

Contents

PART I. INTRODUCTION AND CURRENT STATUS	1	3.4.6 Ongoing planning and priority assessment	21
		3.4.7 Minimal overlap of activities	21
Chapter 1. Introduction	3	Chapter 4. Single-center versus multicenter trials	23
1.1 Definition	3	4.1 Definition	23
1.2 History of clinical trials	3	4.2 National Institutes of Health (NIH) count of single-center and multicenter trials	24
1.3 Terminology conventions	8	4.3 Design characteristics of single-center versus multicenter trials	24
1.4 Focus	10	4.4 The pros and cons of single-center versus multicenter trials	25
Chapter 2. Clinical trials: A state-of-the-art assessment	11	4.5 Initiation of single-center versus multicenter trials	27
2.1 Existing inventories	11	4.6 Investigator incentives for single-center versus multicenter trials	27
2.2 Trials as seen through the published literature	13	4.7 Timing of single-center versus multicenter trials	28
2.3 Small sample size: A common design flaw	15	4.8 Cost of single-center versus multicenter trials	29
2.4 Future needs	15		
Chapter 3. The activities of a clinical trial	18	Chapter 5. Coordinating and other resource centers in multicenter trials	30
3.1 Stages of a clinical trial	18	5.1 Introduction	30
3.2 Division of responsibilities	18	5.2 Coordinating centers	30
3.3 Common impediments to the orderly performance of activities	19	5.2.1 General activities	31
3.3.1 Separation of responsibilities in government-initiated trials	19	5.2.2 Location	31
3.3.2 Structural deficiencies	19	5.2.3 Staffing	33
3.3.3 Overlap of activities from stage to stage	19	5.2.4 Equipment	34
3.3.4 Inadequate time for planning, development, and implementation	20	5.2.5 Relative cost	34
3.3.5 Inadequate funding	20	5.2.6 Internal allocation of funds	36
3.4 Approaches to ensure orderly transition of activities	20	5.3 Central laboratories	36
3.4.1 Phased initiation of data intake	20	5.4 Reading centers	38
3.4.2 An adequate organizational structure	20	5.5 Project offices	38
3.4.3 Opportunities for design modifications in sponsor-initiated trials	21	5.6 Other resource centers	39
3.4.4 Certification as a management tool	21	Chapter 6. Cost and related issues	40
3.4.5 Realistic timetables	21	6.1 Government expenditures for clinical trials	40
		6.2 Who should finance clinical trials?	42
		6.3 Factors that influence the cost of a trial	45

6.3.1 Design	45	PART II. DESIGN PRINCIPLES AND PRACTICES	63
6.3.2 Planning	45		
6.3.3 Multipurpose studies	46		
6.3.4 Ancillary studies	46	Chapter 8. Essential design features of a controlled clinical trial	65
6.3.5 Equating the data collection needs of the trial with those for patient care	46	8.1 Introduction	65
6.3.6 Undisciplined data collection philosophy	46	8.2 Choice of the test and control treatments	65
6.4 Cost control procedures	46	8.3 Principles in the selection of the outcome measure	66
6.4.1 General cost control procedures	46	8.4 Principles in establishing comparable study groups	67
6.4.2 Method of funding	47	8.5 Principles of masking and bias control	68
6.4.3 Cost reviews	47		
6.4.4 Periodic priority assessments	47	Chapter 9. Sample size and power estimates	71
6.4.5 Review and funding for ancillary studies	47	9.1 Sequential versus fixed sample size designs	72
6.4.6 Justification of data items	48	9.2 Sample size and power calculations as planning guides	74
6.4.7 Use of low-technology procedures	48	9.3 Specifications for sample size calculations	74
6.5 Need for better cost data	48	9.3.1 Number of treatment groups	74
		9.3.2 Outcome measure	75
Chapter 7. Impact of clinical trials on the practice of medicine	49	9.3.3 Follow-up period	76
7.1 Introduction	49	9.3.4 Alternative treatment hypothesis	76
7.2 Factors influencing treatment acceptance	49	9.3.5 Detectable treatment difference	76
7.2.1 Prior opinion and previous experience with a treatment	49	9.3.5.1 Binary outcome measures	76
7.2.2 Clinical relevance of the outcome measure	50	9.3.5.2 Continuous outcome measures	77
7.2.3 Degree to which test treatment simulates real- world treatment	50	9.3.6 Error protection	77
7.2.4 Consistency of findings with previous results	50	9.3.7 Choice of allocation ratio	78
7.2.5 Direction of results	50	9.3.8 Losses to follow-up	78
7.2.6 Importance of the treatment	50	9.3.9 Losses due to treatment noncompliance	78
7.2.7 Cost and payment schedule	50	9.3.10 Treatment lag time	79
7.2.8 Treatment facilities and resources	50	9.3.11 Stratification for control of baseline risk factors	80
7.2.9 Design and operating features of the trial	51	9.3.12 Degree of type I and II error protection for multiple comparisons	80
7.2.10 Study population	51	9.3.13 Degree of type I and II error protection for multiple looks for safety monitoring	80
7.2.11 Method of presentation	51	9.3.14 Degree of type I and II error protection for multiple outcomes	81
7.2.12 Counterforces	51		
7.3 Impact assessment	52		
7.4 The University Group Diabetes Program: A case study	52		
7.5 Ways to increase the impact of clinical trials	62		

