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
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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: ≈ 80 pages
  ▶ Statistical analysis plan (SAP): Complete pre-specification of all statistical analysis: ≈ 25 pages (plus tables)
  ▶ Interim statistical analysis plan (ISAP): Complete documentation of the interim analysis plan: ≈ 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

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