Considerations for Event Adjudication in Medical Device Studies

(including drug-device combination products and bioabsorbable drug-eluting stents)

Theodore Heise, PhD
VP Regulatory Science, Cook Medical

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Disclosures

• I am employed by Industry; specifically, Cook Medical
• I am not a physician

That said, I also have unique expertise due to:
• Formal training as an analytical chemist
• More than 20 year career in Regulatory Science
• Designed and analyzed dozens of clinical studies, evaluating many thousands of patients
• A decade of experience in ISO 10993 TC 194
  – Responsible for international consensus standards on biological and clinical evaluation of medical devices
• This background has provided an excellent foundation for my experience with AE adjudication
Lessons from TC 194

• ISO 10993 stresses a risk assessment approach
• Biological response to implanted medical devices is very difficult to assess directly
  – Histopathology is rarely available, for obvious reasons
  – Animal models are limited
    • Species to species variability
    • Few instances of human pathology occur in animals
• Understanding potential links between device and AEs is essential to planning appropriate endpoint assessments
• For example, metal stents may induce:
  – Inflammation
  – Delayed healing
  – Flow disturbances
Extension to Bioabsorbable Stents

• In addition to those for standard metallic implants (inflammation, delayed healing, flow disturbances), the biological response to bioabsorbable stents may include:
  – Embolization of partially absorbed fragments
    • Ischemic effects
    • Damage to distal vessel and surrounding tissue
  – Chemical effects to tissue (e.g., greater potential for inflammation or toxicity, both of which may be chronic)
  – Late discontinuities (e.g., increased flow disturbances)

• It is important to prospectively identify the expected events that can result from each of these effects, and establish adequate endpoint definitions
Stepwise Approach for Devices

• Did an event occur?
  – The literature from over a decade ago (2004-2005) includes reports of clinical events committees (CECs) frequently changing site determinations of cardiovascular (CV) event attributions
  1
  – More recently (2013), a previous CSRC think tank noted that if definitions are adequately crafted and applied (i.e., by CV physicians), a CEC may not be essential
  2
  – Otherwise, there is a need for some human thought process to be applied and a CEC is likely essential, along with
    • clearly defined CEC charter
    • CEC transparent visibility to medical information

Stepwise Approach for Devices – continued

• Given confirmation an event occurred, was it associated with the medical device?
  – Typical to adjudicate relationship of AE to:
    • Underlying disease or condition
    • Procedure or technique
    • Device
  – This has some similarity to the concept of “biological plausibility” used with drugs

• With this foundation, let’s look at some considerations for when a CEC may be needed, especially as it may relate to MDEpiNet interests

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(1) Nature of Study Endpoints

• Quantitative data generally easier to interpret
• Qualitative data inherently more subjective, may have more need of a CEC
• How well defined; can an algorithm “pick ‘em”?
• Hard vs. soft endpoints
  – Death is pretty definitive
  – Myocardial enzyme levels reasonably clear
  – Stroke or PE may be more subjective
  – Revascularization even more subjective
• **Example**: Study of CEC versus register outcomes showed positive predictive value \(\sim 70\%\) for acute MI as compared to \(\sim 42\%\) for unstable angina\(^4\)

(2) Alignment with Practice

• How well the protocol, endpoints, and hypotheses align with the data collected in practice of medicine affects the reliability (and availability) of the data
  – Endpoints differing from practice (especially assessment methods) are often collected incorrectly
  – Additional endpoints sometimes forgotten entirely

• Example: chest x-ray versus study optimized for device
(2) Alignment with Practice
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Example: chest x-ray versus study optimized for device.

Impossible to adjudicate device related event from this SOC imaging.
(3) Time from Procedure

- Greater proximity to index procedure intrinsically increases likelihood of causality
  - As time passes, the likelihood generally decreases
  - Furthermore, the influence of ongoing disease processes (progression of disease) can increasingly confound the causality

- Over time, patient compliance with exercise or medications also affects outcomes
  - **Example**: ABSORB II (study of bioabsorbable DES) is collecting data on patient compliance with prescribed exercise and medication regimens to aid in event adjudication

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(4) Specific Physiology

• Target anatomy can affect endpoints
  – Implication of occlusion in coronary vs. renal artery
    • Severity of outcome (e.g., MI versus kidney infarct)
    • Certainty of outcome occurrence (e.g., threshold level for specific enzymes versus ischemic volume/size of kidney)