10.8.6	Illustration 6: Double-masked allocation schedule using the Moses-Oakford algorithm and a table of random numbers	110	12.5	Item construction	126
10.8.7	Illustration 7: Sample CDP double-masked allocation schedule	112	12.5.1	General	126
Chapter 11. The study plan		113	12.5.2	Language and terminology	126
11.1	Introduction	113	12.5.3	Use of items from other studies	127
11.2	Design factors and details to be addressed in the study plan	113	12.5.4	Closed- versus open-form items	127
11.3	Objective and specific aims	113	12.5.5	Response checklist	128
11.4	The treatment plan	114	12.5.6	<i>Unknown, don't know, and uncertain</i> as response options	129
11.5	Composition of the study population	116	12.5.7	Measurement and calculation items	129
11.6	The plan for patient enrollment and follow-up	118	12.5.8	Instruction items	130
11.7	The plan for close-out of patient follow-up	118	12.5.9	Time and date items	130
Chapter 12. Data collection considerations		119	12.5.10	Birthdate and age items	130
12.1	Introduction	119	12.5.11	Identifying items	131
12.2	Factors influencing the clinic visit schedule	120	12.5.12	Tracer items	131
12.2.1	Introduction	120	12.5.13	Reminder and documentation items	131
12.2.2	Baseline clinic visit schedule	120	12.6	Layout and format considerations	132
12.2.3	Follow-up clinic visit schedule	121	12.6.1	Page layout	132
12.2.4	Visit time limits	122	12.6.2	Paper size and weight	132
12.3	Data requirements by type of visit	122	12.6.3	Type style and form reproduction	132
12.3.1	General considerations	122	12.6.4	Location of instructional material	133
12.3.2	Data needed at baseline visits	122	12.6.5	Form color coding	133
12.3.3	Data needed at follow-up visits	124	12.6.6	Form assembly	134
12.4	Considerations affecting item construction	124	12.6.7	Arrangement of items on forms	134
12.4.1	Implicit versus explicit item form	124	12.6.8	Format	135
12.4.2	Interviewer-completed versus patient-completed items	125	12.6.8.1	Items designed for unformatted written replies	135
12.4.3	Questioning strategy	125	12.6.8.2	Items requiring formatted written replies	135
12.4.4	Single versus multiple-use forms	126	12.6.8.3	Items answered by check marks	135
12.4.5	Format and layout	126	12.6.9	Location of form and patient identifiers	136
			12.6.10	Format considerations for data entry	136
			12.7	Flow and storage of completed data forms	136
			PART III. EXECUTION		139
			Chapter 13. Preparatory steps in executing the study plan		141
			13.1	Essential approvals and clearances	141

13.1.1 IRB and other approvals	141	Chapter 16. Quality assurance	166
13.1.2 IND and IDE submissions	142	16.1 Introduction	166
13.1.3 OMB clearance	144	16.2 Ongoing data intake: An essential prerequisite for quality assurance	166
13.2 Approval maintenance	144	16.3 Data editing	168
13.2.1 IRB	144	16.4 Replication as a quality control measure	171
13.2.2 FDA	144	16.5 Monitoring for secular trends	172
13.2.3 Other approvals	145	16.6 Data integrity and assurance procedures	173
13.3 Developing study handbooks and manuals of operations	145	16.7 Performance monitoring reports	173
13.4 Testing the data collection procedures	145	16.8 Other quality control procedures	175
13.5 Developing and testing the data management system	147	16.8.1 Site visits	175
13.6 Training and certification	147	16.8.2 Quality control committees and centers	176
13.7 Phased approach to data collection	148	16.8.3 Data audits	176
Chapter 14. Patient recruitment and enrollment	149	PART IV. DATA ANALYSIS AND INTERPRETATION	177
14.1 Recruitment goals	149	Chapter 17. The analysis database	179
14.2 Methods of patient recruitment	149	17.1 Introduction	179
14.3 Troubleshooting	152	17.2 Choice of computing facility	179
14.4 The patient shake-down process	152	17.3 Organization of programming resources	181
14.5 The ethics of recruitment	153	17.4 Operational requirements for database maintenance	181
14.6 Patient consent	153	17.5 Data security precautions	182
14.6.1 General guidelines	153	17.6 Filing and storing the original study records	182
14.6.2 The consent process	154	17.7 Preparation of analysis tapes	184
14.6.3 Documentation of the consent	156	Chapter 18. Data analysis requirements and procedures	185
14.6.4 What constitutes an informed consent?	156	18.1 Basic analysis requirements	185
14.6.5 Maintenance of consents	157	18.2 Basic analytic methods	187
14.7 Randomization and initiation of treatment	157	18.2.1 Simple comparisons of proportions	187
14.8 Zelen consent procedure	157	18.2.2 Lifetable analyses	188
Chapter 15. Patient follow-up, closeout, and post-trial follow-up	159	18.2.3 Other descriptive methods	192
15.1 Introduction	159	18.3 Adjustment procedures	193
15.2 Maintenance of investigator and patient interest during follow-up	159	18.3.1 Subgrouping	193
15.2.1 Investigator interest	159	18.3.2 Multiple regression	194
15.2.2 Patient interest	160	18.4 Comment on significance estimation	195
15.3 Losses to follow-up	160		
15.4 Close-out of patient follow-up	163		
15.5 Termination stage	164		
15.6 Post-trial patient follow-up	165		

