TECHNICAL CHALLENGES OF CLINICAL AND ANALYTICAL STUDIES AND MANAGING THEM FOR SUCCESSFUL FDA SUBMISSIONS

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OBJECTIVES

Review common clinical trial challenges and possible solutions

- Sample Collection
- Sample Processing
- Sample Transport
- Subject Enrollment
- Electronic Data Capture
- Precision/Repro. Study
- User Interface Study

All have an impact on integrity of assay results, assay performance and data integrity

Sample Collection

Challenges

- Many assays have dedicated collection systems/kits
- During clinical trial enrollment, the study design requires:
  - Collection by more than one collection system
  - Collection systems have more than one swab
- Two common errors:
  - Incorrect swab used in collection
  - Wrong collection swab used for the indicated assay

A site performing a swab collection protocol took the cleaning swab (large head swab about the size of a quarter) and put it in a transport tube with an opening of about less than a dime!

Sample Collection

Solutions

- ✓ Train the collection sites AND the clinical testing sites
- ✓ Cover every step with detailed instructions. What you think is obvious may not be obvious to the collection teams
- ✓ Use colored labels to differentiate swabs
- ✓ Use pictures demonstrating how to use
- ✓ Provide laminated “quick guide”

Serum Sample Processing

Challenges

- The study design requires the samples to be frozen within two hours. For sites, two hours is an extremely short time period
- Samples are not frozen within two hours

  Loss of study samples

  Sample integrity is compromised affecting performance

Solutions

- ✓ Provide the testing site with a “quick guide” to show the timelines and processing steps
- ✓ Document the requirements on the CRF beside the time entry fields

Sample Transport

Challenge

- Collection site ships frozen serum samples to wrong location
  - Loss of study samples
  - Sample integrity is compromised affecting performance

Solutions

- ✓ Provide pre-labeled shippers and boxes
- ✓ Dedicate days to ship and implement a tracking system
- ✓ If an error is found, call the location to which the package was shipped and ask about process for receiving errant packages
- ✓ Document the shipping accurately. This will keep the chain of custody intact

Subject Enrollment

Challenge

- Enrollment is faster than predicted
  - Site did not understand all protocol requirements during site training

Solutions

- ✓ Establish enrollment threshold (# subjects) and conduct a monitoring visit when threshold is reached
- ✓ Early visit allows you to catch and correct issues in a timely manner
- ✓ Receive and review enrollment logs on a weekly basis
- ✓ Use electronic database to verify enrollment

ELECTRONIC DATA CAPTURE

Challenges

EDC (electronic data capture) is not ready at the time clinical trials start

- Programing for the EDC system should be performed in conjunction with CRF development
- Allow 8-10 weeks for database development and validation

Electronic Data Capture Solutions

Delay start of enrollment

- Electronic dataset beginning with systematic edit checks
- Timelines are usually tight and additional delays are not welcome

Electronic Data Capture Solutions

Start with paper CRF and transfer to electronic CRF

- No delays for enrollment
- Answer unclear questions on CRF

- Double monitoring
- If there are several sites, this can become difficult to manage
- Extra work

Analytical Studies

Two analytical studies that can be conducted at a clinical site

- Precision/Reproducibility Studies
- User Interface

Precision/Reproducibility Study

A panel is given to the clinical site to demonstrate assay precision and reproducibility

Challenge

- Develop an acceptable panel to provide multiple panel members around assay cut off

Solutions

- ✓ Characterize the panel thoroughly (i.e. stability, panel member level)
- ✓ Ensure the panel has enough replicates so that one dropout will not create failure
- ✓ Acceptance criteria:
  - Allow room for random error
  - Not 100% correct

User Interface Study

The study tests correct use and placement of assay controls and correct sample testing procedure. This study is the last time to test for correct directions and clarity of directions

Challenges

Identify appropriate users

- Have never performed the assay
- Familiar with system but not familiar with specific assay
- Trained users in the clinical study do not qualify

Solution

✓ Write protocol to allow for clarification and retesting of package insert directions until 100% is reached

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