Hartcentrum Hasselt

Tailoring best practices for the evaluation of endpoints in clinical device trials.

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- The process by which clinical trials in cardiovascular medicine , and devices in particular, are designed, conducted, analyzed, presented, and published has evolved dramatically over the last decade.
  - Large, truly **global studies** with **relatively long-term clinical endpoints** are conducted to evaluate the effects of a particular treatment strategy on mortality and major morbidity within a disease entity.
  - Unrestricted study populations, including **more complex patients**, have become the norm.

- The process by which clinical trials in cardiovascular medicine , and devices in particular, are designed, conducted, analyzed, presented, and published has evolved dramatically over the last decade.
- An important challenge is to maintain accuracy and consistency in the interpretation of clinical endpoints across geographic areas and over the course of the study.
  - Clinical Event Committees (CEC) are used routinely to adjudicate efficacy and/or safety endpoints in clinical investigations;
  - It is the responsibility of the CEC to review all relevant source data and provide an independent, blinded (**i.e. source documentation: PROBE design**) determination of trial end- points or events.

- The process by which clinical trials in cardiovascular medicine , and devices in particular, are designed, conducted, analyzed, presented, and published has evolved dramatically over the last decade.
- An important challenge is to maintain accuracy and consistency in the interpretation of clinical endpoints across geographic areas and over the course of the study.
  - these expert groups comprise physicians with **particular expertise** in the **relevant therapeutic area** but **without any active involvement** in the study.
  - methods of surveillance and **ascertainment** and **complete reporting** of suspected clinical events;
  - establishment of the **minimal required data** for determination of an endpoint;
  - use of (**blinded!**) medical records and other support documents to augment study case report forms for verification of endpoint definitions (?!);
  - operational issues related to management of the CEC process.

Operational issues related to management of the CEC process:

- is a process that goes beyond a committee of experts reviewing information and deciding if an event has occurred.
- Includes:
  - establishment of (uniform!) study event definitions,
  - capture of (all!) necessary data to allow for complete ascertainment of suspected events,
  - collection of (blinded!) source documentation *and* central laboratory or (blinded!) imaging data where appropriate,

The CEC, study sponsor, and investigators should agree on endpoint definitions before study initiation:

- Ideal, these definitions should follow criteria already established by medical professional societies, independent data standards groups, or prior studies, and be deemed relevant and satisfactory for regulatory objectives;
  - A justification should be provided if event definitions deviate from established criteria.

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- Ideal, these definitions should follow criteria already established by medical professional societies, independent data standards groups, or prior studies, and be deemed relevant and satisfactory for regulatory objectives;
- There should be agreement on:
  - the **minimal data** that are required to determine if an event meets the study definition criteria, as well as on processes to manage adjudication if data are missing.
  - Study case report forms should allow for collection of the necessary data, but in many instances source documents may be needed to provide important (blinded!!) supplemental information for accurate event adjudication.

Capture of (all!) necessary data to allow for complete ascertainment of suspected events:

For many endpoint events (i.e. myocardial infarction), complete ascertainment requires:

- a systematic screening of investigator reports, safety summaries, local and central laboratory data, subsequent hospitalizations, and case report form responses that may indicate an event not directly reported.
- need for an **endpoint trigger process** that casts a wide net over the multiple adverse events reports and other data to identify a unique suspected endpoint event.

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Capture of (all!) necessary data to allow for complete ascertainment of suspected events:

- We need information from the study sponsor regarding the processes used to identify events and obtain the data required for adjudication including:
  - the level of clinical site monitoring for unreported events,
  - database audits for inconsistencies or errors,
  - screening of local or central laboratory reports for potential endpoints,
  - reviews of the safety database for repeat hospitalizations or other adverse events that may indicate that a potential study endpoint has occurred.

