Considerations for Event Adjudication in Medical Device Studies

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

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Disclosures

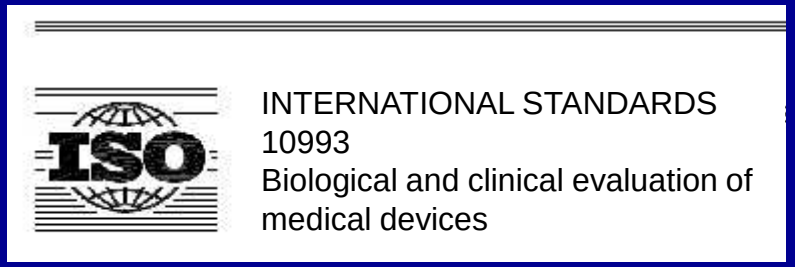
- I am employed by Industry; specifically, Cook Medical
- I am not a physician

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

[1] Dechartres A, Boutron I, Roy C, Ravaud P. Inadequate planning and reporting of adjudication committees in clinical trials: recommendation proposal. J Clin Epidemiol. 2009 Jul;62(7):695-702.

[2] Seltzer JH, Turner JR, Geiger MJ, et al. Centralized adjudication of cardiovascular end points in cardiovascular and noncardiovascular pharmacologic trials: a report from the Cardiac Safety Research Consortium. Am Heart J. 2015 Feb;169(2):197-204.

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[3]
- With this foundation, let's look at some considerations for when a CEC may be needed, especially as it may relate to MDEpiNet interests

Medical Device Epidemiology Network

[3] Sager PT, Seltzer J, Turner JR, et al. Cardiovascular Safety Outcome Trials: A meeting report from the Cardiac Safety Research Consortium. Am Heart J. 2015 Apr;169(4):486-95.

(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 ~70% for acute MI as compared to ~42% for unstable angina[4]

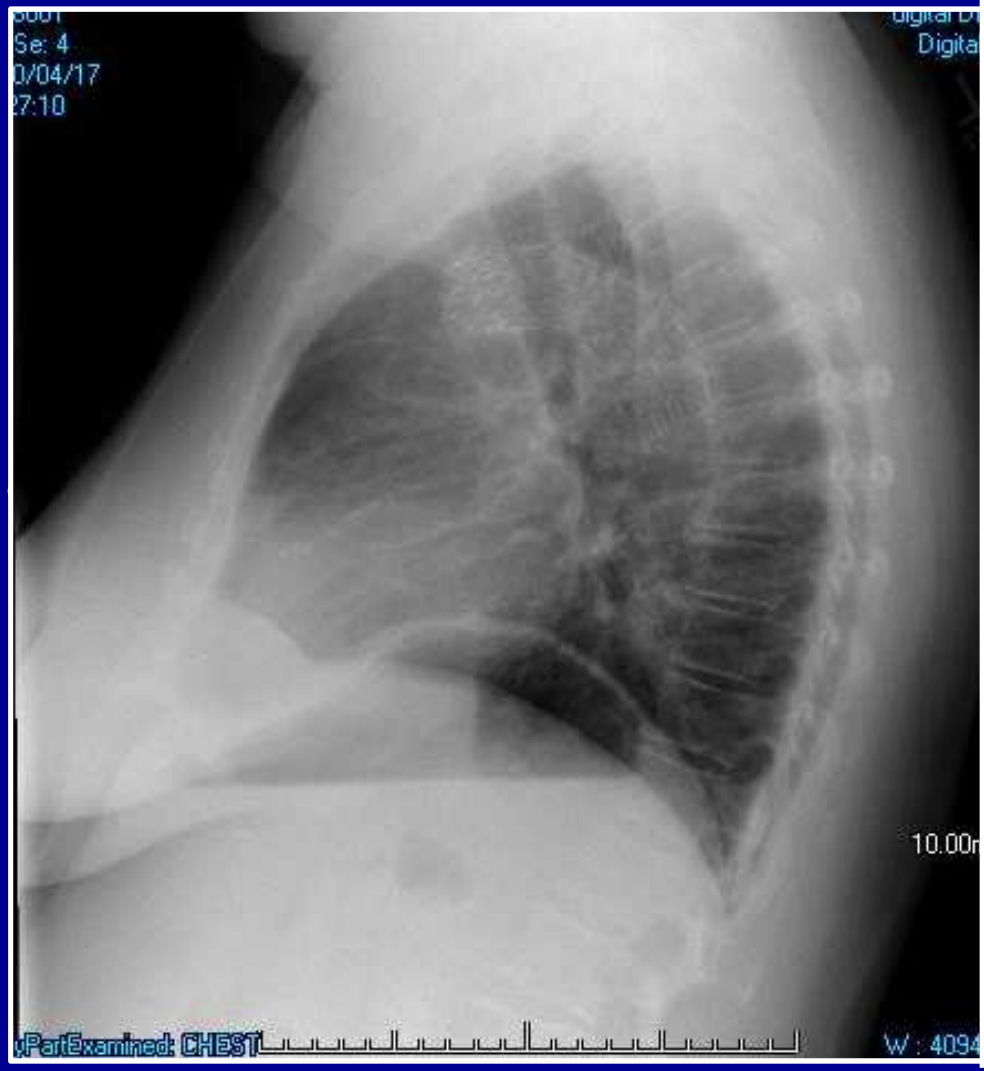
[4] Kjøller E, Hilden J, Winkel P, et al. for the CLARICOR Trial Group. Agreement between public register and adjudication committee outcome in a cardiovascular randomized clinical trial. Am Heart J. 2014 Aug;168(2):197-204

