

# Fundamentals of Clinical Trials



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# Fundamentals of Clinical Trials

Fourth Edition



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# Preface

The clinical trial is “the most definitive tool for evaluation of the applicability of clinical research.” It represents “a key research activity with the potential to improve the quality of health care and control costs through careful comparison of alternative treatments” [1]. It has been called on many occasions, “the gold standard” against which all other clinical research is measured.

Although many clinical trials are of high quality, a careful reader of the medical literature will notice that a large number have deficiencies in design, conduct, analysis, presentation, and/or interpretation of results. Improvements have occurred over the past few decades, but too many trials are still conducted without adequate attention to its fundamental principles. Certainly, numerous studies could have been upgraded if the authors had had a better understanding of the fundamentals.

Since the publication of the first edition of this book, a large number of other texts on clinical trials have appeared, most of which are indicated here [2–21]. Several of them, however, discuss only specific issues involved in clinical trials. Additionally, many are no longer current. The purpose of this fourth edition is to update areas in which major progress has been made since the publication of the third edition. We have revised most chapters considerably and added one on ethical issues.

In this book, we hope to assist investigators in improving the quality of clinical trials by discussing fundamental concepts with examples from our experience and the literature. The book is intended both for investigators with some clinical trial experience and for those who plan to conduct a trial for the first time. It is also intended to be used in the teaching of clinical trial methodology and to assist members of the scientific and medical community who wish to evaluate and interpret published reports of trials. Although not a technically oriented book, it may be used as a reference for graduate courses in clinical trials. Those readers who wish to consult more technical books and articles are provided with the relevant literature.

Because of the considerable differences in background and objectives of the intended readership, we have not attempted to provide exercises at the end of each chapter. We have, however, found two exercises to be quite useful and that apply most of the fundamental principles of this text. First, ask students to critique a clinical trial article from the current literature. Second, require students to develop a protocol on a medically relevant research question that is of interest to

the student. These draft protocols often can be turned into protocols that are implemented. This book is also not meant to serve as guide to regulatory requirements. Those differ among countries and frequently change. Rather, as the title indicates, we hope to provide the fundamentals of clinical trials design, conduct, analysis, and reporting.

The first chapter describes the rationale and phases of clinical trials. Chapter 2 is an addition and it covers selected ethical issues. Chapter 3 describes the questions that clinical trials seek to answer and Chap. 4 discusses the populations from which the study samples are derived. The strengths and weaknesses of various kinds of study designs, including noninferiority trials, are reviewed in Chap. 5. The process of randomization is covered in Chap. 6. In Chap. 7, we discuss the importance of and difficulties in maintaining blindness. How the sample size is estimated is covered in Chap. 8. Chapter 9 describes what constitutes the baseline measures. Chapter 10 reviews recruitment techniques and may be of special interest to investigators not having ready access to trial participants. Methods for collecting high quality data and some common problems in data collection are included in Chap. 11. Chapters 12 and 13 focus on the important areas of assessment of adverse events and quality of life. Measures to enhance and monitor participant adherence are presented in Chap. 14. Chapter 15 reviews techniques of survival analysis. Chapter 16 covers data and safety monitoring. Which data should be analyzed? The authors develop this question in Chap. 17 by discussing reasons for not withdrawing participants from analysis. Topics such as subgroup analysis and meta-analysis are also addressed. Chapter 18 deals with phasing out clinical trials, and Chap. 19 with reporting and interpretation of results. Finally, in Chap. 20 we present information about multicenter, including multinational, studies, which have features requiring special attention. Several points covered in the final chapter may also be of value to investigators conducting single center studies.

This book is a collaborative effort and is based on knowledge gained over almost 4 decades in developing, conducting, overseeing, and analyzing data from a number of clinical trials. This experience is chiefly, but not exclusively, in trials of heart and lung diseases, AIDS, and cancer. As a consequence, many of the examples cited are based on work done in these fields. However, the principles are applicable to clinical trials in general. The reader will note that although the book contains examples that are relatively recent, others are quite old. The fundamentals of clinical trials were developed in those older studies, and we cite them because, despite important advances, many of the basic features remain unchanged.

