novel combinations of cancer therapeutic agents. Biometrics, 66(3):805–812, 2010.
N. A. Wages , M. R. Conaway , and J. O'Quigley . Continual reassessment method for partial ordering. Biometrics, 67(4):1555–1563, 2011.
J. O'Quigley , M. Pepe , and L. Fisher . Continual reassessment method: A practical design for phase I clinical trials in cancer. Biometrics, 46:33–48, 1990.
T. M. Braun and N. Jia . A generalized continual reassessment method for two-agent phase I trials. Statistics in Biopharmaceutical Research, 5:105–115, 2013.
M. K. Riviere , Y. Yuan , F. Dubois , and S. Zohar . A Bayesian dose-finding design for drug combination clinical trials based on the logistic model. Pharmaceutical Statistics, 13(4):247–257, 2014.
C. Y. Cai , Y. Yuan , and Y. Ji . A Bayesian phase I/II design for oncology clinical trials of combining biological agents. Journal of the Royal Statistical Society: Series C, 63:159–173, 2014.
M. K. Riviere , Y. Yuan , F. Dubois , and S. Zohar . A Bayesian dose-finding design for clinical trials combining a cytotoxic agent with a molecularly yargeted agent. Journal of the Royal Statistical Society: Series C, 64:215–229, 2015.
J. O'Quigley and L. Z. Shen . Continual reassessment method: A likelihood approach. Biometrics, 52(2):673–684, 1996.
Y. Chu , H. Pan , and Y. Yuan . Adaptive dose modification for phase I clinical trials. Statistics in Medicine, 35(20):3497–3508, 2016.
S. Y. Liu and Y. Yuan . Bayesian optimal interval designs for phase I clinical trials. Journal of the Royal Statistical Society: Series C (Applied Statistics), 64(3):507–523, 2015.
Y. Yuan , K. R. Hess , S. G. Hilsenbeck , and M. R. Gilbert . Bayesian optimal interval design: A simple and well-performing design for phase I oncology trials. Clinical Cancer Research, 22:4291–4301, 2016.
R. E. Barlow , D. J. Bartholomew , J. M. Bremner , and H. D. Brunk . Statistical inference under order restrictions: The theory and application of isotonic regression. John Wiley & Sons, New York, 1972.
R. Lin and G. Yin . Bayesian optimal interval design for dose finding in drug-combination trials. Statistical Methods in Medical Research, 2015. doi:10.1177/0962280215594494.
Y. Yuan and G. Yin . Sequential continual reassessment method for two-dimensional dose finding. Statistics in Medicine, 27(27):5664–5678, 2008.
L. Zhang and Y. Yuan . A simple Bayesian design to identify the maximum tolerated dose contour for drug-combination trials. Statistics in Medicine, 2016. doi:10.1002/sim.7095.
P. F. Thall , R. E. Millikan , P. Mueller , and S. J. Lee . Dose-finding with two agents in phase I oncology trials. Biometrics, 59(3):487–496, 2003.
K. Wang and A. Ivanova . Two-dimensional dose finding in discrete dose space. Bio-metrics, 61(1):217–222, 2005.
A. P. Mander and M. J. Sweeting . A product of independent β probabilities dose escalation design for dual-agent phase I trials. Statistics in Medicine, 34(8):1261–1276, 2015.
B. Gordon , D. Richard , P. Carolyn , and R. Tim . Isotonic regression in two independent variables. Journal of the Royal Statistical Society: Series C (Applied Statistics), 33(3):352–357, 1984.
A. I. Daud , M. T. Ashworth , J. Strosberg , J. W. Goldman , et al. Phase I dose-escalation trial of checkpoint kinase 1 inhibitor MK-8776 as monotherapy and in combination with gemcitabine in patients with advanced solid tumors. Journal of Clinical Oncology, 33(9):10601066, 2015.
Y. Yuan and G. Yin . Bayesian phase I/II adaptively randomized oncology trials with combined drugs. Annal of Applied Statistics, 5(2A):924–942, 2011.

Dose–Schedule Finding in Early-Phase Clinical Trials

T. M. Braun , Z. Yuan , and P. F. Thall . Determining a maximum-tolerated schedule of a cytotoxic agent. Biometrics, 61:335–343, 2013.
T. M. Braun , P. F. Thall , H. Q. Nguyen , and M. de Lima . Simultaneously optimizing dose and schedule of a new cytotoxic agent. Clinical Trials, 4:113–124, 2007.
C. A. Liu and T. M. Braun . Parametric non-mixture cure models for schedule finding of therapeutic agents. Journal of the Royal Statistical Society: Series C (Applied Statistics), 58:225–236, 2009.
P. F. Thall , H. Q. Nguyen , T. M. Braun , and M. H. Qazilbash . Using joint utilities of the times to response and toxicity to adaptively optimize schedule dose regimes. Biometrics, 69:673–682, 2013.
J. Zhang and T. M. Braun . A phase I Bayesian adaptive design to simultaneously optimize dose and schedule assignments both between and within patients. Journal of American Statistical Association, 108:892–901, 2013.

M. de Lima , S. Giralt , P. F. Thall , L. de Padua Silva , U. Popat , C. Hosing , X. Wang , E. J. Shpall , R. B. Jones , M. Qazilbash , G. McCormick , B. S. Andersson , K. Komanduri , A. Alousi , A. Gulbis , T. M. Braun , H. Q. Nguyen , P. Kebriaei , R. Champlin , and G. Garcia-Manero . Maintenance therapy with low dose azacitidine after allogenic hematopoietic stem cell transplantation for recurrent acute myelogenous leukemia or myelodysplastic syndrome: A dose and schedule finding study. Cancer, 116:5420–5431, 2010.

N. A. Wages , J. O'Quigley , and M. R. Conaway . Phase I design for completely or partially ordered treatment schedules. Statistics in Medicine, 33:569–579, 2013.

Y. Li , B. N. Bekele , Y. Ji , and J. D. Cook . Dose-schedule finding in phase I/II clinical trials using a Bayesian isotonic transformation. Statistics in Medicine, 27:4895–4913, 2008.

B. Guo , Y. Li , and Y. Yuan . A dose-schedule finding design for phase I–II clinical trials. Journal of the Royal Statistical Society: Series C (Applied Statistics), 65:259–272, 2016.

C. Graux , A. Sonet , J. Maertens , J. Duyster , J. Greiner , Y. Chalandon , G. Martinelli , D. Hess , D. Heim , F. J. Giles , K. R. Kelly , A. Gianella-Borradori , B. Longerey , E. Asatiani , N. Rejeb , and O. G. Ottman . A phase I dose-escalation study of MSC1992371A, an oral inhibitor of aurora and other kinases, in advanced hematologic malignancies. Leukemia Research, 37:1100–1106, 2013.

T. Robertson , F. T. Wright , and R. Dykstra . Order Restricted Statistical Inference. John Wiley and Sons, New York, 1988.

N. A. Wages and M. R. Conaway . Specifications of a continual reassessment method for phase I trials of combined drugs. Pharmaceutical Statistics, 12:217–224, 2013.

N. A. Wages , M. R. Conaway , and J. O'Quigley . Continual reassessment method for partial ordering. Biometrics, 67:1555–1563, 2011.

M. L. Slevin , P. I. Clark , S. P. Joel , S. Malik , R. J. Osborne , W. Gregory , D. G. Lowe , R. H. Reznek , and P. F. W. Wrigley . A randomized trial to evaluate the effect of schedule on the activity of etoposide in small-cell lung cancer. Journal of Clinical Oncology, 7:1333–1340, 1989.

C. Blomqvist , I. Elomaa , P. Rissanen , P. Hietanen , K. Nevassari , and L. Helle . Influence of treatment schedule on toxicity and efficacy of cyclophosphamide, epirubicin, and fluorouracil in metastatic breast cancer: A randomized trial comparing weekly and every-4-week administration. Journal of Clinical Oncology, 11:467–473, 1993.

R. Gervais , A. Ducolone , J. L. Breton , D. Braun , B. Lebeau , F. Vaylet , D. Debieuvre , J. L. Pujol , J. Tredaniel , P. Clouet , and E. Quoix . Phase II randomized trial comparing docetaxel given every 3 weeks with weekly schedule as second-line therapy in patients with advanced non-small-cell lung cancer (NSCLC). Annals of Oncology, 16:90–96, 2005.

N. P. Shah , H. M. Kantarjian , D.W. Kim , D. Rea , P. E. Dorlhiac-Llacer , J. H. Milone , C. Nicaise , J. Vela-Ojeda , R. T. Silver , H. J. Khoury , A. Charbonnier , N. Khoroshko , R. L. Paquette , M. Deininger , R. H. Collins , I. Otero , T. Hughes , E. Bleickardt , L. Strauss , S. Francis , and A. Hochhaus . Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic-phase chronic myeloid leukemia. Journal of Clinical Oncology, 26:3204–3212, 2008.

