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Legacy Clinical Trial Data: Challenges and Solutions

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Legacy Studies

- Definition: Prior studies conducted for drug currently being studied
- Possibilities:
  - Studies in a separate indication (abandoned or approved)
  - Studies conducted by another Sponsor (or Sponsors) before drug acquired by current Sponsor

Legacy Studies: Problems

- Studies may have been conducted many years ago and/or span across several years
- Studies may have been developed by multiple companies and/or CROs
  - Lack of consistency across studies
  - Different methods of data collection
  - Lack of electronic datasets
  - Lack of reconciliation

Legacy Studies: Problems

- May not reflect current regulatory requirements
  - Pre-ICH
  - Continuously evolving guidelines and requirements
  - Time span over which data were collected results in enhanced data and measures

So why use legacy study data?

- **Required for submission in an NDA**

Per FDA guidance on format and content of an ISS: *the sponsor **should** "integrate safety information from all sources, including pertinent animal data, clinical pharmacology studies, controlled and uncontrolled clinical trials (including controlled trials for indications not claimed in the application) and foreign marketing experience or epidemiologic studies related to any use of the drug"*

Solution

- How to deal with Legacy Data?

  Create Standards

- CDISC SDTM standards create an opportunity to put legacy data in current data structures to review and report clinical trial data

Benefits of Standards

- Great way to integrate many different structures/ways of collecting data
- Effort initially to convert data but long-term benefits are:
  - Ability to submit to several different regulatory agencies without much modification
  - A smoother review process
    - Fewer regulatory queries during review
    - Respond quickly to queries since data is structured consistently
    - Avoid clock stops and/or extensions

Case Study

- A Sponsor was conducting studies in a new indication for a product that was in-licensed from another Sponsor. There were > 35 legacy studies conducted over 30 years ago. There was no NDA application to support these studies as the program had been abandoned by the previous Sponsor, thus the data had never been previously reviewed by FDA.
- Although these legacy studies were in different indications than the one the new Sponsor was seeking approval for, the data were still required to be integrated with data from current studies per regulation.

Case Study: Challenges

- Over 35 studies, therefore:
  - Multiple protocols and study designs
  - Many different case report form designs used
- Data collected over 30 years ago
  - Data collection methods not up to today's standards
    - No definition of Serious AE
    - Lab normals not available in many cases
    - Study medication dosing dates not always available
    - No visit names or dates available

Applying Standards: 2 Options

Option 1: Keep each study in its own standard and then standardize data across studies at time of study integration

- Advantages:
  - Can be implemented more quickly
  - Datasets reflect each study's unique CRFs and study design
- Disadvantages
  - Time trap during critical stages: submission, regulatory queries, etc.

Applying Standards: 2 Options

- **Option 2**: Standardize each study initially to same standards
  - Advantages:
    - Final steps (TLGs, integrated datasets) require much less programming time and team involvement
    - Able to adjust quickly to changing requests, queries, submissions, safety updates, etc.
  - Disadvantages
    - Initial resource/time investment needed

Applying Standards: 2 Options

Option 2 chosen, as the advantages of initially applying the same standards to each study outweighed the disadvantages for this project.

First Steps

- Upfront planning required
  - Review all studies for overall organization/data collection methods
  - Define how to structure output datasets
  - Determine how to map legacy data to standards
- Critical steps for long term benefits

Organization

- Review each study first to determine:
  - How were data collected
    - Check boxes vs free text
    - Medications and disease history collected together
  - What variables are missing
  - How to handle key missing variables such as gender, dosing
  - How to define Visits and VISITNUM

Organization

- Review each study first to determine:
  - How to incorporate comments
    - Include all comments?
    - What if data normally collected in a CRF is recorded as a comment?
  - Any coding issues
    - Data may not be mapped to current MedDRA or WHO dictionaries
    - What is the process for mapping/reviewing data

Structure

- Initially define with team members best way to implement SDTM standards
  - How to define –TEST and TESTCD variables, i.e. vital signs, labs
  - How to structure SC and QS modules
  - How are lab normals applied
  - How to define dosing variables, i.e. EXDOSRGM, EXDOSFRQ

DOMAIN	VSTESTCD	VSTEST
VS	HGT	Height
VS	WGT	Weight
VS	TEMP	Temperature
VS	RR	Respiratory Rate
VS	PULSE	Pulse Rate
VS	PULSE	Pulse Rate
VS	SYSBP	Systolic Blood Pressure
VS	DIABP	Diastolic Blood Pressure
VS	SYSBP	Systolic Blood Pressure
VS	DIABP	Diastolic Blood Pressure

Mapping

- How to convert legacy data to standards?
  - Variables are not always collected in same way as today's standards
  - AE relationship
  - SAE definition

AE	AEREL	Not Related	No, Not Drug Related
AE	AEREL	Unlikely	Remote, Remotely
AE	AEREL	Possibly	Possible, Possibly, Uncertain
AE	AEREL	Probably	Probable, Probably
AE	AEREL	Related	Severe, Yes

Mapping

- What rules or assumptions apply across all studies?
  - How to define dosing records
  - Substance abuse criteria
- How to deal with data not collected per present day requirements
  - Marital status, religion, patient initials/name

Process

- Standardize code as much as possible
  - Create macros that do a process more than once
    - Example: converting dates to ISO 8601 standard
  - Create macro variables for variables used often
    - Example: Patient id – may be PATID, SUBJID, PAT, etc.
  - Use macro variables to save time changing code for every study
    - Example: Study number

Process

- Have one person review similar data types across all studies
  - Get familiar with different data collections
  - Normalize data across studies
    - For example, labs, AEs, etc.
  - Data structure across all studies will be defined in same way

Process

- Documentation
  - Required variables that are not available
  - Data manipulation needed to create required variables
  - Source for data not available in CRFs
    - treatment group, lab normals, etc.

Conclusions

- Make decision early in process on what data standards will be used
- Involve team in discussions about how best to organize and structure output datasets
- Recognize that time and resources are required but will benefit in long term results
- Streamline process to map data as much as possible to cut time on programming & validation needs