In the first edition, the authors had read or were familiar with much of the relevant literature on the design, conduct, and analysis of clinical trials. Today, that task would be nearly impossible as the literature over the past 3 decades has expanded enormously. The references used in this text are not meant to be exhaustive but rather to include the older literature that established the fundamentals and newer publications that support those fundamentals.

The views expressed in this book are those of the authors and do not necessarily represent the views of the institutions with which the authors have been or are affiliated.

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# Contents

<b>1</b>	<b>Introduction to Clinical Trials .....</b>	<b>1</b>
	Fundamental Point .....	2
	What Is a Clinical Trial?.....	2
	Clinical Trial Phases .....	3
	Phase I Studies.....	4
	Phase II Studies .....	6
	Phase III/IV Trials .....	7
	Why Are Clinical Trials Needed?.....	8
	Problems in the Timing of a Trial .....	11
	Study Protocol.....	12
	References.....	14
<b>2</b>	<b>Ethical Issues .....</b>	<b>19</b>
	Fundamental Point .....	20
	Planning and Design .....	20
	Does the Question Require a Clinical Trial?.....	20
	Randomization.....	21
	Control Group.....	22
	Protection from Conflict of Interest .....	23
	Informed Consent .....	24
	Conduct .....	27
	Trials in Developing Countries.....	27
	Recruitment .....	28
	Safety and Efficacy Monitoring.....	29
	Early Termination for Other than Scientific or Safety Reasons .....	29
	Privacy and Confidentiality .....	30
	Data Falsification.....	31
	Reporting.....	31
	Publication Bias, Suppression, and Delays .....	31
	Conflicts of Interest and Publication .....	32
	References.....	32

<b>3 What Is the Question?</b>	37
Fundamental Point .....	37
Selection of the Questions .....	38
Primary Question.....	38
Secondary Questions .....	38
Adverse Events .....	39
Ancillary Questions, Substudies.....	40
Natural History .....	40
Large, Simple Clinical Trials.....	41
Superiority vs. Noninferiority Trials .....	41
Intervention .....	42
Response Variables .....	43
Specifying the Question .....	45
Biomarkers and Surrogate Response Variables .....	47
General Comments.....	50
References.....	51
<b>4 Study Population</b> .....	55
Fundamental Point .....	55
Definition of Study Population .....	55
Rationale.....	55
Considerations in Defining the Study Population .....	57
Generalization .....	62
Recruitment.....	64
References.....	65
<b>5 Basic Study Design</b> .....	67
Fundamental Point .....	68
Randomized Control Trials .....	69
Nonrandomized Concurrent Control Studies.....	72
Historical Controls and Databases .....	73
Strengths of Historical Control Studies .....	73
Limitations of Historical Control Studies.....	74
Role of Historical Controls.....	78
Cross-Over Designs .....	79
Withdrawal Studies .....	81
Factorial Design .....	82
Group Allocation Designs.....	83
Hybrid Designs .....	84
Large, Simple and Pragmatic Clinical Trials .....	84
Studies of Equivalency and Noninferiority .....	86
Adaptive Designs .....	90
References.....	91