R. Gyergyay , K. Nagyvanyi , I. Bodrogi , and Hungary National Institute of Oncology, Budapest. Decreased toxicity schedule of sunitinib in renal cell cancer: 2 weeks on/1 week off. Journal of Clinical Oncology, 27:suppl, abstract e16113, 2009.

N. P. Shah , C. Kasap , C. Weier , M. Balbas , J. M. Nicoll , E. Bleickardt , C. Nicaise , and C. L. Sawyers . Transient potent BCR-ABL inhibition is sufficient to commit chronic myeloid leukemia cells irreversibly to apoptosis. Cancer Cell, 14:485–493, 2008.

J.P. J. Issa , G.M. Guillermo , F. J. Giles , R. Mannari , D. Thomas , S. Faderl , E. Bayar , J. Lyons , C. S. Rosenfeld , J. Cortes , and H. M. Kantarjian . Phase I study of low-dose prolonged exposure schedules of the hypomethylating agent 5-aza-2′-deoxycytidine (decitabine) in hematopoietic malignancies. Blood, 103:1635–1640, 2004.

Dale J. R. Global cross-ratio models for bivariate, discrete, ordered responses. Biometrics, 42:909–917, 1986.

W. R. Gilks , N. G. Best , and K. K. C. Tan . Adaptive rejection Metropolis sampling within Gibbs sampling. Journal of the Royal Statistical Society: Series C (Applied Statistics), 44:455–472, 1995.

S. Dunbar and S. Peddada . Bayesian inference on order-constrained parameters in generalized linear models. Biometrics, 59:286–295, 2003.

M. Conaway , S. Dunbar , and S. Peddada . Designs for single- or multiple-agent phase I trials. Biometrics, 60:661–669, 2004.

P. I. Clark , M. L. Slevin , S. P. Joel , R. J. Osborne , D. I. Talbot , P. W. Johnson , R. Reznek , T. Masud , W. Gregory , and P. F. W. Wrigley . A randomized trial of two etoposide schedules in small-cell lung cancer: The influence of pharmacokinetics on efficacy and toxicity. Journal of Clinical Oncology, 12:1427–1435, 1994.

J. H. Albert and S. Chib . Bayesian analysis of binary and ploytomous response data. Journal of American Statistical Association, 88:669–679, 1993.

Patient Heterogeneity in Dose-Finding Trials

J. Babb and A. Rogatko . Patient specific dosing in a cancer phase I clinical trial. Statistics in Medicine, 20:2079–2090, 2001.

J. Babb , A. Rogatko , and S. Zacks . Cancer phase I clinical trials: Efficient dose escalation with overdose control. Statistics in Medicine, 17:1103–1120, 1998.

S. Bailey , B. Neuenschwander , G. Laird , and M. Branson . A Bayesian case study in oncology phase I combination dose-finding using logistic regression with covariates. Journal of Biopharmaceutical Statistics, 19:469–484, 2009.

B. Bekele and P. Thall . Dose-finding based on multiple toxicities in a soft tissue sarcoma trial. Journal of the American Statistical Association, 99:261–265, 2004.

A. Ivanova and K. Wang . Bivariate isotonic design for dose-finding with ordered groups. Statistics in Medicine, 25:2018–2026, 2006.

K. Kim , H. Kim , S. Sym , K. Bae , Y. Hong , H. Chang , J. Lee , Y. Kang , J. Lee , J. Shin , and T. Kim . A UGT1A1*28 and *6 genotype-directed phase I dose-escalation trial of irinotecan with fixed-dose capecitabine in Korean patients with metastatic colorectal cancer. Cancer Chemotherapy and Pharmacology, 71:1609–1617, 2013.

A. Legedza and J. Ibrahim . Heterogeneity in phase I clinical trials: Prior elicitation and computation using the continual reassessment method. Statistics in Medicine, 20:867–882, 2001.

S. Liu , H. Pan , J. Xia , Q. Huang , and Y. Yuan . Bridging continual reassessment method for phase I clinical trials in different ethnic populations. Statistics in Medicine, 34:1681–1694, 2015.

P. LoRusso , K. Venkatakrishnan , R. Ramanathan , J. Sarantopoulos , D. Mulkerin , S. Shibata , A. Hamilton , A. Dowlati , S. Mani , M. Rudek , C. Takimoto , R. Neuwirth , D. Esseltine , and P. Ivy . Pharmacokinetics and safety of bortezomib in patients with advanced

malignancies and varying degrees of liver dysfunction: Phase I NCI Organ Dysfunction Working Group Study NCI-6432. Clinical Cancer Research, 18(10): 1–10, 2012.
J. O'Quigley . Phase I and phase I/II dose finding algorithms using continual reassessment method. In Handbook of Statistics in Clinical Oncology, 2nd ed., J. Crowley and D. Ankherst (eds). Chapman and Hall/CRC Biostatistics Series, Boca Raton, FL, 2006.
J. O'Quigley and M. Conaway . Extended model-based designs for more complex dose-finding studies. Statistics in Medicine, 30:2062–2069, 2011.
J. O'Quigley and A. Iasonos . Bridging solutions in dose-finding problems. Journal of Biopharmaceutical Statistics, 6(2):185–197, 2014.
J. O'Quigley and X. Paoletti . Continual reassessment method for ordered groups. Bio-metrics, 59:430–440, 2003.
J. O'Quigley , M. Pepe , and L. Fisher . Continual reassessment method: A practical design for phase I clinical trials in cancer. Biometrics, 46(1):33–48, 1990.
J. O'Quigley , L. Shen , and A. Gamst . Two sample continual reassessment method. Journal of Biopharmaceutical Statistics, 9:17–44, 1999.
R. Ramanathan , M. Egorin , C. Takimoto , S. Remick , J. Doroshow , P. LoRusso , D. Mulkerin , J. Grem , A. Hamilton , A. Murgo , D. Potter , C. Belani , M. Hayes , B. Peng , and P. Ivy . Phase I and pharmacokinetic study of imatinib mesylate in patients with advanced malignancies and varying degrees of liver dysfunction: A study by the National Cancer Institute Organ Dysfunction Working Group. Journal of Clinical Oncology, 26:563–569, 2008.
M. Raphael , M.C. Le Deley , G. Vassal , and X. Paoletti . Operating characteristics of two independent sample design in phase I trials in paediatric oncology. European Journal of Cancer, 46:1392–1398, 2010.
T. Robertson , F. T. Wright , and R. Dykstra . Order Restricted Statistical Inference. John Wiley & Sons, New York, 1988.
L. Shen and J. O'Quigley . Continual reassessment method: A likelihood approach. Biometrics, 52(2):673–684, 1996.
M. Tighiouart , G. Cook-Wiens , and A. Rogatko . Incorporating a patient dichotomous characteristic in cancer phase I clinical trials using escalation with overdose control. Journal of Probability and Statistics, 2012. Article ID 567819, doi:10.1155/2012/567819.
N. Wages , P. Read , and G. Petroni . A phase I/II adaptive design for heterogeneous groups with application to a stereotactic body radiation therapy trial. Pharmaceutical Statistics, 14(4):302–310, 2015.
Z. Yuan and R. Chappell . Isotonic designs for phase I cancer clinical trials with multiple risk groups. Clinical Trials, 1(6):499–508, 2004.

Nonparametric Optimal Design in Adaptive Dose-Finding Studies

B. Storer . Design and analysis of phase I clinical trials. Biometrics, 45(3):925–937, 1989.
J. O'Quigley , M. Pepe , and L. Fisher . Continual reassessment method: A practical design for phase I clinical trials in cancer. Biometrics, 46(1):33–48, 1990.
J. Babb , A. Rogatko , and S. Zacks . Cancer phase I clinical trials: Efficient dose escalation with overdose control. Statistics in Medicine, 17:1103–1120, 1998.
M. Stylianou and N. Flournoy . Dose finding using the biased coin up-and-down design and isotonic regression. Biometrics, 58(1):171–177, 2002.
Y. Ji , Y. Li , and B. Bekele . Dose-finding in phase I clinical trials based on toxicity probability intervals. Clinical Trials, 4:235–244, 2007.
A. Iasonos and J. O'Quigley . Adaptive dose-finding studies: A review of model-guided phase I clinical trials. Journal of Clinical Oncology, 32:2505–2511, 2014.
J. O'Quigley , X. Paoletti , and J. Maccario . Non-parametric optimal design in dose finding studies. Biostatistics, 3:51–56, 2002.
S. Zohar and J. O'Quigley . Optimal designs for estimating the most successful dose. Statistics in Medicine, 25:4311–4320, 2006.
X. Paoletti , J. O'Quigley , and J. Maccario . Design efficiency in dose finnding studies. Computational Statistics and Data Analysis, 45:197–214, 2004.
X. Paoletti . Comparative evaluation of phase I trial designs, Ph.D. Thesis, University of Paris VII Jussieu, 2001.
Y. K. Cheung . Dose Finding by the Continual Reassessment Method. Chapman and Hall/CRC Biostatistics Series, New York, 2011.
N. Wages , M. Conaway , and J. O'Quigley . Performance of two-stage continual reassessment method relative to an optimal benchmark. Clinical Trials, 10:862–875, 2013.
J. O'Quigley and L. Shen . Continual reassessment method: A likelihood approach. Biometrics, 52:673–684, 1996.
J. O'Quigley and S. Zohar . Retrospective robustness of the continual reassessment method. Journal of Biopharmaceutical Statistics, 25:903–920, 2010.
N. A. Wages and C. Tait . Seamless phase I/II adaptive design for oncology trials of molecularly targeted agents. Journal of Biopharmaceutical Statistics, 20:1013–1025, 2015.
J. O'Quigley , M. Hughes , and T. Fenton . Dose-finding design for HIV studies. Biometrics, 57:1018–1029, 2001.
Y. K. Cheung . Simple benchmark for complex dose finding studies. Biometrics, 70:389–397, 2014.
B. Bekele and P. Thall . Dose-finding based on multiple toxicities in a soft tissue sarcoma trial. Journal of the American Statistical Association, 99:26–35, 2004.
S. Lee , B. Cheng , and Y. K. Cheung . Continual reassessment method with mutliple toxicity constraints. Biostatistics, 12:386–398, 2011.
S. Lee , D. Hershman , P. Martin , J. Leonard , and Y. K. Cheung. Toxicity burden score: A novel approach to summarize multiple toxic effects. Annals of Oncology, 23:537–541, 2012.

