Quality Control in Clinical Trials Blinding, Clinical Event Committees, Core Labs, and Data Standards

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Documentation

- Most important tool for assuring quality control in clinical trials is adequate documentation of methods used to maintain quality
- All of the following techniques have the underlying requirement of documentation at each step.
- Whether it's approval forms, annotation of SAS coding, or completion of a CRF, following strict documentation guidelines will assure that anyone looking at the clinical trial can understand the quality of the data and the analysis.

Blinding

- **Prior to study start**
  - **Develop list of personnel**
    - **Their roles**
    - **Access rights to study information**
    - **When they have access to information**
  - **Develop rules for unblinding**
    - **When it should occur**
    - **Who will have access to the unblinded information**

Blinding

- **During the study**
  - Use different site personnel (Investigator and Site Coordinator) to perform the procedure vs. the follow-up so the treatment will remain blinded during the follow-up
  - Develop a script for follow-up personnel to use in obtaining information from patients
  - Train follow-up personnel to avoid sections of the patient's record that would cause unblinding
- **Control communication channels**
  - Who can send and/or receive information
  - By what methods (phone, email, reports, letters) and password protection
  - What information can be provided by each method

Blinding

- **Managing data**
  - Limit access to data
  - Develop list of assigned personnel and their roles
  - Limit printing of data including where to print
  - Shred printed items unless required for recordkeeping
    - do not place in trash (too easy for others to pick up and read)
  - Provide isolated area for data review, analysis, data entry, source document collection for safety monitoring
  - Use computer screen shades when working in open areas

Blinding

- **Safety monitoring**
  - **Limit access to incoming source documentation**
  - **Redact key identifiers (patient information, product usage)**

Clinical Event Committees

- **Develop standardized processes for source document collection**
  - **Request and receipt logs**
  - **Review for completeness and compile into written dossier prior to CEC meeting**
  - **Follow-up for ongoing events**
- **Develop CEC Charter for each trial**
  - **Determine well-defined and consistent terms in the protocol / investigational plan so these definitions can be used for consistency during the adjudication**
  - **Determine which events are to be adjudicated**

Clinical Event Committees

- **Develop standardized CEC processes**
  - Meeting schedule and required attendees
  - Signature form for each meeting
  - Adjudication process
  - Meeting minutes
  - Tracking process for event adjudication status
- **Develop a reconciliation process**
  - For events discovered by the CEC during adjudication that meet study endpoints but were not coded or reported as such by site staff
  - Reconciliation of the clinical database site reported events against CEC adjudicated events and all database entries (multiple Core Lab database entries- QCA, IVUS, ECG, etc.) and CEC adjudicated outcomes

Clinical Event Committees

- **Include CEC members who are**
  - Independent from the study
  - Knowledgeable in the therapeutic area being studied
  - Experienced in the conduct of clinical research
- **Train CEC members to**
  - Study protocol, study definitions, CEC procedures, case report forms, adjudication forms

Core Labs

- **CRF Design**
  - Design of CRF (and analysis) tailored to protocol and knowledge of software capabilities for valid reproducible analysis
  - CRF programming requires validation and built in cross checks
  - Data entry requires 100% QC: double data entry is optimal, if single data entry then second pass visual validation should be employed
- **Site training**
  - Provide detailed, but easy to use instructions to the sites to acquire medium in a standard manner to ensure data quality

Core Labs

- **Core Lab analysis**
  - Trained personnel with current training records, daily feedback, weekly training sessions, and annual training updates
  - Establish a standard process for the Core lab cycle: receiving, labeling, analyzing, reviewing, managing data, and communicating with data management group and sponsor
  - QC of analysis varies: US standard is 100% review of technical aspects of analysis
  - Validation with measurement accuracy and precision of quantitative measures and qualitative measures
  - Process, validations, analysis must be detailed in SOPs that are well maintained and current

Data Standards

- **Design effective CRFs**
  - Design with the final analysis in mind
  - Well designed CRFs limit data issues and increase data entry efficiency and compliance
- **Validate Databases**
  - Ensures proper data collection and reporting
  - Perform for both the data collection database and associated edit checks
  - Require independent review (programmers and other associates who did not develop the database should perform the validation)

Data Standards

- **Develop Data Management Plan**
  - Provides a clear map for how data will be collected, stored, cleaned, protected and reported
  - Ensures understanding of required functions and study personnel responsibilities
- **Develop Edit Checks, Queries and Reports**
  - Ensures data quality prior to analysis
  - Review how data points interact with other data points
  - Design with the final analysis in mind
  - Track queries to ensure resolutions are made in a timely manner
  - Develop database reporting tools to communicate with investigative sites, manage enrollment, visit data entry, outstanding queries and event reportings

Data Standards

- **Determine Access Control and Accountability**
  - Prevents unexpected and unauthorized changes to the database
  - Databases should be equipped with audit trails so any changes, additions or deletions can be easily traced
- **Develop Data Recovery Strategy**
  - Develop a plan and test it prior to data collection
  - Back-up databases routinely to ensure easy recovery if needed due to unexpected failures

