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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

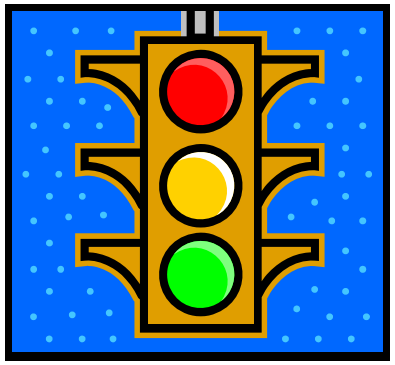
- Title
- Sponsor information, designated authority, medical expert
- Table of contents
- Information on designated investigators and labs
- The product
- History (non-clinical and previous clinical information, pharmacology)
- Known safety issues

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

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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

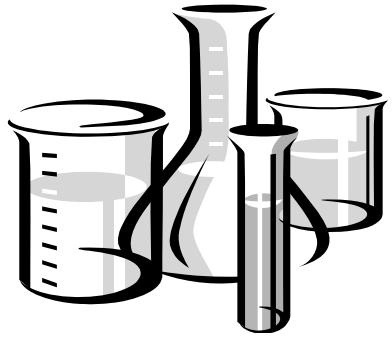
Things to Consider

- 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?