Practical Implementation: Protocol Development

Y. Cheung . Sample size formulae for the Bayesian continual reassessment method. Clin Trials, 10(6):852–861, 2013.

Y. Cheung and R. Chappell . Sequential designs for phase I clinical trials with late-onset toxicities. Biometrics, 56(4):1177–1182, 2000.

Y. Cheung and R. Chappell . A simple technique to evaluate model sensitivity in the continual reassessment method. Biometrics, 58(3):671–674, 2002.

C. Gatsonis and J. Greenhouse . Bayesian methods for phase I clinical trials. Stat Med J Clin Oncol, 11:1377–1389, 1992.

S. N. Goodman , M. L. Zahurak , and S. Piantadosi . Some practical improvements in the continual reassessment method for phase I studies. Stat Med, 14:1149–1161, 1995. doi:10.1002/sim.4780141102.

A. Iasonos , M. Gönen , and G. Bosl . Scientific review of phase I protocols with novel dose-escalation designs: How much information is needed? J Clin Oncol, 33(19):2221–2225, 2015.

A. Iasonos and J. O'Quigley . Adaptive dose-finding studies: A review of model-guided phase I clinical trials. J Clin Oncol, 32(23):2505–2511, 2014. doi:10.1200/JCO.2013.54.6051.

A. Iasonos and J. O'Quigley . Integrating the escalation and dose expansion studies into a unified phase I clinical trial. Contemp Clin Trials, 22(9):2114–2120, 2016.

A. Iasonos and J. O'Quigley . Interplay of priors and skeletons in two-stage continual reassessment method. Stat Med, 31:4321–4336, 2012. doi:10.1002/sim.5559.

A. Iasonos and J. O'Quigley . Phase I designs that allow for uncertainty in the attribution of adverse events. J R Stat Soc: Ser C, 2017. doi:10.1111/rssc.12195.

A. Iasonos and I. Ostrovnaya . Estimating the dose-toxicity curve in completed phase I studies. Stat Med, 30(17):2117–2129, 2011.

A. Iasonos , N. A. Wages , M. R. Conaway , K. Cheung , Y. Yuan , and J. O'Quigley . Dimension of model parameter space and operating characteristics in adaptive dose-finding studies. Stat Med, 2016. doi:10.1002/sim.6966.

A. Iasonos , A. S. Wilton , E. R. Riedel , V. E. Seshan , and D. R. Spriggs . A comprehensive comparison of the continual reassessment method to the standard 3 + 3 dose escalation scheme in phase I dose-finding studies. Clin Trials, 5(5):465–477, 2008. doi:10.1177/1740774508096474.A.

A. Iasonos , S. Zohar , and J. O'Quigley . Incorporating lower grade toxicity information into dose finding designs. Clin Trials, 8(4):370–379, 2011. doi:10.1016/j.biotechadv.2011.08.021.Secreted.

X. Jia , L. Shing , and Y. Cheung . Characterization of the likelihood continual reassessment method. Biometrika, 101(3):599–612, 2014.

C. Le Tourneau , A. Stathis , L. Vidal , M. Moore , and L. Siu . Choice of starting dose for molecularly targeted agents evaluated in first-in-human phase I cancer clinical trials. J Clin Oncol, 28(8):1401–1407, 2010.

D. J. Lunn , A. Thomas , N. Best , and D. Spiegelhalter . WinBUGS—A Bayesian modelling framework: Concepts, structure, and extensibility. Stat Comput, 10:325–337, 2000.

P. Mathew , P. Thall , D. Jones , C. Perez , C. Bucana , P. Troncoso , S. Kim , I. Fidler , and C. Logothetis . Platelet-derived growth factor receptor inhibitor imatinib mesylate and docetaxel: A modular phase I trial in androgen-independent prostate cancer. J Clin Oncol, 22(16):3323–3329, 2004.

S. Møller . An extension of the continual reassessment methods using a preliminary up-and-down design in a dose finding study in cancer patients, in order to investigate a greater range of doses. Stat Med 14(9–10):911–922, 1995; discussion 923 .

J. H. Muler , C. McGinn , D. Normolle , T. Lawrence , D. Brown , G. Hejna , and M. M. Zalupsk . Phase I trial using a time-to-event continual reassessment strategy for dose escalation of cisplatin combined with gemcitabine and radiation therapy in pancreatic cancer. J Clin Oncol, 22(2):238–243, 2004.

J. H. Murphy and D. Hall . A logistic dose-ranging method for phase I clinical investigations trial. J Biopharm Stat, 7(4):635–647, 1997.

B. Neuenschwander , M. Branson , and T. Gsponer . Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med, 27:2420–2439, 2008.

J. O'Quigley . Another look at two phase I clinical trial designs. Stat Med, 18(20):2683–2690, 1999.

J. O'Quigley . Theoretical study of the continual reassessment method. J Stat Plan Inference, 136:1765–1780, 2006.

J. O'Quigley , X. Paoletti , and J. Maccario . Non-parametric optimal design in dose finding studies. Biostatistics, 3(1):51–56, 2002.

J. O'Quigley , M. Pepe , and L. Fisher . Continual reassessment method: A practical design for phase I clinical trials in cancer. Biometrics, 46(1):33–48, 1990.

J. O'Quigley and S. Chevret . Methods for dose finding studies in cancer clinical trials: a review and results of a Monte Carlo study. Stat Med, 10(11):1647–1664, 1991.

J. O'Quigley and E. Reiner . Miscellanea: A stopping rule for the continual reassessment method. Biometrika, 85(3):741–748, 1998.

J. O'Quigley and L. Z. Shen . Continual reassessment method: A likelihood approach. Biometrics, 52(2):673–684, 1996.

X. Paoletti and A. Kramar . A comparison of model choices for the continual reassessment method in phase I cancer trials. Stat Med, 28:3012–3028, 2009. doi:10.1002/sim.3682.

G. R. Petroni , N. A. Wages , G. Paux , and F. Dubois . Implementation of adaptive methods in early-phase clinical trials. Stat Med, 2016. doi:doi:10.1002/sim.6910.

J. Shu and J. O'Quigley . Dose-escalation designs in oncology: ADEPT and the CRM. Stat Med, 27(26):5345–5353, 2008.

B. E. Storer . Design and analysis of phase I clinical trials. Biometrics, 45(3):925–937, 1989.

B. Storer . Small-sample confidence sets for the MTD in a phase I clinical trial. Biometrics, 49(4):1117–1125, 1993.

M. Tighiouart and A. Rogatko . Dose finding with escalation with overdose control (EWOC) in cancer clinical trials. Stat Sci, 25(2):217–226, 2010.

M. Tighiouart , A. Rogatko , and J. Babb . Flexible Bayesian methods for cancer phase I clinical trials. Dose escalation with overdose control. Stat Med, 30(24):2183–2196, 2005.

N. A. Wages and M. R. Conaway . Specifications of a continual reassessment method design for phase I trials of combined drugs. Pharm Stat, 12(4):217–224, 2013. doi:10.1002/pst.1575.

N. Wages , M. Conaway , and J. O'Quigley . Dose-finding design for multi-drug combinations. Clin Trials, 8(4):380–389, 2011a.

N. A. Wages , M. R. Conaway , and J. O'Quigley . Continual reassessment method for partial ordering. Biometrics, 67(4):1555–1563, 2011. doi:10.1111/j.1541-0420.2011.01560.x.

G. M. Wheeler . Incoherent dose-escalation in phase I trials using the escalation with overdose control approach. Stat Papers, 1–11, 2016. doi:10.1007/s00362-016-0790-7.

