

Contents

- 1 Cut Costs and Increase Profits **1**
 - No Excuse for the Wastage **1**
 - Front-Loaded Solution **2**
 - Downsizing **3**
 - Think Transnational **3**
 - A Final Word **4**

- 2 Guidelines **7**
 - Start with Your Reports **7**
 - The Wrong Way **9**
 - Keep It in the Computer **9**
 - Don't Push the River **10**
 - KISS **11**
 - Plug the Holes as They Arise **12**
 - Pay for Results, Not Intentions **13**
 - Plan, Do, Then Check **13**

PART I PLAN 15

- 3 Prescription for Success **17**
 - Plan **17**
 - A. Predesign Phase **17**
 - B. Design the Trials **17**
 - Do **19**
 - C. Obtain Regulatory Agency Approval for the Trials **19**
 - D. Form the Implementation Team **19**

E.	Line Up Your Panel of Physicians	19
F.	Develop the Data Entry Software	19
G.	Test the Software	20
H.	Train	20
I.	Recruit Patients	20
J.	Set Up External Review Committees	20
K.	Conduct the Trials	20
L.	Develop Suite of Programs for Use in Data Analysis	20
M.	Analyze and Interpret the Data	21
Check		21
N.	Complete the Submission	21
4	Staffing for Success	23
The People You Need		23
Design Team		23
Obtain Regulatory Approval for the Trials		25
Track Progress		25
Implementation Team		26
Develop Data Entry Software		26
Test the Software		27
Line Up Your Panel of Physicians		28
External Laboratories		28
Site Coordinators		28
External Review Committees		29
Recruit and Enroll Patients		29
Transnational Trials		30
Conduct the Trials		30
Programs for Data Analysis		30
Analyze and Interpret the Data		31
The People You Don't Need		31
For Further Information		33
5	Design Decisions	35
Should the Study Be Performed?		36
Should the Trials Be Transnational?		37
Study Objectives		37
End Points		38
Secondary End Points		39
Should We Proceed with a Full-Scale Trial?		41
Tertiary End Points		41
Baseline Data		41

Who Will Collect the Data?	41
Quality Control	42
Study Population	44
Timing	45
Closure	46
Planned Closure	46
Unplanned Closure	46
Be Defensive. Review, Rewrite, Review Again	49
Checklist for Design	50
Budgets and Expenditures	50
For Further Information	51
6 Trial Design	55
Baseline Measurements	56
Controlled Randomized Clinical Trials	57
Randomized Trials	58
Blocked Randomization	59
Stratified Randomization	60
Single- vs. Double-Blind Studies	60
Allocation Concealment	62
Exceptions to the Rule	62
Sample Size	63
Which Formula?	64
Precision of Estimates	64
Bounding Type I and Type II Errors	66
Equivalence	68
Software	68
Subsamples	69
Loss Adjustment	69
Number of Treatment Sites	70
Alternate Designs	70
Taking Cost into Consideration	72
For Further Information	73
7 Exception Handling	75
Patient Related	75
Missed Doses	75
Missed Appointments	75
Noncompliance	76
Adverse Reactions	76
Reporting Adverse Events	76
When Do You Crack the Code?	77

- Investigator Related **77**
 - Lagging Recruitment **77**
 - Protocol Deviations **78**
 - Site-Specific Problems **78**
 - Closure **79**
 - Intent to Treat **80**
 - Is Your Planning Complete? **80**

PART II DO 81

- 8 Documentation **83**
 - Guidelines **84**
 - Common Technical Document **84**
 - Reporting Adverse Events **86**
 - Initial Submission to the Regulatory Agency **87**
 - Sponsor Data **88**
 - Justifying the Study **88**
 - Objectives **89**
 - Patient Selection **89**
 - Treatment Plan **90**
 - Outcome Measures and Evaluation **90**
 - Procedures **90**
 - Clinical Follow-Up **90**
 - Adverse Events **91**
 - Data Management, Monitoring, Quality Control **91**
 - Statistical Analysis **91**
 - Investigator Responsibilities **92**
 - Ethical and Regulatory Considerations **93**
 - Study Committees **93**
 - Appendixes **94**
 - Sample Informed Consent Form **94**
 - Procedures Manuals **95**
 - Physician's Procedures Manual **96**
 - Laboratory Guidelines **97**
 - Interim Reports **97**
 - Enrollment Report **98**
 - Data in Hand **98**
 - Adverse Event Report **99**
 - Annotated Abstract **99**
 - Final Reports(s) **102**