Chapter 19. Questions concerning the design, analysis, and interpretation of clinical trials	196	21.2 NIH grant proposals	220
19.1 Introduction	196	21.2.1 Deadlines and review process	220
19.2 Questions concerning the study design	196	21.2.2 Application outline	221
19.3 Questions concerning the source of study patients	197	21.2.3 Content suggestions	221
19.4 Questions concerning randomization	198	21.3 NIH requests for contract proposals	223
19.5 Questions concerning masking	200	21.3.1 Deadlines and review process	223
19.6 Questions concerning the comparability of the treatment groups	201	21.3.2 Factors to consider when deciding whether or not to respond	223
19.7 Questions concerning treatment administration	201	21.3.3 The response	224
19.8 Questions concerning patient follow-up	202	21.4 The study budget	224
19.9 Questions concerning the outcome measure	203	21.4.1 Grants	224
19.10 Questions concerning data integrity	203	21.4.2 Contracts	225
19.11 Questions concerning data analysis	204	21.5 Budget breakdown	225
19.12 Questions concerning conclusions	206	21.5.1 Personnel	226
Chapter 20. Interim data analyses for treatment monitoring	208	21.5.2 Consultants	228
20.1 Introduction	208	21.5.3 Equipment	228
20.2 Procedural issues	209	21.5.4 Supplies	228
20.3 Treatment monitoring reports	209	21.5.5 Travel	228
20.4 Special statistical problems	211	21.5.6 Patient care costs	228
20.4.1 The multiple looks problem	212	21.5.7 Alterations and renovations	228
20.4.2 The multiple outcomes problem	212	21.5.8 Consortium/contractual costs	228
20.4.3 The multiple comparisons problem	213	21.5.9 Other expenses	229
20.5 Data dredging as an analysis technique	214	21.5.10 Budget justification	229
20.6 The pros and cons of stopping rules in monitoring trials	215	21.6 Preparation and submission of the funding proposal	229
20.7 Steps in terminating a treatment	216	21.7 Negotiations and award	230
PART V. MANAGEMENT AND ADMINISTRATION	217	21.8 Grant and contract administration	230
Chapter 21. Funding the trial	219	21.9 Special funding issues	230
21.1 Introduction	219	21.9.1 Direct versus indirect funding for multicenter trials	230
		21.9.2 Work unit payment schedules	231
		Chapter 22. Essential management functions and responsibilities	232
		22.1 Management requirements	232
		22.2 Management deficiencies	232
		22.2.1 Failure to delegate authority with responsibility	232
		22.2.2 Inadequate provisions for personnel backup	233
		22.2.3 Ill-defined decision-making structure	233
		22.2.4 Inadequate funding	233
		22.2.5 Lack of performance standards	233