G. M. Wheeler , M. J. Sweeting , and A. P. Mander . AplusB: A Web Application for Investigating A + B Designs for Phase I Cancer Clinical Trials. PLos One, 11(7): e0159026 , 2016. doi:10.1371/journal.pone.0159026.
G. M. Wheeler , M. Sweeting , A. Mander , S. Lee , and Y. Cheung . Modelling semiattributable toxicity in dual-agent phase I trials with non-concurrent drug administration. Stat Med, 2016. doi:doi:10.1002/sim.6912.
J. Whitehead and H. Brunier . Bayesian decision procedures for dose determining experiments. Stat Med, 14:885–893, 1995.
Y. Yuan and G. Yin . Bayesian model averaging continual reassessment method in phase I clinical trials. J Am Stat Assoc, 104(487):954–968, 2009.

Dose-Finding Studies in Phase II: Introduction and Overview

ICH. ICH Topic E4: Dose-response information to support drug registration, E4 , 1994. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002834.pdf.
J. Cross , H. Lee , A. Westelinck , J. Nelson , C. Grudzinskas , and C. Peck . Postmarketing drug dosage changes of 499 FDA-approved new molecular entities, 1980–1999. Pharmacoepidemiology and Drug Safety, 11(6):439–446, 2002.
L. V. Sacks , H. H. Shamsuddin , Y. I. Yasinskaya , K. Bouri , M. L. Lanthier , and R. E. Sherman . Scientific and regulatory reasons for delay and denial of FDA approval of initial applications for new drugs, 2000–2012. Journal of the American Medical Association, 311(4):378–384, 2014.
A. Mullard . Regulators and industry tackle dose finding issues. Nature Reviews Drug Discovery, 14:371–372, 2015.
European Medicines Agency. Report from dose finding workshop, 2015. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2015/04/WC500185864.pdf.
European Medicines Agency . Qualification opinion of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty, 2014. http://goo.gl/imT7IT.
Food and Drug Administration. Determination letter, 2016. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM508700.pdf.
A. K¨allén . Computational Pharmacokinetics. Chapman and Hall, Boca Raton, FL, 2007.
M. Lavielle . Mixed Effects Models for the Population Approach: Models, Tasks, Methods and Tools. CRC Press, Boca Raton, FL, 2014.
J. Gabrielsson and D. Weiner . Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications, 4th edition. Swedish Pharmaceutical Press, Stockholm, 2007.
T. P. Kenakin . A Pharmacology Primer: Theory, Applications, and Methods, 3rd edition. Elsevier Academic Press, London, UK, 2009.
N. Thomas , K. Sweeney , and V. Somayaji . Meta-analysis of clinical dose–response in a large drug development portfolio. Statistics in Biopharmaceutical Research, 6:302–317, 2014.
F. Lagarde , C. Beausoleil , S. M. Belcher , L. P. Belzunces , C. Emond , M. Gueret , and C. Rousselle . Non-monotonic dose–response relationships and endocrine disruptors: A qualitative method of assessment. Environmental Health, 14:13, 2015.
N. Ting . Dose Finding in Drug Development. Springer, New York, 2006.
F. Bretz , J. C. Hsu , J. C. Pinheiro , and Y. Liu . Dose finding—A challenge in statistics. Biometrical Journal, 50:480–504, 2008.
R. Hemmings . Philosophy and methodology of dose finding—A regulatory perspective. In S. Chevret , Ed., Statistical Methods for Dose-Finding Experiments, pp. 19–57. John Wiley & Sons, Hoboken, NJ, 2006.
C.- F. Burman , F. Miller , and K. W. Wong . Improving dose finding: A philosophic view. In A. Ping and S.-C. Chow , Eds, Handbook of Adaptive Designs in Pharmaceutical and Clinical Development, p. 10. CRC Press, Boca Raton, FL, 2011.
B. Bornkamp , F. Bretz , A. Dmitrienko , G. Enas , B. Gaydos , C.-H. Hsu , F. König , M. Krams , Q. Liu , B. Neuenschwander , T. Parke , J. C. Pinheiro , A. Roy , R. Sax , and F. Shen . Innovative approaches for designing and analyzing adaptive dose-ranging trials. Journal of Biopharmaceutical Statistics, 17:965–995, 2007.
V. Dragalin , B. Bornkamp , F. Bretz , F. Miller , S. Padmanabhan , N. Patel , I. Perevozskaya , J. Pinheiro , and J. Smith . A simulation study to compare new adaptive dose-ranging designs. Statistics in Biopharmaceutical Research, 487–512, 2010. doi:10.1198/sbr.2010.09045.
N. Thomas . Hypothesis testing and Bayesian estimation using a sigmoid Emax model applied to sparse dose designs. Journal of Biopharmaceutical Statistics, 16:657–677, 2006.
B. Bornkamp . Practical considerations for using functional uniform prior distributions for dose–response estimation in clinical trials. Biometrical Journal, 56:947–962, 2014.
A. P. Grieve and M. Krams . ASTIN: A Bayesian adaptive dose–response trial in acute stroke. Clinical Trials, 2:340–351, 2005.
B. Bornkamp and K. Ickstadt . Bayesian nonparametric estimation of continuous monotone functions with applications to dose–response analysis. Biometrics, 65:198–205, 2009.
R. Prado and M. West . Time Series Modeling, Computation and Inference. Chapman and Hall, Boca Raton, FL, 2010.
S. M. Berry , B. P. Carlin , J. J. Lee , and P. Müller . Bayesian Adaptive Methods for Clinical Trials. CRC Press, Boca Raton, FL, 2011.
P. Müller , D. A. Berry , A. P. Grieve , and M. Krams . A Bayesian decision-theoretic dose finding trial. Decision Analysis, 3:197–207, 2006.
C. Kelly and J. Rice . Monotone smoothing and its applications to dose–response curves and the assessment of synergy. Biometrics, 46:1071–1085, 1990.
C. Köllmann , B. Bornkamp , and K. Ickstadt . Unimodal regression using Bernstein-Schoenberg splines and penalties. Biometrics, 70:783–793, 2014.
F. Bretz , J. C. Pinheiro , and M. Branson . Combining multiple comparisons and modeling techniques in dose–response studies. Biometrics, 61:738–748, 2005.
H. Dette , F. Bretz , A. Pepelyshev , and J. C. Pinheiro . Optimal designs for dose finding studies. Journal of the American Statisical Association, 103:1225–1237, 2008.
F. Bretz , H. Dette , and J. Pinheiro . Practical considerations for optimal designs in clinical dose finding studies. Statistics in Medicine, 29:731–742, 2010.
A. C. Atkinson , A. N. Donev , and R. D. Tobias . Optimum Experimental Design, with SAS. Oxford University Press, Oxford, UK, 2007.

V. V. Fedorov and S. L. Leonov . Optimal Design for Nonlinear Response Models. Chapman and Hall, Boca Raton, FL, 2014.
V. Dragalin , F. Hsuan , and S. K. Padmanabhan . Adaptive designs for dose finding studies based on the sigmoid Emax model. Journal of Biopharmaceutical Statistics, 17:1051–1070, 2007.
A. Ivanova , J. Bolognese , and I. Perevozskaya . Adaptive design based on t-statistic for dose–response trials. Statistics in Medicine, 27:1581–1592, 2008.
V. Dragalin , V. V. Fedorov , and Y. Wu . Two-stage design for dose finding that accounts for both efficacy and safety. Statistics in Medicine, 27:5156–5176, 2008.
S. Berry , W. Spinelli , G. S. Littman , J. Z. Liang , P. Fardipour , D. A. Berry , R. J. Lewis , and M. Krams . A Bayesian dose finding trial with adaptive dose expansion to flexibly assess efficacy and safety of an investigational drug. Clinical Trials, 7:121–135, 2010.
M. Vandemeulebroecke , F. Bretz , J. Pinheiro , and B. Bornkamp . Adaptive dose-ranging studies. In A. Ping and S.-C. Chow , Eds, Handbook of Adaptive Designs in Pharmaceutical and Clinical Development, p. 11. CRC Press, Boca Raton, FL, 2011.
B. Jones , G. Layton , H. Richardson , and N. Thomas . Model-based Bayesian adaptive dose finding designs for a phase II trial. Statistics in Biopharmaceutical Research, 3:276–287, 2011.
A. T. Cohen , R. Boyd , J. Mandema , L. DiCarlo , and R. Pak . An adaptive-design dose-ranging study of PD 0348292, an oral factor Xa inhibitor, for thromboprophylaxis after total knee replacement surgery. Journal of Thrombosis and Haemostasis, 11:1503–1510, 2013.
F. Mercier , B. Bornkamp , D. Ohlssen , and E. Wallstroem . Characterization of dose–response for count data using a generalized MCP-Mod approach in an adaptive dose-ranging trial. Pharmaceutical Statistics, 14(4):359–367.
H. Dette , B. Bornkamp , and F. Bretz . On the efficiency of two-stage response-adaptive designs. Statistics in Medicine, 32:1646–1660, 2013.
E. McCallum and B. Bornkamp . Accounting for parameter uncertainty in two-stage designs for phase II dose–response studies. In O. Sverdlov , Ed., Modern Adaptive Randomized Clinical Trials: Statistical and Practical Aspects, pp. 427–449. CRC Press, Boca Raton, FL, 2015.
F. Miller . When is an adaptive design useful in clinical dose finding trials? In E. Fackle-Fornius , Ed. Festschrift in Honor of Hans Nyquist on the Occasion of His 65th Birthday, pp. 28–43. Department of Statistics, Stockholm University, Stockholm, 2015. https://su.diva-portal.org/smash/get/diva2:881610/FULLTEXT01.pdf.
H. Tan , D. Gruben , J. French , and N. Thomas . A case study of model-based Bayesian dose response estimation. Statistics in Medicine, 30:2622–2633, 2011.
F. Bretz , T. Hothorn , and P. Westfall . Multiple Comparisons Using R. CRC Press, Boca Raton, FL, 2011.
Z. Antonijevic , J. Pinheiro , P. Fardipour , and R. J. Lewis . Impact of dose selection strategies used in phase II on the probability of success in phase III. Statistics in Biopharmaceutical Research, 2:469–486, 2010.
N. Patel , J. Bolognese , C. Chuang-Stein , D. Hewitt , A. Gammaitoni , and J. Pinheiro . Designing phase II trials based on program-level considerations a case study for neuropathic pain. Therapeutic Innovation and Regulatory Science, 46:439–454, 2012.
Z. Antonijevic , Ed. Optimization of Pharmaceutical R&D Programs and Portfolios. Springer, Heidelberg, Germany, 2015.

