Current State of Clinical Event Adjudication in Device Trials
CDRH Regulatory View

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Disclaimer

I have never sat on a clinical events adjudication committee.

6 Adjudication Questions

Who, What, Why,
When, Where, How?

Adjudication in Device Studies: Who

- Committee members
  - Independent physicians (i.e., members not involved with the study itself)
  - No financial COIs
  - Expertise in the clinical condition being studied
    - Current standard of care in targeted patient population

Adjudication in Device Studies: Who

- Committee members
  - Study-specific operator expertise in the key procedures being performed in the study, for example:
    - Interventional cardiologists
    - Cardiac or vascular surgeons
    - Electrophysiologists and structural heart disease interventionalists

Technical skills, operator experience, and learning curves often play a large role in device studies

Adjudication in Device Studies: Who

- Committee members
  - Cross-cutting expertise
    - Increased frequency of cardiovascular interventions used to prevent or treat non-cardiac conditions, for example:
      - LAA occlusion in AFib patients to prevent ischemic stroke
      - Neurohormonal modulation to treat resistant HTN
    - Need to broaden membership outside of cardiovascular medicine, for example:
      - Stroke neurologist and neuro-radiologists
      - HTN experts, endocrinologists, and nephrologists

Adjudication in Device Studies: What

- Review (with masking of treatment assignment when possible):
  - Clinical summaries and reports
  - Source documents
    - Including actual images when needed as imaging studies often play a key role in adjudicating cardiac events
      - Coordination with core labs may be appropriate for selected events (e.g., stent thrombosis)

Adjudication in Device Studies: Why

- Enhance validity of study outcomes
  - More consistent event assessments
  - Increased accuracy of event rates
- Reduce bias
  - Particularly important for device trials
    - Rarely double-blind and sometimes not even single-blind
    - Greater frequency of pivotal trials that utilize historical controls or are single arm studies
      - Adjudication committee unblinded treatment assignment
      - Uniform event definitions with historical data important

Adjudication in Device Studies: When

- Event adjudication aligned with study enrollment and follow-up
  - Timely identification of safety signals
  - Enhances study subject protection
  - Fulfills requirements for periodic study progress reporting to regulatory bodies
  - Provides the information needed to addresses pre-specified study stopping rules (if applicable)

Adjudication in Device Studies: Where

Practical considerations for meeting setting alternatives:

- Face-to-face
- Cyberspace/Web-based
- Teleconferences

Adjudication in Device Studies: How

- Committee administration
  - Written CEC Charter provided in the IDE submission
    - SOPs, meeting schedules
  - Staffing (independent of the sponsor) to coordinate data accumulation for adjudication review
- Complete (as possible) data capture
  - Relies on the competence and dedication of study site personnel
  - Appropriate study monitoring plan
  - Systematic review of reports, lab and imaging studies, and case report forms

Adjudication in Device Studies: How

- Utilize pre-specified event definitions
  - Multi-stakeholder efforts such as the Academic Research Consortia particularly helpful
- Establish approaches to adjudicate events when portions of expected data are missing
- Create protocols for document review and resolution of disagreements to reach consensus
- Define circumstances in which re-adjudication is allowable
- Document meeting records in minutes

Special Considerations for Device Study Adjudication: Mechanistic insights

- Allows for a more complete assessment of factors contributing to adverse events or benefits
- Can address the relatedness of an event to the device or procedure
  - Typically more relevant to device vs. to drug studies, as the mechanism of action of devices is typically better understood compared with drugs
  - Causality may reflect on the safety or effectiveness of the device (and impact a regulatory decisions) and assigning causality isn't always obvious

When is Clinical Event Adjudication Not Appropriate or Needed?

- When the value of adjudication is likely to be undermined by ambiguous or missing data such that reaching a conclusion of causality or relatedness to an intervention may be misplaced
- When events are not counted unless they are adjudicated as device or procedure-related
  - A potentially important issue in single arm studies
- Some small early feasibility or first-in-human studies

FDA's Role Viz a Vis Adjudication Committees

FDA:

- Reviews event narratives and, in some cases source documents, and may pose questions to the Adjudication Committee for clarification
  - When applicable, may point out areas of concern or limitations in the adjudication of selected events
  - Not intended to re-adjudicate events or second guess the conclusions reached by the Committee
- Appreciates the challenges of the adjudication process and the need for clinical judgment, particularly in cases in which the event dossier is incomplete

Adjudication in Device Studies: Why

- It's what FDA typically expects…
  - Reflects best practices
  - Raises the profile of the study to a higher level of scientific evidence to guide regulatory decision-making
- But FDA is acknowledges the high costs and long duration of current clinical studies and is interested in new approaches to increase study efficiency without sacrificing quality
  - And this includes a re-assessment of the adjudication process

Back-ups

Use of Insurance Claims Data

- Being proposed for prospective trials embedded in ongoing registries
- Opportunities for efficient data collection and cost savings
- Limited validation studies appear promising compared with typical industry run IDE studies with respect to agreement in cumulative event rates