



Streamlining Protocol Design: The Cost of Complexity

Presenter: Alexandra Stout, CCRA



TOPICS

Protocol

- Elements
- Time & Event Schedule
- Visit Windows
- Abnormal Labs
- AEs/SAEs

Clinical Trial Protocol

- Study plan on which a clinical trial is based
- A required regulatory document included with the submission of an Investigational New Drug (IND) application to FDA, an Investigational device exemption (IDE), observational studies or investigator initiated protocols
- A plan that is carefully designed to safeguard the health of the participants as well as answer specific research questions

Elements of a Protocol

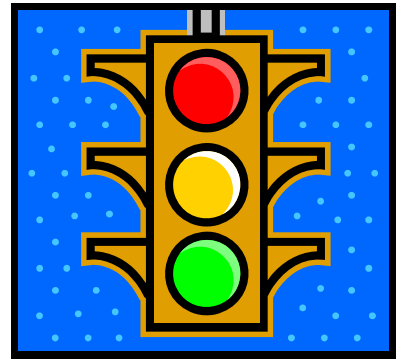
- Title
- Sponsor information, designated authority, medical expert
- Table of contents
- Information on designated investigators and labs
- The product
- History (non-clinical and previous clinical information, pharmacology)
- Known safety issues

Elements of a Protocol (cont'd)

- How the product will be administered and why this route was chosen
- Description of population, inclusion and exclusion criteria
- Objectives of study (Endpoints)
- Design of study and how bias will be avoided
- Duration of study
- Risk/Benefit
- Randomization process

Elements of a Protocol (cont'd)

- Stopping rules (single subject, part of trial, entire trial) (Discontinuation criteria)
- How will efficacy and safety will be determined
- The statistical methods used (Statistical analysis plan)
- **STATEMENT BY SPONSOR THAT GCP REGULATIONS WILL BE FOLLOWED**



Protocol Table of Contents

TABLE OF CONTENTS	
	<u>Page</u>
STUDY TEAM ROSTER.....	1
PARTICIPATING STUDY SITES.....	1
PRÉCIS.....	1
1. Study objectives.....	2
1.1 Primary Objective.....	2
1.2 Secondary Objectives.....	2
2. BACKGROUND AND RATIONALE.....	2
2.1 Background on Condition, Disease, or Other Primary Study Focus.....	2
2.2 Study Rationale.....	2
3. STUDY DESIGN.....	2
4. SELECTION AND ENROLLMENT OF PARTICIPANTS.....	3
4.1 Inclusion Criteria.....	3
4.2 Exclusion Criteria.....	4
4.3 Study Enrollment Procedures.....	4
5. STUDY INTERVENTIONS.....	5
5.1 Interventions, Administration, and Duration.....	5
5.2 Handling of Study Interventions.....	5
5.3 Concomitant Interventions.....	6
5.3.1 Allowed Interventions.....	6
5.3.2 Required Interventions.....	6
5.3.3 Prohibited Interventions.....	6
5.4 Adherence Assessment.....	6

Protocol Table of Contents

6. STUDY PROCEDURES.....	6
6.1 Schedule of Evaluations.....	7
6.2 Description of Evaluations.....	8
6.2.1 Screening Evaluation.....	8
6.2.2 Enrollment, Baseline, and/or Randomization.....	8
6.2.3 Follow-up Visits.....	9
6.2.4 Completion/Final Evaluation.....	10
7. SAFETY ASSESSMENTS.....	10
7.1 Specification of Safety Parameters.....	10
7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters.....	10
7.3 Adverse Events and Serious Adverse Events.....	10
7.4 Reporting Procedures.....	11
7.5 Follow-up for Adverse Events.....	11
7.6 Safety Monitoring.....	11
8. INTERVENTION DISCONTINUATION.....	11
9. STATISTICAL CONSIDERATIONS.....	12
9.1 General Design Issues.....	12
9.2 Sample Size and Randomization.....	12
9.2.1 Treatment Assignment Procedures.....	12
9.3 Interim analyses and Stopping Rules.....	13
9.4 Outcomes.....	13
9.4.1 Primary outcome.....	13
9.4.2 Secondary outcomes.....	13
9.5 Data Analyses.....	14

