Streamlined Approaches to Data Collection in Clinical Trials

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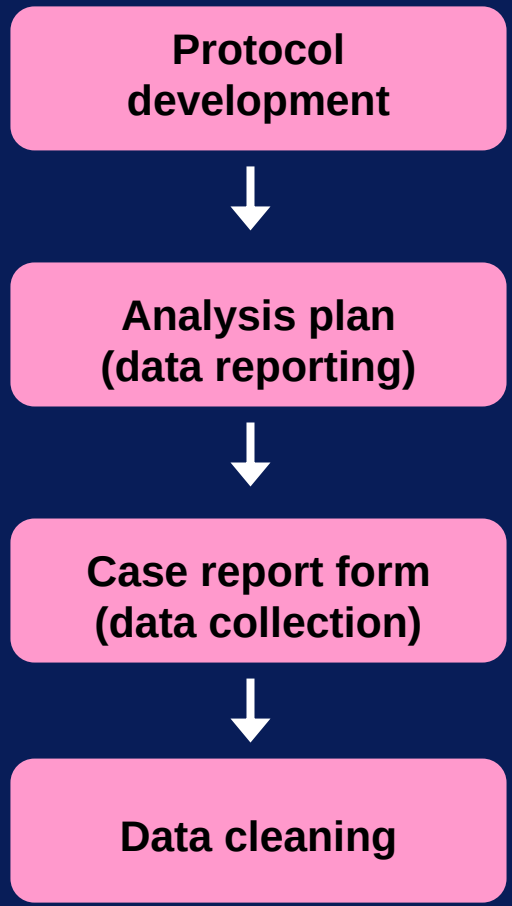
Introduction

- Sponsors have historically taken a risk-averse approach
  - FDA guidance documents for data reporting have been interpreted conservatively
  - Number of data points collected and extent of data cleaning have been comprehensive
- There is a clear need for cost-disciplined approaches that balance several important considerations:
  - Financial constraints
  - Finite resources
  - Time to completion of studies (access to study results)
  - Quality assurance (site monitoring, data accuracy, data sufficiency)

Question:

Can we run clinical trials more efficiently without sacrificing scientific integrity and patient safety?

Overview



To identify opportunities for streamlining, we need to start from the initial stages of study design and work our way down.

Protocol Development

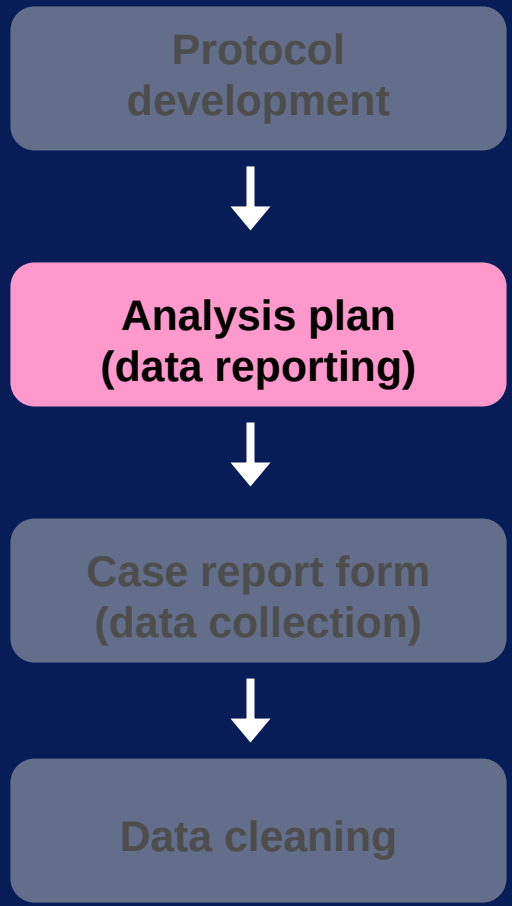
Protocol Development

- Past or current practices
  - Complex study design, attempting to answer too many questions
    - Multiple protocol review cycles, leading to delay in study start-up
  - Excessive number of secondary objectives (5-20), without scientific focus or appropriate control of Type I error
    - No differentiation between secondary and exploratory objectives
    - Exploratory endpoints lacking sufficient scientific rationale
  - Not enough granularity in defining safety endpoints

Protocol Development

- Opportunities for streamlining protocols and study design
  - **Objectives:** Focus scientific and strategic objectives of a trial and limit number of questions being addressed
  - **Secondary endpoints:** Specify 2-3 key secondary endpoints (in addition to the primary endpoint) for hypothesis testing with appropriate multiplicity control
  - **Exploratory endpoints:** Contain the number of exploratory endpoints to reduce non-value added objectives
  - **Safety:** Pre-specify adverse events of special interest
- Key stakeholders must be engaged in upfront planning
  - Clinical, statistics, regulatory, commercial

Data Reporting



Data Reporting

- Past or current practices
  - Statistical analysis plan (SAP) includes analyses that are not tied to the study objectives and do not meaningfully contribute to the interpretation of study results.
  - Inherent risks to having a large number of secondary and exploratory analyses:
    - High false positive rate: A real finding cannot be differentiated from a finding that occurred by chance
    - Reporting bias: Favorable findings will be more likely to be reported and published than unfavorable ones
  - Many tertiary / exploratory analyses → increase # of SAP review cycles → backloaded statistical programming and clinical review