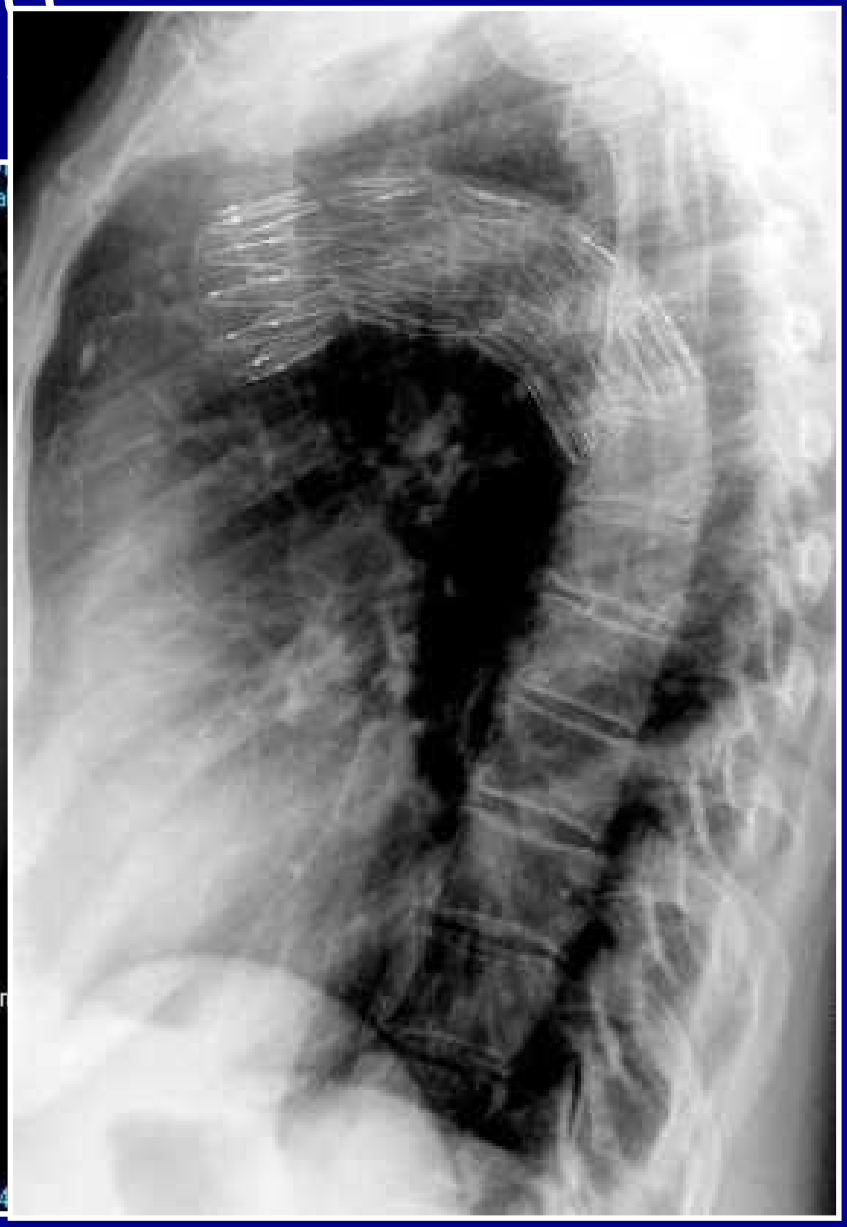
(2) Alignment with Practice

- 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

- How well the protocol, endpo





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[5]

[5] Diletti R, Serruys PW, Farooq V, et al. ABSORB II randomized controlled trial. Am Heart J. 2012 Nov;164(5):654-63.

(4) Specific Physiology

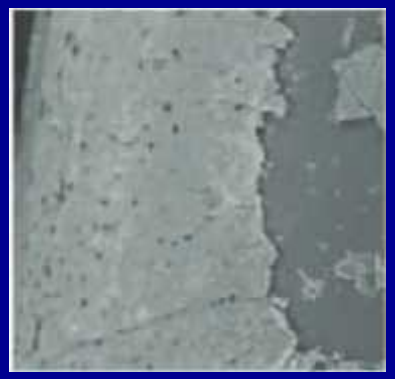
- Target anatomy can affect endpoints
  - Implication of occlusion in coronary vs. renal artery
    - Severity of outcome (e.g., MI versus kidney infarct)
    - Certainty of outcome occurrence (e.g., threshold level for specific enzymes versus ischemic volume/size of kidney)
- Availability of consensus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

(6) 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



[6] Zeller T, Baumgartner I, Scheinert D, et al. Drug-eluting balloon versus standard balloon angioplasty for infrapopliteal arterial revascularization in critical limb ischemia: 12-month results From the IN.PACT DEEP randomized trial. J Am Coll Cardiol. 2014;64:1568-1576.

(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 locations[2]

[2] Seltzer JH, Turner JR, Geiger MJ, et al. Centralized adjudication of cardiovascular end points in cardiovascular and noncardiovascular pharmacologic trials: a report from the Cardiac Safety Research Consortium. Am Heart J. 2015 Feb;169(2):197-204.

(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

[7] Sager PT, Seltzer J, Turner JR, et al. Cardiovascular Safety Outcome Trials: A meeting report from the Cardiac Safety Research Consortium. Am Heart J. 2015 Apr;169(4):486-95.

[8] Mauri L, Hsieh WH, Massaro JM, et al. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med. 2007 Mar 8;356(10):1020-9.

(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

[9] Vranckx P, McFadden E, Cutlip DE, et al. Clinical endpoint adjudication in a contemporary all-comers coronary stent investigation: methodology and external validation. Contemp Clin Trials. 2013 Jan;34(1):53-9.

Summary of Considerations for CEC Need

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