The MCP-Mod Methodology: Practical Considerations and the DoseFinding R Package

European Medicines Agency . Qualification opinion of MCP-Mod as an efficient statistical methodology for model-based design and analysis of phase II dose finding studies under model uncertainty, 2014. http://goo.gl/imT7IT.
J. W. Tukey , J. L. Ciminera , and J. F. Heyse . Testing the statistical certainty of a response to increasing doses of a drug. Biometrics, 41:295–301, 1985.
F. Bretz , J. C. Pinheiro , and M. Branson . Combining multiple comparisons and modeling techniques in dose–response studies. Biometrics, 61:738–748, 2005.
J. C. Pinheiro , B. Bornkamp , E. Glimm , and F. Bretz . Model-based dose finding under model uncertainty using general parametric models. Statistics in Medicine, 33:1646–1661, 2014.
B. Bornkamp , J. C. Pinheiro , and F. Bretz . DoseFinding: Planning and Analyzing Dose Finding Experiments. R Package Version 0.9-13, 2015.
R. P. Abelson and J. W. Tukey . Efficient utilisation of non-numerical information in quantitative analysis: General theory and the case of simple order. Annals of Mathematical Statistics, 34:1347–1369, 1963.
W. Schaafsma and L. J. Smid . Most stringent somewhere most powerful tests against alternatives restricted by a number of linear inequalities. Annals of Mathematical Statistics, 37:1161–1172, 1966.
H. Mukerjee , T. Roberston , and F. T. Wright . Comparison of several treatments with a control using multiple contrasts. Journal of the American Statistical Association, 82:902–910, 1987.
S. T. Buckland , K. P. Burnham , and N. H. Augustin . Model selection: An integral part of inference. Biometrics, 53:603–618, 1997.
B. Bornkamp . Comparison of model-based and model-free approaches for the analysis of dose–response studies, Diploma thesis, Fachbereich Statistik, Universität Dortmund, Germany, 2006.
B. Bornkamp , F. Bretz , and J. C. Pinheiro . Request for CHMP qualification opinion, 2013. http://www.ema.europa.eu/docs/enGB/documentlibrary/Other/2014/02/WC500161026.pdf.
F. König . Confirmatory testing for a beneficial treatment effect in dose-response studies using MCP-Mod and an adaptive interim analysis, July 9, 2015 . Isaac Newton Institute, http://www.turing-gateway.cam.ac.uk/sites/default/files/asset/doc/1606/Franz%20Konig.pdf.
B. Bornkamp , F. Bretz , H. Dette , and J. C. Pinheiro . Response-adaptive dose-finding under model uncertainty. Annals of Applied Statistics, 5:1611–1631, 2011.
V. Dragalin , B. Bornkamp , F. Bretz , F. Miller , S. K. Padmanabhan , N. Patel , I. Perevozskaya , J. C. Pinheiro , and J. R. Smith . A simulation study to compare new adaptive dose-ranging designs. Statistics in Biopharmaceutical Research, 2:487–512, 2010.
Y. Franchetti , S. J. Anderson , and A. R. Sampson . An adaptive two-stage dose–response design method for establishing proof of concept. Journal of Biopharmceutical Statistics, 23:1124–1154, 2013.
F. Miller . Adaptive dose-finding: Proof of concept with type I error control. Biometrical Journal, 52:577–589, 2010.

S. Krasnozhon , A. Graf , B. Bornkamp , F. Bretz , G. Wassmer , and F. König . Adaptive designs for confirmatory model based decisions using MCP-Mod. Poster presented at the 35th Annual Conference of the International Society for Clinical Biostatistics, Vienna, Austria, 2014.
N. Benda . Model-based approaches for time-dependent dose finding with repeated binary data. Statistics in Medicine, 29:1096–1106, 2010.
B. Klingenberg . Proof of concept and dose estimation with binary responses under model uncertainty. Statistics in Medicine, 28:274–292, 2009.
Food and Drug Administration . Guidance for industry: Exposure-response relationships—Study design, data analysis, and regulatory applications, 2003. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072109.pdf.
J. R. Nedelman , D. B. Rubin , and L. B. Sheiner . Diagnostics for confounding in PK/PD models for oxcarbazepine. Statistics in Medicine, 26(2):290–308, 2007.
B. Bornkamp , F. Bretz , A. Dmitrienko , G. Enas , B. Gaydos , C. H. Hsu , F. König , M. Krams , Q. Liu , B. Neuenschwander , T. Parke , J. C. Pinheiro , A. Roy , R. Sax , and F. Shen . Innovative approaches for designing and analyzing adaptive dose-ranging trials (with discussion). Journal of Biopharmaceutical Statistics, 17:965–995, 2007.
European Medicines Agency . Report from dose finding workshop, 2014. http://www.ema.europa.eu/docs/enGB/documentlibrary/Report/2015/04/WC500185864.pdf.
A. Hamlett , N. Ting , R. C. Hanumara , and J. S. Finman . Dose spacing in early dose response clinical trial designs. Drug Information Journal, 36:855–864, 2002.
H. Dette , F. Bretz , A. Pepelyshev , and J. C. Pinheiro . Optimal designs for dose finding studies. Journal of the American Statisical Association, 103:1225–1237, 2008.
F. Bretz , H. Dette , and J. C. Pinheiro . Practical considerations for optimal designs in clinical dose finding studies. Statistics in Medicine, 29:731–742, 2010.
H. Dette , C. Kiss , N. Benda , and F. Bretz . Optimal designs for dose finding studies with an active control. Journal of the Royal Statistical Society, Series B, 76:265–295, 2014.
H. Dette , K. Kettelhake , and F. Bretz . Designing dose finding studies with an active control for exponential families. Biometrika, 102(4):937–950, 2015.
H. Helms , N. Benda , and T. Friede . Point and interval estimators of the target dose in clinical dose-finding studies with active control. Journal of Biopharmaceutical Statistics, 25:939–957, 2015.
H. Helms , N. Benda , P. Zinserling , T. Kneib , and T. Friede . Spline-based procedures for dose-finding studies with active control. Statistics in Medicine, 34:232–248, 2015.
N. Thomas . Hypothesis testing and Bayesian estimation using a sigmoid Emax model applied to sparse dose designs. Journal of Biopharmaceutical Statistics, 16:657–677, 2006.
N. Thomas , K. Sweeney , and V. Somayaji . Meta-analysis of clinical dose–response in a large drug development portfolio. Statistics in Biopharmaceutical Research, 6:302–317, 2014.
J. C. Pinheiro , B. Bornkamp , and F. Bretz . Design and analysis of dose finding studies combining multiple comparisons and modeling procedures. Journal of Biopharmaceutical Statistics, 16:639–656, 2006.
J. Bernardo and A. Smith . Bayesian Theory. John Wiley & Sons, Chichester, UK, 1994.
J. C. Pinheiro , F. Bretz , and M. Branson . Analysis of dose–response studies—modeling approaches. In N. Ting , editor, Dose Finding in Drug Development, pp. 146–171. Springer, New York, 2006.
C. Baayen , P. Hougaard , and C. B. Pipper . Testing effect of a drug using multiple nested models for the dose-response. Biometrics, 71:417–427, 2015.
H. Dette , S. Titoff , S. Volgushev , and F. Bretz . Dose response signal detection under model uncertainty. Biometrics, 71:996–1008, 2015.
G. Gutjahr and B. Bornkamp . Likelihood ratio tests for a dose–response effect using multiple nonlinear regression models. Biometrics, 2016. doi:10.1111/biom.12563.
M. Fu . A resampling based approach in evaluation of dose–response models. Doctoral dissertation, Temple University, 2014.
C. Chatfield . Model uncertainty, data mining and statistical inference (with discussion). Journal of the Royal Statistical Society Series A, 158:419–466, 1995.
H. Leeb and B. M. Poetscher . Model selection and inference: Facts and fiction. Econometric Theory, 21:21–59, 2005.
L. Breiman . Bagging predictors. Machine Learning, 24:123–140, 1996.
K. Schorning , B. Bornkamp , F. Bretz , and H. Dette . Model selection versus model averaging in dose finding studies. Statistics in Medicine, 2016. doi:10.1002/sim.6991.
D. Verrier , S. Sivapregassam , and A. C. Solente . Dose-finding studies, MCP-Mod, model selection, and model averaging: Two applications in the real world. Clinical Trials, 11:476–484, 2014.
A. Wakana , I. Yoshimura , and C. Hamada . A method for therapeutic dose selection in a phase II clinical trial using contrast statistics. Statistics in Medicine, 26:498–511, 2007.
W. Wouter . The power and type I error of statistical analysis approaches for longitudinal toxicological data. M.Sc. thesis, University of Ghent, 2012.
A. Tao , Y. Lin , J. C. Pinheiro , and W. J. Shih . Dose finding method in joint modeling of efficacy and safety endpoints in phase II studies. International Journal of Statistics and Probability, 4:33–45, 2015.
H. Dette , K. Kettelhake , K. Schorning , W. K. Wong , and F. Bretz . Optimal designs for active controlled dose finding trials with efficacy-toxicity outcomes, 2016. Available at https://arXiv:1601.00797v1.
H. Dette , K. Moelenhoff , S. Volgushev , and F. Bretz . Equivalence of dose response curves, 2015. Available at https://arxiv.org/abs/1505.05266.
F. Bretz , J. C. Pinheiro , and M. Branson . On a hybrid method in dose finding studies. Methods of Information in Medicine, 43:457–461, 2004.
S. Gsteiger , F. Bretz , and W. Liu . Simultaneous confidence bands for non-linear regression models with application to population pharmacokinetic analyses. Journal of Biopharmaceutical Statistics, 21:708–725, 2011.
W. Liu . Simultaneous Inference for Regression. Taylor & Francis, Boca Raton, FL, 2010.

