Introduction to Clinical Trials - Day 2

Session 8 - Documentation for a Clinical Trial

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Documenting the study

Motivation, need, and processes

- Problem:
  - Trial design is pre-specified in order to assure a carefully designed experiment
  - Changes will be necessary during trial implementation:
    - Unanticipated design elements (hopefully minimal)
    - Results on safety or tertiary endpoints that are discovered at interim analyses
    - New results from other trials of similar agents
    - Changes in study-related procedures
  - These changes must be implemented in a manner that maintains the integrity of the original design:
    - Avoid data-driven changes to the design
    - Pre-specify the process
    - Provide framework for documentation

Documenting the study

Key elements of trial oversight and documentation

- Key elements:
  - Trial oversight
    - Trial steering committee
    - Institutional Review Boards (IRB's)
    - FDA
    - Trial sponsor (NIH or pharmaceutical company)
  - Trial documentation
    - Trial protocol: complete documentation of the experiment: $\approx$ 80 pages
    - Statistical analysis plan (SAP): Complete pre-specification of all statistical analysis: $\approx$ 25 pages (plus tables)
    - Interim statistical analysis plan (ISAP): Complete documentation of the interim analysis plan: $\approx$ 20 pages
    - ClinicalTrials.gov: central repository for all trials
  - DSMB documents:
    - DSMB charter
    - DSMB open-report template
    - DSMB closed-report template

Documenting the study

Trial Protocol

- Purpose:

  Complete documentation to assure reproducibility

- Key elements:
  - Background
  - Objectives
  - Study design
  - Materials and methods
  - Human subjects
- Note: the protocol is supplemented by the manual of procedures (MOP):
  - Documentation of specific trial procedures (e.g., measurement methods)
  - Documents refinements to procedures (changes or details that are specified in the midst of a trial)
  - Documents nuance of eligibility/exclusions
  - MOP is updated as needed (incorporating mid-trial refinements)

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Statistical Analysis Plan

- Purpose:
  - Prespecification of all analyses
  - Prespecification of interpretation of multiple analyses (how will results be synthesized to answer trial questions)
- Key elements:
  - Summarize design (from protocol)
  - Preliminary data checking process
  - Primary analysis
  - Secondary analyses
  - Tertiary/exploratory analyses
  - Data-driven (post-hoc) analyses (keep a running record)
  - Draft shells for result tables

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Interim Statistical Analysis Plan

- Purpose: prespecify interim decision plans (related to trial outcomes)
- Key elements:
  - Summarize trial design and SAP
  - Define endpoint(s) for interim analyses
  - Specify interim decision criteria
  - Evaluate properties of interim decision criteria (power, ASN, inference at boundary, etc)
  - Specify process for implementing the monitoring plan:
    - Error-spending vs constrained boundary approaches
    - How revised decision rules are calculated:
      Boundary shape function
      Linear interpolation
    - Method for bias-adjusted inference upon completion
      BAM, RB-adjusted, MUE,
      analysis time ordering, sample mean ordering

Documenting the study

Key resources

- ICH guidelines (www.ich.org):
  - Part E8: General Considerations
  - Part E9: Statistical Principals
  - Part E10: Choice of Control Group
- CONSORT Statement (www.consort-statement.org):
  - Standards for reporting results (25 parts):
    - Title
    - Introduction
    - Methods
    - Results
    - Discussion
    - Other information