<b>6 The Randomization Process.....</b>	97
Fundamental Point .....	97
Fixed Allocation Randomization .....	98
Simple Randomization .....	99
Blocked Randomization .....	100
Stratified Randomization.....	102
Adaptive Randomization Procedures.....	105
Baseline Adaptive Randomization Procedures.....	105
Response Adaptive Randomization.....	108
Mechanics of Randomization .....	109
Recommendations.....	111
Appendix.....	111
Adaptive Randomization Algorithm .....	111
References.....	113
<b>7 Blindness .....</b>	119
Fundamental Point .....	119
Types of Trials.....	119
Unblinded .....	119
Single-Blind.....	120
Double-Blind .....	122
Triple-Blind .....	123
Protecting the Double-Blind Design.....	124
Matching of Drugs.....	125
Coding of Drugs .....	127
Official Unblinding.....	127
Inadvertent Unblinding.....	128
Assessment and Reporting of Blindness.....	129
References.....	131
<b>8 Sample Size .....</b>	133
Fundamental Point .....	133
Statistical Concepts.....	134
Dichotomous Response Variables.....	139
Two Independent Samples.....	139
Paired Dichotomous Response .....	144
Adjusting Sample Size to Compensate for Nonadherence.....	145
Sample Size Calculations for Continuous Response Variables .....	147
Two Independent Samples.....	147
Paired Data .....	148
Sample Size for Repeated Measures.....	150
Sample Size Calculations for “Time to Failure” .....	152
Sample Size for Testing “Equivalency” or Noninferiority of Interventions.....	155

Sample Size for Cluster Randomization .....	157
Estimating Sample Size Parameters.....	159
Multiple Response Variables.....	161
References.....	162
<b>9 Baseline Assessment.....</b>	<b>169</b>
Fundamental Point .....	169
Uses of Baseline Data .....	169
Baseline Comparability.....	170
Stratification.....	171
Subgrouping.....	171
Pharmacogenetics .....	172
Changes of Baseline Measurement.....	173
Natural History Analyses.....	173
What Constitutes a True Baseline Measurement? .....	174
Screening for Participants .....	174
Regression Toward the Mean.....	175
Interim Events.....	176
Uncertainty About Qualifying Diagnosis .....	177
Contamination of the Intervention .....	178
Assessment of Baseline Comparability .....	179
Testing for Baseline Imbalance.....	180
References.....	181
<b>10 Recruitment of Study Participants.....</b>	<b>183</b>
Fundamental Point .....	183
Considerations Before Participant Enrollment .....	184
Selection of Study Sample .....	184
Common Recruitment Problems.....	184
Planning .....	186
Recruitment Sources .....	188
Conduct .....	190
Monitoring .....	192
Approaches to Lagging Recruitment .....	194
References.....	197
<b>11 Data Collection and Quality Control .....</b>	<b>199</b>
Fundamental Point .....	200
Problems in Data Collection .....	201
Major Types .....	201
Minimizing Poor Quality Data.....	203
Design of Protocol and Manual .....	203
Development of Forms.....	203
Training and Certification .....	204
Pretesting.....	205

Techniques to Reduce Variability .....	206
Data Entry .....	206
Quality Monitoring .....	207
Monitoring of Forms.....	208
Monitoring of Procedures .....	208
Monitoring of Drug Handling .....	209
Audits Leader.....	210
References.....	212
<b>12 Assessing and Reporting Adverse Events.....</b>	<b>215</b>
Fundamental Point .....	216
Clinical Trials in the Assessment of Adverse Events .....	216
Strengths .....	216
Limitations in Identification of SAEs .....	217
Determinants of Adverse Events.....	218
Definitions.....	218
Classification of Adverse Events .....	219
Ascertainment .....	220
Dimensions .....	221
Length of Follow-Up .....	221
Analyzing Adverse Events.....	223
Types of Analysis.....	223
Analysis of Data from Nonadherent Participants .....	224
Reporting of Adverse Events .....	224
Scientific .....	224
Published Reports .....	225
Regulatory.....	226
Identification of SAEs.....	227
Potential Solutions .....	228
References.....	229
<b>13 Assessment of Health-Related Quality of Life.....</b>	<b>233</b>
Fundamental Point .....	234
Defining Health-Related Quality of Life .....	234
Primary HRQL Dimensions.....	235
Additional HRQL Dimensions .....	236
Uses of Health-Related Quality of Life .....	237
Methodological Issues .....	239
Trial Design.....	239
Study Population.....	240
Intervention .....	240
Selection of HRQL Instruments.....	241
Modes of Administration .....	242
Frequency of Assessment (Acute Vs. Chronic).....	243
Symptom Expression (Episodic Vs. Constant).....	244