22.2.6 Failure to separate essential activities	233	23.8 Center-to-center communications	250
22.2.7 Ill-defined communication structure	233		
22.3 Patient safety monitoring: An essential function	233	PART VI. REPORTING PROCEDURES	253
22.4 Advisory-review functions	234		
22.5 Committee procedures	234	Chapter 24. Study publication and information policies	255
22.6 Preferred separation of responsibilities and functions	235	24.1 Information constraints	255
22.6.1 Separation of treatment administration and data collection personnel in unmasked trials	235	24.2 Publication questions	256
22.6.2 Separation of personnel responsible for patient care and safety monitoring	236	24.2.1 When to publish?	256
22.6.3 Separation of investigative and advisory-review roles	236	24.2.2 Presentation or publication?	256
22.6.4 Separation of sponsor and investigative roles	236	24.2.3 Where to publish?	257
22.6.5 Separation of data collection and data processing functions	236	24.2.4 What to publish?	257
22.6.6 Separation of centers in multicenter trials	237	24.2.5 Journal supplements versus regular issues	258
22.7 Special management issues	237	24.3 Authorship and internal review procedures	259
22.7.1 Disclosure requirements for potential conflicts of interest	237	24.3.1 Introduction	259
22.7.2 Level of compensation for committee members outside the trial	238	24.3.2 Individual versus corporate authorship	259
22.7.3 Review and approval of proposed ancillary studies	238	24.3.3 Writing responsibilities	260
22.7.4 Publication and internal editorial review procedures	238	24.3.4 Credit rosters	260
22.7.5 Publicity and information access policy issues	239	24.3.5 Internal review procedures	260
		24.4 Information access policy issues	261
Chapter 23. Committee structures of multicenter trials	240	24.4.1 Access to study data during the trial by outside parties	261
23.1 Introduction	240	24.4.2 Access to study data at the conclusion of the trial	262
23.2 Study chairman	242	24.4.3 Access to study forms and manuals	262
23.3 Steering committee	244	24.4.4 Inquiries from the press	262
23.4 Executive committee	245	24.4.5 Special analyses in response to criticisms	263
23.5 Other subcommittees of the steering committee	246	24.4.6 Outside audits	263
23.6 Treatment effects monitoring and advisory-review committees	246	Chapter 25. Preparation of the study publication	264
23.7 Committee-sponsor interaction	248	25.1 Introduction	264
		25.2 Preparatory steps	264
		25.3 Content suggestions	264
		25.3.1 Title section	264
		25.3.2 Abstract section	265
		25.3.3 Introductory section	268
		25.3.4 Methods section	268
		25.3.5 Results section	268
		25.3.6 Discussion section	268
		25.3.7 Conclusion section	268
		25.3.8 Reference section	268
		25.3.9 Appendix section	269

25.4 Internal review and submission	269	absence of a finding or condition	380
25.5 Acceptance and publication	270	F.3 Unnecessary words	382
Chapter 26. Locating and reading published reports	271	F.4 Double negatives	383
26.1 Introduction	271	F.5 Compound questions	383
26.2 Bibliography development	271	F.6 Comparative evaluations	385
26.3 Questions and factors to consider when reading a report from a clinical trial	272	F.7 Inverted meaning of a yes reply	386
26.4 Valid and invalid criticisms	276	F.8 Presence versus absence of a condition	386
26.5 Desirable characteristics of a critic	277	F.9 Time references	386
PART VII. APPENDIXES	279	F.10 Direction of response	388
Appendix A. Glossary	281	F.11 Leading questions	389
A.1 Preface	281	F.12 Vertical versus horizontal response lists	390
A.2 Glossary	281	F.13 Unit specifications	392
Appendix B. Sketches of selected trials	309	F.14 Precision specifications	394
B.1 Introduction	309	F.15 Calculation items	395
B.2 Methods	309	F.16 Instruction items	398
B.3 Results	309	F.17 Age and birthdate items	399
Appendix C. Year 1980 clinical trial publications	355	F.18 Reminder and documentation items	400
C.1 Papers reviewed	355	F.19 Full-page versus two-column layout	401
C.2 Papers excluded	359	F.20 Layout for SKIP items	405
Appendix D. Activities by stage of trial	363	F.21 Instructional information	408
Appendix E. Sample consent statements	374	F.22 Unformatted responses	409
E.1 Consent statement for the Macular Photocoagulation Study (MPS): Senile Macular Degeneration Study	374	F.23 Formatted responses	410
E.2 Consent statement for the Persantine Aspirin Reinfarction Study (PARIS)	376	F.24 Layout for check positions	411
E.3 Consent statement for the Hypertension Prevention Trial (HPT)	377	F.25 Field designations and precoded responses	414
Appendix F. Data items and forms illustrations	379	Appendix G. Sample manual of operations, handbook, and monitoring report	417
F.1 Item numbering	379	G.1 Introduction	417
F.2 Items that indicate presence or		G.2 Table of contents of the National Cooperative Gallstone Study Clinic Manual of Operations (July 1975 version)	417
		G.3 Listing of pages in the Hypertension Prevention Trial Handbook (April 7, 1983 version)	419
		G.4 Sample tables from Macular Photocoagulation Study Treatment Monitoring Report (January 31, 1982 Report)	421
		G.5 Listing of tables in the Final Treatment Effects Monitoring Report of the Persantine Aspirin Reinfarction Study (October 15, 1979, Database)	423

Appendix H. Budget summary for Hypertension Prevention Trial Data Coordinating Center	425	Appendix I. Combined bibliography	430
		Index	453