Z. Antonijevic , J. Pinheiro , P. Fardipour , and R. J. Lewis . Impact of dose selection strategies used in phase II on the probability of success in phase III. Statistics in Biopharmaceutical Research, 2(4):469–486, 2010.
O. Siddiqui , H. M. J. Hung , and R. O'Neill . MMRM vs. LOCF: A comprehensive comparison based on simulation study and 25 NDA datasets. Journal of Biopharmaceutical Statistics, 19(2):227–246, 2009.
M. Akacha and N. Benda . The impact of dropouts on the analysis of dose-finding studies with recurrent event data. Statistics in Medicine, 29:1635–1646, 2010.
B. Bornkamp , V. Bezlyak , and F. Bretz . Implementing the MCP-Mod procedure for dose–response testing and estimation. In S. Menon and R. C. Zink editors Modern Approaches to Clinical Trials Using SAS: Classical, Adaptive, and Bayesian Methods, pp. 193–224. SAS Institute Inc., Cary, NC, 2015.

Designing Phase II Dose-Finding Studies: Sample Size, Doses, and Dose Allocation Weights

B. Bornkamp , J. Pinheiro , and F. Bretz . Dose Finding: Planning and Analyzing Dose Finding Experiments. R Package Version 0.9-13, 2016.
ADDPLAN, Inc, an Aptiv Solutions Company . ADDPLAN DF Version 3.1 Methodology Overview, 2014.
A. Mullard . Regulators and industry tackle dose-finding issues. Nature Reviews Drug Discovery, 14:371–372, 2015.
European Medicines Agency . Report from dose finding workshop, 2015.
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2015/04/WC500185864.pdf.
B. Bornkamp , F. Bretz , A. Dmitrienko , G. Enas , B. Gaydos , C.H. Hsu , F. König , M. Krams , Q. Liu , B. Neuenschwander , T. Parke , J. C. Pinheiro , A. Roy , R. Sax , and F. Shen . Innovative approaches for designing and analyzing adaptive dose-ranging trials. Journal of Biopharmaceutical Statistics, 17:965–995, 2007.
A. C. Atkinson , A. N. Donev , and R. D. Tobias . Optimum Experimental Design, with SAS. Oxford University Press, Oxford, UK, 2007.
V. V. Fedorov and S. L. Leonov . Optimal Design for Nonlinear Response Models. Chapman and Hall, Boca Raton, 2014.
H. Dette , F. Bretz , A. Pepelyshev , and J. C. Pinheiro . Optimal designs for dose finding studies. Journal of the American Statisical Association, 103:1225–1237, 2008.
F. Bretz , H. Dette , and J. Pinheiro . Practical considerations for optimal designs in clinical dose finding studies. Statistics in Medicine, 29:731–742, 2010.
J. C. Pinheiro , B. Bornkamp , and F. Bretz . Design and analysis of dose finding studies combining multiple comparisons and modeling procedures. Journal of Biopharmaceutical Statistics, 16:639–656, 2006.
S. Kotz and S. Nadarajah . Multivariate t Distributions and Their Applications. Cambridge University Press, Cambridge, 2004.
A. Genz and F. Bretz . Methods for the computation of multivariate t-probabilities. Journal of Computational and Graphical Statistics, 11:950–971, 2002.
A. Genz , F. Bretz , and T. Hothorn . mvtnorm: Multivariate Normal and Distributions, R package, 2008.

Two-Stage Designs in Dose Finding

H. Dette , L. Haines , and L. Imhof . Maximin and Bayesian optimal designs for regression models. Statistica Sinica, 17:463–480, 2007.
H. Dette , F. Bretz , A. Pepelyshev , and J. Pinheiro . Optimal designs for dose-finding studies. Journal of the American Statistical Association, 103:1225–1237, 2008.
B. Bornkamp , F. Bretz , A. Dmitrienko , G. Enas , B. Gaydos , C. H. Hsu , F. Koenig , M. Krams , Q. Liu , B. Neuenschwander , et al. Innovative approaches for designing and analyzing adaptive dose-ranging trials (with discussion). Statistics in Biopharmaceutical Research, 17:965–995, 2010.
V. Dragalin , B. Bornkamp , F. Bretz , F. Miller , S. K. Padmanabhan , N. Patel , I. Perevozskaya , J. Pinheiro , and J. R. Smith . A simulation study to compare new adaptive dose-ranging designs. Statistics in Biopharmaceutical Research, 2:487–512, 2010.
F. Mercier , B. Bornkamp , D. Ohlssen , and E. Wallstroem . Characterization of dose–response for count data using a generalized MCP-Mod approach in an adaptive dose-ranging trial. Pharmaceutical Statistics, 14:359–367, 2015.
K. Selmaj , D. K. Li , H. P. Hartung , B. Hemmer , L. Kappos , M. S. Freedman , O. Stüve , P. Rieckmann , X. Montalban , T. Ziemssen , et al. Siponimod for patients with relapsingremitting multiple sclerosis (BOLD): An adaptive dose-ranging, randomised, phase 2 study. The Lancet Neurology, 12:756–767, 2013.
S. K. Padmanabhan and V. Dragalin . Adaptive Dc-optimal designs for dose finding based on a continuous efficacy endpoint. Biometrical Journal, 52:836–852, 2010.
H. Dette , B. Bornkamp , and F. Bretz . On the efficiency of two-stage response-adaptive designs. Statistics in Medicine, 32:1646–1660, 2012.
J. Quinlan , B. Gaydos , J. Maca , and M. Krams . Barriers and opportunities for implementation of adaptive designs in pharmaceutical product development. Clinical Trials, 7:167–173, 2010.
V. Dragalin . Optimal design of experiments for delayed responses in clinical trials. In mODa 10—Advances in Model-Oriented Design and Analysis, D. Ucinski , A. C. Atkinson , M. Patan (eds), pp. 55–61. Springer, New York, 2013.
B. Bornkamp , F. Bretz , H. Dette , and J. Pinheiro . Response-adaptive dose-finding under model uncertainty. Annals of Applied Statistics, 5:1611–1631, 2011.
V. Fedorov , Y. Wu , and R. Zhang . Optimal dose-finding designs with correlated continuous and discrete responses. Statistics in Medicine, 31: 217–234, 2011.
F. Bretz , F. Koenig , W. Brannath , E. Glimm , and M. Posch . Adaptive designs for confirmatory clinical trials. Statistics in Medicine, 28:1181–1217, 2009.
ADDPLAN, Inc., An Aptiv Solutions Company . ADDPLAN MC Version 6.1 User Manual. Aptiv Solutions, Cologne, Germany, 2014.