Functional Impact (Present Vs. Absent) .....	244
Interpretation.....	244
Scoring of HRQL Measures.....	245
Determining the Significance of HRQL Measures .....	245
Utility Measures/Preference Scaling.....	246
References.....	247
<b>14 Participant Adherence .....</b>	<b>251</b>
Fundamental Point .....	252
Considerations Before Participant Enrollment .....	253
Design Factors .....	253
Participant Factors.....	255
Maintaining Good Participant Adherence.....	258
Adherence Monitoring .....	262
Dealing with Low Adherence .....	265
Special Populations.....	266
References.....	267
<b>15 Survival Analysis.....</b>	<b>269</b>
Fundamental Point .....	269
Estimation of the Survival Curve.....	270
Kaplan–Meier Estimate .....	274
Cutler–Ederer Estimate .....	278
Comparison of Two Survival Curves .....	279
Point-by-Point Comparison .....	279
Comparison of Median Survival Times .....	279
Total Curve Comparison .....	280
Generalizations .....	285
Covariate Adjusted Analysis.....	287
References.....	290
<b>16 Monitoring Response Variables .....</b>	<b>293</b>
Fundamental Point .....	295
Monitoring Committee.....	295
Repeated Testing for Significance .....	299
Decision for Early Termination .....	301
Decision to Extend a Trial .....	310
Statistical Methods Used in Monitoring .....	313
Classical Sequential Methods .....	314
Group Sequential Methods .....	315
Flexible Group Sequential Procedures: Alpha Spending Functions.....	318
Applications of Group Sequential Boundaries .....	321

<b>Contents</b>	<b>xvii</b>
Asymmetric Boundaries.....	324
Curtailed Sampling and Conditional Power Procedures.....	325
Other Approaches .....	330
Trend Adaptive Designs and Sample Size Adjustments.....	332
References.....	334
 <b>17 Issues in Data Analysis .....</b>	<b>345</b>
Fundamental Point .....	345
Which Participants Should Be Analyzed? .....	346
Ineligibility.....	347
Nonadherence .....	350
Missing or Poor Quality Data .....	355
Competing Events .....	362
Composite Outcomes .....	363
Covariate Adjustment .....	364
Surrogates as Covariates .....	365
Baseline Variables as Covariates.....	368
Subgroup Analyses .....	371
Not Counting Some Events.....	376
Comparison of Multiple Variables.....	377
Use of Cutpoints .....	378
Noninferiority Trial Analysis.....	379
Meta-Analysis of Multiple Studies .....	382
Rationale and Issues.....	382
Statistical Methods.....	386
Analysis Following Trend Adaptive Designs .....	389
Appendix.....	389
Mantel-Haenszel Statistic.....	389
References.....	390
 <b>18 Closeout.....</b>	<b>399</b>
Fundamental Point .....	399
Termination Procedures .....	399
Planning .....	399
Scheduling of Closeout Visits .....	400
Final Response Ascertainment.....	401
Transfer of Posttrial Care .....	402
Data and Other Study Material .....	403
Cleanup and Verification.....	403
Storage .....	404
Dissemination of Results .....	405
Poststudy Follow-Up.....	407
References.....	409

<b>19 Reporting and Interpreting of Results .....</b>	411
Fundamental Point .....	412
Guidelines for Reporting.....	413
Authorship.....	413
Disclosure of Conflict of Interest.....	414
Presentation of Data.....	414
Interpretation.....	415
Publication Bias .....	416
Did the Trial Work as Planned? .....	417
Baseline Comparability.....	417
Blindness.....	417
Adherence and Concomitant Treatment .....	418
Limitations .....	418
Analysis.....	419
How Do the Findings Compare with Results from Other Studies? .....	420
What are the Clinical Implications of the Findings? .....	421
References.....	422
<b>20 Multicenter Trials .....</b>	427
Fundamental Point .....	427
Reasons for Multicenter Trials.....	428
Conduct of Multicenter Trials.....	429
Globalization of Trials .....	436
General Comments.....	437
References.....	438
<b>Index.....</b>	443