Regulatory Agency Submissions	102
e-Subs	104
Journal Articles	104
For Further Information	105
9 Recruiting and Retaining Patients and Physicians	107
Selecting Your Clinical Sites	107
Recruiting Physicians	108
Teaching Hospitals	109
Clinical Resource Centers	109
Look to Motivations	110
Physician Retention	111
Get the Trials in Motion	111
Patient Recruitment	112
Factors in Recruitment	112
Importance of Planning	113
Ethical Considerations	114
Mass Recruiting	114
Patient Retention	115
Ongoing Efforts	116
Run-In Period	117
Budgets and Expenditures	118
For Further Information	118
10 Computer-Assisted Data Entry	123
Pre-Data Screen Development Checklist	124
Develop the Data Entry Software	124
Avoid Predefined Groupings in Responses	126
Screen Development	126
Radio Button	128
Pull-Down Menus	129
Type and Verify	129
When the Entries Are Completed	130
Audit Trail	132
Electronic Data Capture	132
Data Storage: CDISC Guidelines	133
Testing	136
Formal Testing	137
Stress Testing	138
Training	139
Reminder	139

Support	140
Budgets and Expenditures	141
For Further Information	141
11 Data Management	143
Options	143
Flat Files	143
Hierarchical Databases	145
Network Database Model	146
Relational Database Model	146
Which Database Model?	149
Object-Oriented Databases	150
Clients and Servers	150
One Size Does Not Fit All	151
Combining Multiple Databases	151
A Recipe for Disaster	152
Transferring Data	154
Quality Assurance and Security	155
Maintaining Patient Confidentiality	155
Access to Files	155
Maintaining an Audit Trail	157
Security	157
For Further Information	158
12 Are You Ready?	161
Pharmaceuticals/Devices	161
Software	162
Hardware	162
Documentation	162
Investigators	162
External Laboratories	163
Review Committees	163
Patients	163
Regulatory Agency	163
Test Phase	163
13 Monitoring the Trials	165
Roles of the Monitors	165
Before the Trials Begin	167
Kick-Off Meetings	168
Duties During Trial	169
Site Visits	169

Between Visits	170
Other Duties	173
Maintaining Physician Interest in Lengthy Trials	173
14 Managing the Trials	175
Recruitment	176
Supplies	176
Late and Incomplete Forms	176
Dropouts and Withdrawals	178
Protocol Violations	178
Adverse Events	179
Quality Control	179
Visualize the Data	180
Roles of the Committees	183
Termination and Extension	184
Extending the Trials	186
Budgets and Expenditures	186
For Further Information	187
15 Data Analysis	189
Report Coverage	189
Understanding Data	190
Categories	190
Metric Data	192
Statistical Analysis	194
Categorical Data	196
Ordinal Data	197
Metric Data	198
An Example	199
Time-to-Event Data	200
Step By Step	203
The Study Population	203
Reporting Primary End Points	204
Exceptions	204
Adverse Events	207
Analytical Alternatives	207
When Statisticians Can't Agree	208
Testing for Equivalence	209
Simpson's Paradox	210
Estimating Precision	211
Bad Statistics	213
Using the Wrong Method	213

- Deming Regression **213**
- Choosing the Most Favorable Statistic **214**
- Making Repeated Tests on the Same Data **214**
- Ad Hoc, Post Hoc Hypotheses **215**
- Interpretation **217**
- Documentation **218**
- For Further Information **219**
- A Practical Guide To Statistical Terminology **222**

PART III CHECK 225

- 16 Check **227**
 - Closure **227**
 - Patient Care **227**
 - Data **228**
 - Spreading the News **228**
 - Postmarket Surveillance **228**
 - Budget **228**
 - Controlling Expenditures **229**
 - Process Review Committee **229**
 - Trial Review Committee **230**
 - Investigatory Drug or Device **230**
 - Interactions **232**
 - Adverse Events **232**
 - Collateral Studies **233**
 - Future Studies **234**
 - For Further Information **234**

- Appendix Software **237**
 - Choices **237**
 - All In One **237**
 - Almost All In One **238**
 - Project Management **238**
 - Data Entry **239**
 - Handheld Devices **239**
 - Touch Screen **239**
 - Speech Recognition **239**
 - e-CRFs **240**
 - Do It Yourself **240**
 - Data Collection Via the Web **240**

Preparing the Common Technical Document	241
Data Management	241
Data Entry and Data Management	242
Small-Scale Clinical Studies	242
Clinical Database Managers	242
Data Analysis	243
Utilities	244
Sample Size Determination	244
Screen Capture	245
Data Conversion	245
Author Index	247
Subject Index	251