J. Kiefer and J. Wolfowitz . The equivalence of two extremum problems. Canadian Journal of Mathematics, 12:363–366, 1960.
ADDPLAN, Inc ., An Aptiv Solutions Company . ADDPLAN DF—Adaptive Designs, Plans and Analysis—Dose Finding Module. Aptiv Solutions, Cologne, Germany, 2014.
B. Bornkamp , J. Pinheiro , and F. Bretz . Dosefinding: Planning and analyzing dose finding experiments. R Package Version 0.9–13, 2015.
R. L. Lalonde , K. G. Kowalski , M. M. Hutmacher , W. Ewy , D. J. Nichols , P. A. Milligan , B. W. Corrigan , P. A. Lockwood , S. A. Marshall , L. J. Benincosa , et al. Model-based drug development. Clinical Pharmacology and Therapeutics, 82:21–32, 2007.
R. Berger and J. Hsu . Bioequivalence trials, intersection-union tests and equivalence confidence sets. Statistical Science, 11:283–319, 1996.
B. Bornkamp , J. Pinheiro , and F. Bretz . MCPMod: An R package for the design and analysis of dose-finding studies. Journal of Statistical Software, 29:1–23, 2010.
E. McCallum and B. Bornkamp . Accounting for parameter uncertainty in two-stage designs for phase II dose-response studies. In Modern Adaptive Randomized Trials: Statistical and Practical Aspects, pp. 427–450. CRC Press, Boca Raton, 2012.

Longitudinal Dose–Response Models

N. Schlesinger , E. Mysler , H.Y. Lin , M. De Meulemeester , J. Rovensky , U. Arulmani , A. Balfour , G. Krammer , P. Sallstig , and A. So . Canakinumab reduces the risk of acute gouty arthritis flares during initiation of allopurinol treatment: Results of a double-blind, randomised study. Annals of the Rheumatic Diseases, 70(7):1264–1271, 2011.
H. Tan , D. Gruben , J. French , and N. Thomas . A case study of model-based Bayesian dose response estimation. Statistics in Medicine, 30(21):2622–2633, 2011.
G. D. Schmith , R. Singh , R. Gomeni , O. Graff , A. G. Hamedani , J. S. Troughton , and S. M. Learned . Use of longitudinal dose–response modeling to support the efficacy and tolerability of alitretinoin in severe refractory chronic hand eczema (CHE). CPT: Pharmacometrics & Systems Pharmacology, 4(4):255–262, 2015.
G. E. P. Box and N. R. Draper . Empirical Model-Building and Response Surfaces. John Wiley & Sons, New York, 1987.
R. G. Langley , B. E. Elewski , M. Lebwohl , K. Reich , C. E. M. Griffiths , K. Papp , L. Puig , H. Nakagawa , L. Spelman , B. Sigurgeirsson , et al. Secukinumab in plaque psoriasis—Results of two phase 3 trials. New England Journal of Medicine, 371(4):326–338, 2014.
G. Levy . Kinetics of pharmacological effects. Clinical Pharmacology & Therapeutics, 7(3):362–363, 1966.
J. Gabrielsson and D. Weiner . Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications, 3rd edn. CRC Press, Boca Raton, FL, 2001.
D. Verotta and L. B. Sheiner . Semiparametric analysis of non-steady-state pharmacodynamic data. Journal of Pharmacokinetics and Biopharmaceutics, 19(6):691–712, 1991.
J. Gabrielsson , W. J. Jusko , and L. Alari . Modeling of dose–response-time data: Four examples of estimating the turnover parameters and generating kinetic functions from response profiles. Biopharmaceutics & Drug Disposition, 21(2):41–52, 2000.
P. Jacqmin , E. Snoeck , E. A. van Schaick , R. Gieschke , P. Pillai , J.L. Steimer , and P. Girard . Modelling response time profiles in the absence of drug concentrations: Definition and performance evaluation of the K-PD model. Journal of Pharmacokinetics and Pharmacodynamics, 34(1):57–85, 2007.
M. R. Lange and H. Schmidli . Analysis of clinical trials with biologics using dose–time–response models. Statistics in Medicine, 34(22):3017–3028, 2015.
F. G. Holz , J.F. Korobelnik , P. Lanzetta , P. Mitchell , U. Schmidt-Erfurth , S. Wolf , S. Markabi , H. Schmidli , and A. Weichselberger . The effects of a flexible visual acuity-driven ranibizumab treatment regimen in age-related macular degeneration: Outcomes of a drug and disease model. Investigative Ophthalmology & Visual Science, 51(1):405–412, 2010.
K. Wu , M. Looby , G. Pillai , G. Pinault , A. F. Drollman , and S. Pascoe . Population pharmacodynamic model of the longitudinal FEV1 response to an inhaled long-acting anti-muscarinic in COPD patients. Journal of Pharmacokinetics and Pharmacodynamics, 38(1):105–119, 2011.
M. Tod . Evaluation of drugs in pediatrics using K-PD models: Perspectives. Fundamental & Clinical Pharmacology, 22(6):589–594, 2008.
G. Segre . Kinetics of interaction between drugs and biological systems. Farmaco-Edizione Scientifica, 23(10):907–918, 1968.
T. Jacobs , R. Straetemans , G. Molenberghs , J. A. Bouwknecht , and L. Bijnens . A latent pharmacokinetic time profile to model dose-response survival data. Journal of Biopharmaceutical Statistics, 20(4):759–767, 2010.
M. Gibaldi and D. Perrier . Pharmacokinetics. CRC Press, Boca Raton, FL, 1982.
J. Gabrielsson and L. A. Peletier . Dose-response-time data analysis involving nonlinear dynamics, feedback and delay. European Journal of Pharmaceutical Sciences, 59:36–48, 2014.
D. M. Bates and D. G. Watts . Nonlinear Regression: Iterative Estimation and Linear Approximations. John Wiley & Sons, New York, 1988.
M. Davidian and D. M. Giltinan . Nonlinear Models for Repeated Measurement Data. CRC Press, Boca Raton, FL, 1995.
J. Pinheiro and D. Bates . Mixed-Effects Models in S and S-PLUS. Statistics and Computing. Springer, New York, 2000.
G. A. F. Seber and C. J. Wild . Nonlinear Regression. John Wiley & Sons, New York, 1989.
H. Schmidli , S. Gsteiger , S. Roychoudhury , A. O'Hagan , D. Spiegelhalter , and B. Neuenschwander . Robust meta-analytic-predictive priors in clinical trials with historical control information. Biometrics, 70(4):1023–1032, 2014.
B. Bornkamp . Functional uniform priors for nonlinear modeling. Biometrics, 68(3):893–901, 2012.
A. Gelman , J. B. Carlin , H. S. Stern , D. B. Dunson , A. Vehtari , and D. B. Rubin . Bayesian Data Analysis. Chapman & Hall, New York, 2014.
D. Lunn , C. Jackson , N. Best , A. Thomas , and D. Spiegelhalter . The BUGS Book: A Practical Introduction to Bayesian Analysis. Chapman & Hall/CRC Texts in Statistical Science. CRC Press, Baco Raton, FL, 2012.
M. Plummer . JAGS: A program for analysis of Bayesian graphical models using Gibbs sampling. In Proceedings of the 3rd International Workshop on Distributed Statistical Computing, Vol. 124, p. 125. Technical University Vienna, Austria, 2003.
A. Gelman , D. Lee , and J. Guo . Stan: A probabilistic programming language for Bayesian inference and optimization. Journal of Educational and Behavioral Statistics, 40(5):530–543, 2015.