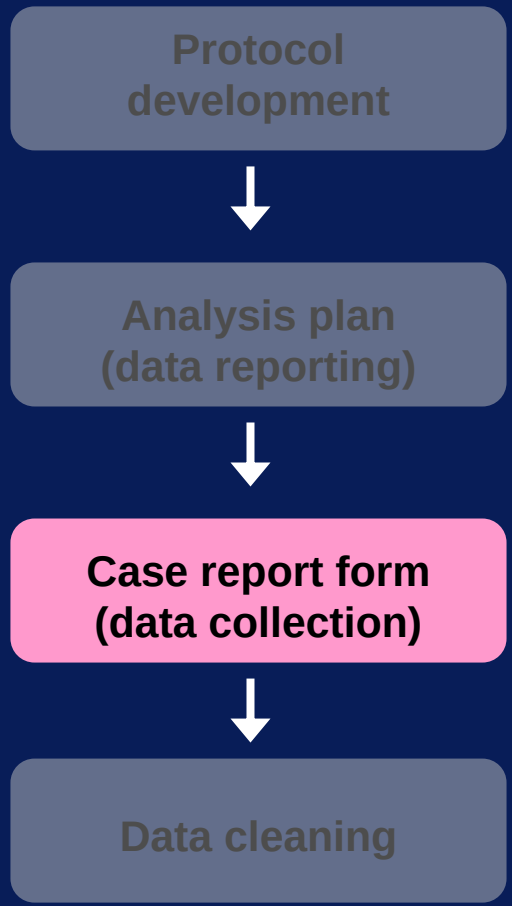
Data Reporting

- A focused protocol will lead to a more focused SAP
- Opportunities for streamlining data reporting
  - **Focused pre-specification:** Limit SAP (pre-specified) analyses to those that address study objectives and scientific questions defined in the protocol (avoid data mining)
    - Benefits: control of false positive rate, reporting bias less likely
  - **Ad hoc analyses:** Have a system for handling ad hoc analyses to determine whether they are scientifically appropriate and/or warranted

Data Reporting

- Opportunities for streamlining data reporting (cont.)
  - **Total number of analyses:** Evaluate standard data domains (e.g., efficacy, safety, dosing, etc.) to estimate number of tables, listings, and figures and set an overall target number of analyses
  - **Listings:** Reduce the number of listings to those that are absolutely needed (e.g., for safety narratives or per FDA guidance)
  - **Superfluous analyses:** Pay attention to non-value added analyses (e.g., redundant displays or too many exploratory endpoints)

Data Collection



Data Collection

- Past or current practices
  - Different approaches, within and across companies / organizations
    - Case report form (CRF) design
    - Database structure
  - Examples of inefficiencies
    - "Reinventing the wheel"
      - CRF development → database structure → statistical programming
    - Heavy reliance on pre-existing infrastructure (specific to therapeutic area)
    - "Starting from square one" with important external relationships (e.g., FDA, CRO)
      - Outsourcing of data management to CRO
      - Electronic database submissions to FDA
    - Time burden to investigative sites involved in multiple clinical trials
  - Longer timelines for study start-up, completion, and reporting

Data Collection

- Opportunities for standardizing data collection
  - Standardized CRF and database structure for common data domains
    - Examples: Demography, medical history, physical examination, adverse events, local laboratory data, death data, subject status
  - Standardized definitions for combining adverse events of special interest
  - Electronic data capture
  - Integration of clinical and pharmacovigilance safety databases
  - Clinical Data Interchange Standards Consortium (CDISC)
    - Clinical Data Acquisition Standards Harmonization (CDASH)

Data Collection

- Benefits of standardized data collection procedures
  - Facilitates standardization of other downstream activities
    - Statistical programs
    - Data displays
    - Study report organization

    Operational timelines can be compressed → study results available sooner
  - Helps regulators
    - To review submission packages more efficiently
    - To make cross-study comparisons (→ improved safety review)

Data Cleaning

Data Cleaning

- Past or current practices
  - Clean all baseline information
    - Medical history, physical examination, labs, demography, prior treatment, disease characteristics, etc.
  - Clean all data related to all efficacy endpoints (primary and secondary)
    - Through programmed “edits” as well as manual listing review
  - Clean all adverse event data
    - Dates (onset, resolution) and other attributes (severity, relatedness, action taken) for all events
    - Reconciliation of SAEs between clinical and pharmacovigilance databases

Data Cleaning

- Opportunities for streamlining data collection
  - Define **priority data** as those that
    1. support key reporting objectives for a protocol
    2. support product labeling claims and messages
    3. are required for internal clinical development decision-making
  - Priority data should be primary focus of data review and cleaning
    - Maximized electronic edits
    - Manual listing review
  - Examples of priority data:
    - Primary efficacy assessment
    - Key secondary efficacy assessments (with hierarchical hypothesis testing)
    - SAEs
    - AEs of special interest
    - AEs leading to discontinuation
    - Extent of exposure
    - Subject disposition

Data Cleaning

- Opportunities for streamlining data collection (cont.)
  - Define **supportive data** as those that do not meet the definition of "priority data"
  - Supportive data should have less intensive data cleaning
    - Simple electronic edits focused on analysis and reporting needs
    - No manual listing review
  - Example 1: Adverse events that do not qualify as
    1. SAE
    2. AE leading to discontinuation
    3. AE of special interest

    would primarily require attribution and toxicity grade. Having complete dates is less critical.
  - Example 2: Some safety measurements (e.g., ECG, labs) may require only an outlier review of clinically significant results.

Summary

- The interconnected nature of clinical trial workstreams requires a top-down strategy for streamlining
  - Mobilize the key stakeholders for upfront planning to ensure study design and protocol objectives are focused
  - Pre-specified analyses in the SAP should be linked directly to the scientific questions in the protocol
  - Standardized data collection (electronic CRF and database structure) will allow standardized data reporting and facilitate safety data review by health authorities
  - Targeted data cleaning can be tied to the priorities defined by the protocol objectives

Thank you