• Availability of consensus definitions may vary
  – ARC versus PARC
  – Despite best efforts of top experts, it may be more difficult to define endpoints with precision in some areas than others

• Example: Thrombosis in SFA as compared to coronary
  – Enzyme biomarkers not established for SFA
  – Return of claudication less clinically definite than MI
(5) Operator Variability

• Medical devices known to have greater reliance of operator skill and judgment than for drugs
  – Selection of patients suited to design parameters
  – Selection of devices to fit patient anatomy
  – Use of recommended techniques
  – Placement in correct location

• Example: Failed AAA endograft deployment
  – Anatomical angulation exceeded IFU recommendations
  – Inadequately supportive wireguide chosen, contrary to IFU
  – Significant rotation of delivery system, contrary to IFU
  – Adjudication essential to correct doctor’s attribution of event

• Concerns for liability may influence reporting
  – Activity within a PSO may partially mitigate this risk
Device Design Factors

- Greater device complexity and novelty may increase value of adjudication
  - Not strictly device complexity (e.g., pacemakers are quite complex, but generally well understood)
  - Bioabsorbable and/or drug coated devices may introduce new potential AEs
- **Example**: Drug coated balloon (DCB)
  - Drug coating not entirely delivered to vessel wall
  - Potential for distal embolization
  - One below-the-knee trial stopped due to an apparent increased amputation rate observed with DCB\(^6\)
  - Adjudication critical to determine causality

(7) Heterogeneity of Venues

• Reliability of endpoint reporting can be influenced by
  – Variation in medical practice
  – Variations in definitions

• Each of these can be affected by
  – Applicable regional or national standards or norms
  – Medical specialty

• **Example:** Meaning of lower extremity vessel “patency” may be discordant between surgical versus endovascular practitioners

• **Example:** Reports of heart failure in a multi-national study may have variable meaning when the diagnoses differ among reporting locations²

(8) Expected Frequency of AE

• Adjudication may be more important where AEs are expected to be rare
  – Serious CV events are often relatively infrequent\(^7\)
  – Uncertainty in rates increases with smaller sample size
  – Greater reliability in the small number of events may help mitigate risk of incorrect conclusions
  – Adjudication may be more necessary for rare AEs

• **Example**: Academic Research Consortium definitions of stent thrombosis\(^8\) were developed to reduce uncertainty and variability in event reporting
  – Adjudication still needed, but reliability of conclusions was enhanced

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(9) Completeness of Data

- Effective event adjudication relies on adequacy of the underlying data
- If too much data is missing, adjudication may of little value (e.g., an “unable to adjudicate” conclusion) – GIGO
- On the other hand, adjudication may be helpful in cases where only some essential data are missing
- **Example**: An event of repeat MI based on biomarker evidence alone would strictly speaking require evidence of post-index drop followed by another rise in value\(^9\) - In absence of these data, adjudication is more important

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Summary of Considerations for CEC Need

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<thead>
<tr>
<th>LESS</th>
<th>NEED FOR CEC</th>
<th>MORE</th>
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<tbody>
<tr>
<td>Hard/Quantitative</td>
<td>Nature of Endpoints</td>
<td>Soft/Qualitative</td>
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<tr>
<td>Better</td>
<td>Alignment with Practice</td>
<td>Poorer</td>
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<tr>
<td>Shorter</td>
<td>Time from Procedure</td>
<td>Longer</td>
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<td>Better Known</td>
<td>Specific Physiology</td>
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<tr>
<td>Lesser</td>
<td>Operator Variability</td>
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<tr>
<td>Less</td>
<td>Device Design Novelty</td>
<td>More</td>
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<tr>
<td>Less</td>
<td>Heterogeneity (venue/practice)</td>
<td>More</td>
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<tr>
<td>Higher</td>
<td>AE Frequency</td>
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<td>Data Completeness</td>
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Degree of accordance with IFU recommendations could be added
Conclusions

• Need for CEC adjudication of adverse events can vary
• Prospectively established definitions are highly important
• Design factors associated with novel technologies (e.g., drug-device combinations and bioabsorbable devices) may drive need to anticipate and adjudicate novel event types
• Knowledge of the science (including the chemistry) is essential
• An outline of factors to consider in determining need for CEC adjudication has been presented
• These could have utility in assessing the reliability of endpoints to be evaluated, whether or not a CEC is used