Protocol Table of Contents

10. DATA COLLECTION AND QUALITY ASSURANCE.....	14
10.1 Data Collection Forms	14
10.2 Data Management	14
10.3 Quality Assurance	14
10.3.1 Training	14
10.3.2 Quality Control Committee.....	14
10.3.3 Metrics.....	14
10.3.4 Protocol Deviations	15
10.3.5 Monitoring.....	15
11. PARTICIPANT RIGHTS AND CONFIDENTIALITY.....	15
11.1 Institutional Review Board (IRB) Review.....	15
11.2 Informed Consent Forms.....	15
11.3 Participant Confidentiality	15
11.4 Study Discontinuation.....	16
12. COMMITTEES.....	16
13. PUBLICATION OF RESEARCH FINDINGS.....	16
14. REFERENCES.....	16
15. SUPPLEMENTS/APPENDICES.....	16

I. Procedures Schedule

II. Informed Consent Form Template

III. Other *(add as many appendices as necessary)*

Trends (Fear) in Protocols

- Expense of clinical trials encourages using one study to support multiple primary and non-primary end points
- Want to collect as much data as possible to support these multiple end points
- Fear of missing information needed to answer FDA questions encourages large efforts (big case report forms)

- **Protocol Complexity is increasing**



Unnecessary Procedures

- Blood drawn at every visit but blood analyzed only at baseline, middle visit and final visit.
- Lab tests that have no relation to the study outcomes
- Duplicate assessments or examinations

Remember – It is not just collecting the data. After it's collected you have to monitor the data, clean it and generate reports.

**The more stuff you collect the more stuff a monitor reviews and there is more chance of discrepancies.*



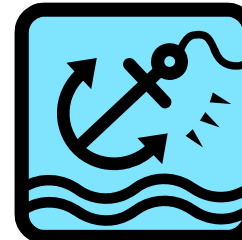
Implications to protocol

- Focus on the primary endpoints
- Review what is being collected – eliminate un-needed data points
- Think about simplification and standardization
- Consider the cost and effect on recruitment and being able to close-out study on time
- If it's a regulated study discuss the primary endpoints with the FDA and what has to be collected
- Keep asking why before you add something to the protocol



Things to Consider

- Time and Event Schedule (T&E)
 - Provides at a glance what happens and when
 - Indicates clear visit windows
 - Define 1 month
 - 30 days
 - 4 weeks
 - November 12 to December 12
 - Define anchor visit
 - Baseline
 - Prior Visit
 - What to do if prior visit is out of window
 - Ensure the T&E matches what is outlined in the protocol
 - Only collect data points that will be analyzed or are required
 - Ensure collection of safety data at all times



Assessment	Screening	Baseline, Enrollment, Randomization	Treatment Visit	Treatment Visit	Phone Call	Treatment Visit	Treatment Visit	Follow-up: Final Visit / ET
Visit	Visit 1 (Day -14 to Day -1)	Visit 2 (Day 0)	Visit 3 (Day 7)	Visit 4 (Day 14)	Visit 5 (Day 21)	Visit 6 (Day 28)	Visit 7 (Day 60)	Visit 8 (Day 90)
Visit Window			(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days from Visit 6)	(± 5 days from Visit 7)
Informed Consent Form	X							
Demographics	X							X
DXA	X							X
Medical History	X							
General Physical Examination	X	X	X				X	X
Current Medications	X	X						
Blood Chemistries	X	X	X			X		X
Hematology	X	X	X			X		X
Urine Analysis	X	X	X			X		X
Vital Signs	X	X	X	X	X	X	X	X
Inclusion/Exclusion Criteria		X						
Enrollment/Randomization		X						
Treatment Administration Form			X	X	X	X	X	
Concomitant Medications		X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X

Things to Consider

- Laboratory Assessments

- Determine what labs will be collected, when and where
- Specify the relationship between the time of collection with the date of the visit
- Determine out-of-range lab values for the population under study (not all abnormal labs are Adverse Events)
- Investigator review (print, sign, file)



Serious Adverse Events (SAEs) or Adverse Drug Reactions (ADRs)

An adverse event is any undesirable experience and is considered serious when the outcome is:

- Death
- Life Threatening
- Results in an In-Patient Hospitalization (24 hr) or Prolongs a Hospitalization
- Results in Persistent or Significant Disability (permanent or substantial disruption of one's ability to conduct normal life functions)
- Results in Congenital Anomaly/Birth Defect
- Required intervention to prevent permanent impairment or damage (devices)
- Medically Significant (Important Medical Event – IME)

Things to Consider

- Define time period for reporting SAEs
 - From Screening Visit
 - From Baseline/Randomization Visit
 - Establish length of follow-up
- Define reporting parameters
 - Disease progression
 - Pre-existing medical conditions
 - Surgical procedures vs medical conditions
- Protocols involving hospitalized participants
 - Define what is a SAE
 - Determine required documentation
 - Outline reporting procedures



Questions?