W. Wang , K. M. Hallow , and D. A. James . A tutorial on RxODE: Simulating differential equation pharmacometric models in R. CPT: Pharmacometrics & Systems Pharmacology, 2015.
J. Pinheiro , D. Bates , S. DebRoy , D. Sarkar , and R Core Team . nlme: Linear and Nonlinear Mixed Effects Models, R Package Version 3.1-123, 2016.
S. D. Silvey . Optimal Design. Chapman & Hall, New York, 1980.
L. B. Sheiner . Learning versus confirming in clinical drug development. Clinical Pharmacology & Therapeutics, 61(3):275–291, 1997.
V. V. Fedorov and S. L. Leonov . Optimal Design for Nonlinear Response Models. CRC Press, Boca Raton, FL, 2013.
X. Fang and A. S. Hedayat . Locally D-optimal designs based on a class of composed models resulted from blending Emax and one-compartment models. The Annals of Statistics, 36(1):428–444, 2008.
H. Dette , A. Pepelyshev , and W. K. Wong . Optimal designs for composed models in pharmacokinetic–pharmacodynamic experiments. Journal of Pharmacokinetics and Pharmacodynamics, 39(3):295–311, 2012.
M. R. Lange and H. Schmidli . Optimal design of clinical trials with biologics using dose–time–response models. Statistics in Medicine, 33(30):5249–5264, 2014.
K. Chaloner and I. Verdinelli . Bayesian experimental design: A review. Statistical Science, 10(3):273–304, 1995.
D. V. Lindley . On a measure of the information provided by an experiment. The Annals of Mathematical Statistics, 26:986–1005, 1956.
E. G. Ryan , C. C. Drovandi , M. H. Thompson , and A. N. Pettitt . Towards Bayesian experimental design for nonlinear models that require a large number of sampling times. Computational Statistics & Data Analysis, 70:45–60, 2014.
E. G. Ryan , C. C. Drovandi , J. M. McGree , and A. N. Pettitt . A review of modern computational algorithms for bayesian optimal design. International Statistical Review, 84:128–154, 2015.
S. S. Saini , C. Bindslev-Jensen , M. Maurer , J.J. Grob , E. B. Baskan , M. S. Bradley , J. Canvin , A. Rahmaoui , P. Georgiou , O. Alpan , et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H 1 antihistamines: A randomized, placebo-controlled study. Journal of Investigative Dermatology, 135(1):67–75, 2015.
M. Maurer , K. Rosén , H.J. Hsieh , S. Saini , C. Grattan , A. Giménez-Arnau , S. Agarwal , R. Doyle , J. Canvin , A. Kaplan , et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. New England Journal of Medicine, 368(10):924–935, 2013.
A. Kaplan , D. Ledford , M. Ashby , J. Canvin , J. L. Zazzali , E. Conner , J. Veith , N. Kamath , P. Staubach , T. Jakob , et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. Journal of Allergy and Clinical Immunology, 132(1):101–109, 2013.

Multiple Test Strategies for Comparing Several Doses with a Control in Confirmatory Trials

ICH . ICH Topic E9: Notes for Guidance on Statistical Principles for Clinical Trials. International Conference on Harmonization, London, UK, 1998.
EMEA . CPMP: Points to Consider on Multiplicity Issues in Clinical Trials. Committee for Medical Product for Human Use, London, UK, 2002.
Y. Hochberg and A. C. Tamhane . Multiple Comparison Procedures. John Wiley, New York, 1987.
F. Bretz , T. Hothorn , and P. Westfall . Multiple Comparisons Using R. CRC Press, Boca Raton, FL, 2010.
S. Holm . A simple sequentially rejective multiple test procedure. Scandinavian Journal of Statistics, 6:65–70, 1979.
R. J. Simes . An improved Bonferroni procedure for multiple tests of significance. Biometrika, 73:751–754, 1986.
K. Lu . Graphical approaches using a Bonferroni mixture of weighted Simes tests. Statistics in Medicine, 35(22):4041–4055, 2016.
Y. Hochberg . A sharper Bonferroni procedure for multiple significance testing. Biometrika, 75:800–802, 1988.
C. W. Dunnett . A multiple comparison procedure for comparing several treatments with a control. Journal of the American Statistical Association, 50(272):1096–1121, 1955.
A. Genz and F. Bretz . Methods for the computation of multivariate t-probabilities. Journal of Computational and Graphical Statistics, 11:950–971, 2002.
W. Maurer , L. A. Hothorn , and W. Lehmacher . Multiple comparisons in drug clinical trials and preclinical assays: A priori ordered hypotheses. Biometrie in der Chemisch-Pharmazeutischen Industrie, 6:3–18, 1995.
P. H. Westfall and A. Krishen . Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. Journal of Statistical Planning and Inference, 99(1):25–40, 2001.
R. Marcus , E. Peritz , and K. R. Gabriel . On closed testing procedures with special reference to ordered analysis of variance. Biometrika, 63(3):655–660, 1976.
G. Hommel . A stagewise rejective multiple test procedure based on a modified Bonferroni test. Biometrika, 75:383–386, 1988.
F. König . Confirmatory testing for a beneficial treatment effect in dose-response studies using MCP-Mod and an adaptive interim analysis, July 9, 2015. Isaac Newton Institute, http://www.turing-gateway.cam.ac.uk/sites/default/files/asset/doc/1606/Franz%20Konig.pdf.
B. Bornkamp , J. Pinheiro , and F. Bretz . DoseFinding: Planning and analyzing dose finding experiments. R Package Version 0.9–13, 2016.

A Regulatory View on Dose-Finding Studies and on the Value of Dose–Exposure–Response Analysis

Antoniou, M. , Jorgensen, A. L. , and Kolamunnage-Dona, R. , 2016. Biomarker-guided adaptive trial designs in phase II and phase III: A methodological review. PLOS One, 11(2):e0149803.
Cross, J. , Lee, H. , Westelinck, A. , Nelson, J. , Grudzinskas, C. , and Peck, C. , 2002. Postmarketing drug dosage changes of 499 FDA-approved new molecular entities, 1980–1999. Pharmacoepidemiology and Drug Safety, 11(6):439–446.
European Medicines Agency , 2012. Guideline on the Investigation of Drug Interactions. Committee for Human Medicinal Products (CHMP). (CPMP/EWP/560/95/Rev. 1 Corr. 2**). Retrieved from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf.

European Medicines Agency , 2015a. Lenvima EPAR. Committee for Human Medicinal Products (CHMP).
European Medicines Agency , 2015b. Report from Dose Finding Workshop, EMA/117491/2015.
European Medicines Agency , 2016a. Guideline on the Clinical Development of Medicinal Products for the Treatment of HIV Infection. Committee for Human Medicinal Products (CHMP). Retervied from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500209918.pdf.
European Medicines Agency , 2016b. Guideline on the Use of Pharmacokinetics and Pharmacodynamics in the Development of Antimicrobial Medicinal Products. Committee for Human Medicinal Products (CHMP). Retrieved from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500210982.pdf.
Food and Drug Administration , 2014. Guidance for Industry–Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications. US Food and Drug Administration, Washington, DC. Retrieved from http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072109.pdf.
International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) , 1994. Guidance on Dose-Response Information to Support Drug Registration, E4. Accessed at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E4/Step4/E4_Guideline.pdf.
Kang, D. , Schwartz, J. B. , and Verotta, D. , 2005. Sample size computations for PK/PD population models. Journal of Pharmacokinetics and Pharmacodynamics, 32(5–6):685–701.
Karlsson, K. E. , Vong, C. , Bergstrand, M. , Jonsson, E. N. , and Karlsson, M. O. , 2013. Comparisons of analysis methods for proof-of-concept trials. CPT: Pharmacometrics & Systems Pharmacology, 2(1):1–8.
Lee, J. J. , Gu, X. , and Liu, S. , 2010. Bayesian adaptive randomization designs for targeted agent development. Clinical Trials, 7(5):584–596.
Marshall, S. F. , Burghaus, R. , Cosson, V. , Cheung, S. Y. A. , Chenel, M. , Della Pasqua, O. , Frey, N. , Hamren, B. , Harnisch, L. , Ivanow, F. , and Kerbusch, T. , 2015. Good practices in model-informed drug discovery and development (MID3): Practice, application and documentation. CPT: Pharmacometrics & Systems Pharmacology, 5:93–122.
Ogungbenro, K. , Aarons, L. , and Graham, G. , 2006. Sample size calculations based on generalized estimating equations for population pharmacokinetic experiments. Journal of Biopharmaceutical Statistics, 16(2):135–150.
Ogungbenro, K. , Dokoumetzidis, A. , and Aarons, L. , 2009. Application of optimal design methodologies in clinical pharmacology experiments. Pharmaceutical Statistics, 8(3):239–252.
Sacks, L. V. , Shamsuddin, H. H. , Yasinskaya, Y. I. , Bouri, K. , Lanthier, M. L. , and Sherman, R. E. , 2014. Scientific and regulatory reasons for delay and denial of FDA approval of initial applications for new drugs, 2000–2012. JAMA, 311(4):378–384.
Santen, G. , van Zwet, E. , Danhof, M. , and Della Pasqua, O. , 2009. From trial and error to trial simulation. Part 1: The importance of model-based drug development for antidepressant drugs. Clinical Pharmacology and Therapeutics, 86(3):248–254.
Svensson, E. M. , Acharya, C. , Clauson, B. , Dooley, K. E. , and Karlsson, M. O. , 2016. Pharmacokinetic interactions for drugs with a long half-life—Evidence for the need of model-based analysis. The AAPS Journal, 18(1):171–179.
Tannenbaum, S. J. , Holford, N. H. , Lee, H. , Peck, C. C. , and Mould, D. R. , 2006. Simulation of correlated continuous and categorical variables using a single multivariate distribution. Journal of Pharmacokinetics and Pharmacodynamics, 33(6):773–794.
Vong, C. , Bergstrand, M. , Nyberg, J. , and Karlsson, M. O. 2012. Rapid sample size calculations for a defined likelihood ratio test-based power in mixed-effects models. AAPS Journal, 14(2):176–186.