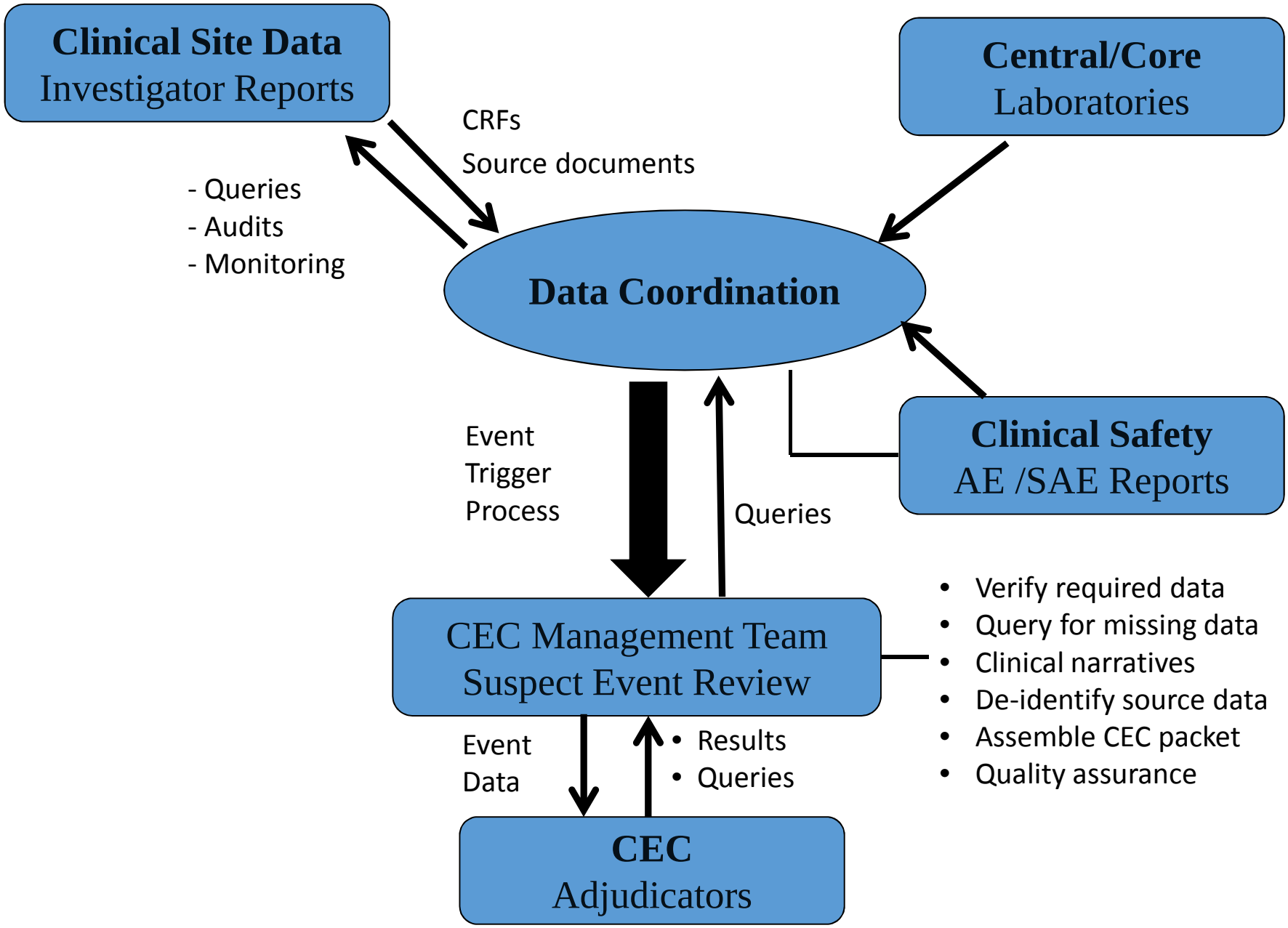
Capture of (all!) necessary data to allow for complete ascertainment of suspected events:

- We need information from the study sponsor regarding the processes used to identify events and obtain the data required for adjudication
- The personnel or group involved in the identification of suspected endpoint events and the preparation of the data for the CEC (and whether these individuals have other roles in the clinical study) should also be noted.
  - the process must be clearly separate from other clinical trial management activities and performed only by those who are blinded to treatment assignment (especially in non-randomized or single arm studies).

To maintain the integrity of the adjudication process, treatment assignment and other information, including study clinical center or investigator, that could possibly introduce bias must be appropriately masked.

Central Core Labs reduce variability in interpretations with the use of a limited number of experienced observers with standardized training (GD).

Site reporting may be based on bedside clinical impressions that vary from protocol-based definitions, and interpretation of angiographic, ultrasound or other images may differ from central core laboratories or the CEC itself.


Clinical Site Data
Investigator Reports
Central/Core
Laboratories
CRFs
Source documents
- Queries
- Audits
- Monitoring
Data Coordination
Event
Trigger
Process
Queries
Clinical Safety
AE /SAE Reports
CEC Management Team
Suspect Event Review
• Verify required data
• Query for missing data
• Clinical narratives
• De-identify source data
• Assemble CEC packet
• Quality assurance
Event
Data
• Results
• Queries
CEC
Adjudicators

Process quality assurance includes:

- verification of complete ascertainment of endpoint events based on the final available data;
- Support for the accuracy of the CEC determinations based on the endpoint definitions;
- Methods for recording of CEC results into the study database that minimize data entry errors (i.e. electronic double data entry);
- Audit of the CEC results for variability (i.e. blinded re-adjudication of of a reasonable sample (depending on the number of events) of previously adjudicated events.

A blinded and independent adjudication proces using uniformly applied endpoint definitions, terminology, and processes for endpoint reporting enhance freedom from bias and more generalizable interpretability of study results.

Sham/Mock Interventions

ARGUMENTS IN FAVOR

Increase the scientific validity and the benefits to society while at the same time the risks and harm can be acceptable.

ARGUMENTS AGAINST

- they pose unacceptable risks to participants, and present difficulties with informed consent
- the use of deceptive tactics is unethical, and that the feasibility of such controls is compromised because of a lack of public support.

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