History of DSMB

- First used for large randomized multicenter trials in 1960s that were federally funded in the U.S.
- Recognition that interim monitoring of accumulating study data was essential to ensure the ongoing safety of participants
- Involvement of expert advisors external to trial would address problems in an unbiased way

Functions of DSMB

- Reviews the accumulating data from clinical trial on an ongoing basis
- Advises sponsor regarding continuing safety of trial subjects
- Advises sponsor regarding continuing validity and scientific merit of the trial

Determining Need for DSMB

- What is the risk to trial participants?
  - An interim analysis of a study endpoint could be so highly favorable or unfavorable that study termination would be required
  - Reasons exist for a safety concern
  - Fragile population
  - Large, long duration and multicenter trial

Determining Need for DSMB (2)

- Is DSMB review practical?
  - Short duration of trial would limit the meaningful impact of DSMB
  - Limited value for early studies (Phase I or early Phase 2) where accumulating results are known to sponsor and statistical interpretation of interim data is less relevant

Determining Need for DSMB (3)

- **Will DSMB help assure scientific validity of the trial?**
  - **Changes over time in understanding of disease, affected population and standard of care during long duration can lead to modifications to trial – best if recommended by unbiased group**
  - **Accumulating event rates may suggest need for modifications**

DSMB Relation to Other Groups

- IRBs / Ethics Committees
- Clinical Trial Steering Committee
- Endpoint Adjudication Committee or Clinical Events Committee (CEC)
- Site / Clinical Monitoring
- Investigators
- Sponsor

DSMB Composition

- Clinicians with expertise in relevant clinical specialty
- Statistician familiar with statistical methods for clinical trials and sequential analysis of data
- Others might include epidemiologist, ethicist, pharmacologist
- No conflicts of interest (financial, intellectual, influence on trial)

DSMB Charter

- Procedural issues
  - Meeting schedule, format, structure, quorum, minutes
  - Report formats and codes
- Statistical methods
  - Group sequential methods with interim analyses defined by time intervals or amount of information
  - Stopping rules

DSMB Responsibilities

- Interim monitoring
  - Monitoring for effectiveness
  - Monitoring for safety
  - Monitoring study conduct
  - Consideration of external data
- Making recommendations
- Maintaining meeting records

Independence of DSMB

- Independence from sponsor
  - DSMB remains objective
  - Increases credibility of trial's conclusions
  - Sponsor maintains ability to make trial modifications in response to external data without introducing bias

Independence of DSMB (2)

- Sponsor interaction with DSMB
  - "Open" part of meeting to review enrollment, compliance, event rates in aggregate as well as sponsor goals, plans, and resources
  - DSMB can address questions from interim comparative data review to sponsor

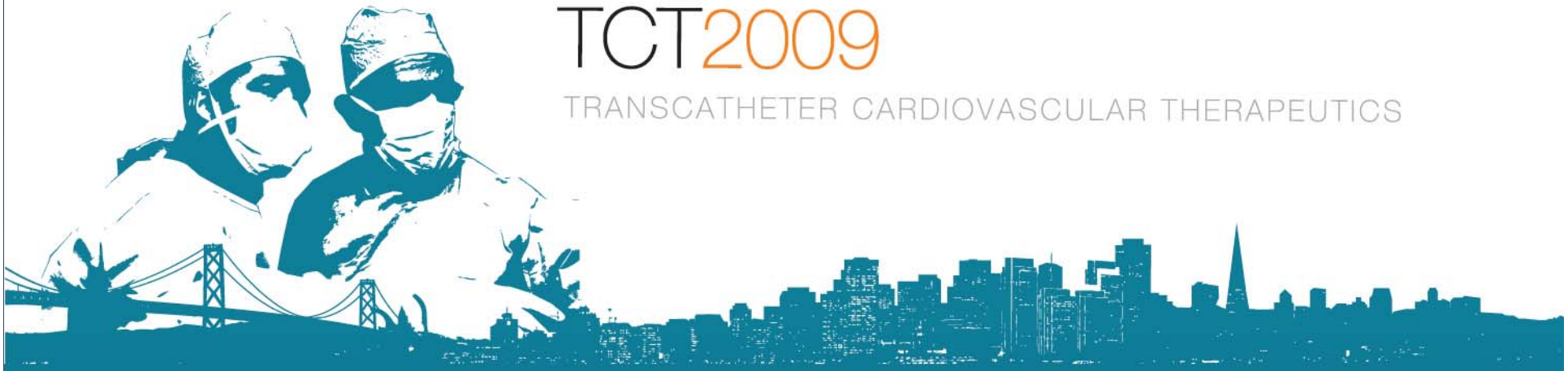
Independence of DSMB (3)

- Independence of statistician
  - Primary trial statistician has most knowledge about trial but doing interim analysis and participating in DSMB would compromise objectivity of DSMB as well as statistician's objectivity with ongoing study management
  - Recommendation is to employ a contractor statistician

Reference:

Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees

US Food and Drug Administration (FDA)
OMB Control No. 0910-0581 (March 2006)



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