Importance of Event Ajudication
(Clinical Events Committee) and
Core Laboratories

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Clinical Trials

Seek the truth about a population of interest based on a study of a limited sample –

- Study hypothesis/question – endpoints >> data collection requirements

- Selection of control group – endpoint rate assumptions >> sample size, power, significance

- Data Quality
  - Accuracy
  - Limit variability
  - Limit bias
Clinical Trial Endpoints

Standardized Definitions (and process)

- Improves accuracy of endpoint reporting
  - Within trial
    - Standard definitions assure reporting of same event criteria across centers and treatment groups
    - Accuracy confirmed by central application of standard definitions for adjudication by independent committee (CEC)
  - Across trials and treatments

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Clinical Trial Endpoints

Objective for market approval: Demonstrate reasonable assurance of safety and effectiveness

Historical Stent Trial Endpoints

- MACE – safety
- Target vessel failure – effectiveness

Issues

- MACE and TVF composite = “average” of safety and effectiveness but driven by TLR
- Some suggest bleeding be added for endpoint of net clinical benefit
Clinical Trial Endpoints

FDA Guidance for DES Trials

• Effectiveness
  – Target lesion failure (composite of cardiac death, TV MI and TLR)
  – Target lesion revascularization

• Safety
  – Cardiac death or MI
  – Stent thrombosis (including after 1 year)
Clinical Trial Endpoints

Standardized Definitions - Examples

• Myocardial infarction
  – Disagreement among operators/centers based on MI criteria – symptoms, ECG, type and level of biomarker
  – Potential for over- and underreporting of events
  – Standardized definition from Global Task Force and Academic Research Consortium specifies criteria depending on presentation, timing etc.
Clinical Trial Endpoints

Standardized Definitions – Examples

• Stent Thrombosis
  – Different definitions across early DES trials for defining and reporting
  – Misrepresentation of possible device differences
  – Standardized definition from Academic Research Consortium specifies criteria depending on level of certainty
Clinical Trial Endpoints

Standardized Definitions – Examples

• Clinically Driven TLR
  – Revascularization decision affected by operator tendencies
  – Routine angiographic follow-up leads to increased risk for both clinically-driven and non-clinically driven TLR
Impact of Routine Angiography
PES vs. BMS – TAXUS IV Trial

Clinical F/U Only

Routine Angiography

Clinical Effectiveness
EES vs. PES

SPIRIT III Results - TLR

- 8M in-stent late loss (0.16 vs 0.30, p= 0.002)
- ? effect of routine angio

Clinical Trial Endpoints

Standardized Definitions – Examples

• Clinically Driven TLR
  – Evidence of ischemia (symptoms, + functional study)
  – Severity of stenosis (>50% diameter stenosis)
Clinical Trial Endpoints

Standardized Definitions – Examples

• Clinically Driven TLR
  – What if % diameter stenosis severe but no symptoms or + functional study?
  – Options
    • No event = no endpoint met
    • Censor at time of TLR = lose power for endpoint assessment at later time point
    • Determine level of severity for which clinically indicated
Standardized Definitions
Role of Core Laboratories

• Improve standardization of endpoint criteria by central measures

• Assures definition criteria applied by the adjudication committee are attained uniformly

• Examples
  – MLD measures by angiographic core laboratory (late loss, clinically driven TLR)
  – Cardiac biomarkers (CKMB, troponin)
    • Normalizing to site URL impacts application of truly standardized definition
Standardized Definitions
Role of Core Laboratories

• Limits variability
  – Example: single central lab for measures of biomarkers or laboratory measures reduces standard error (variance) compared with multiple laboratories performing the test
  – Result is increased statistical power and narrow confidence intervals (better estimate of result)

• Reduces bias
  – Example: Central core lab for assessing angiography (% diameter stenosis) removes potential for bias on part of investigator
Importance of the CEC Process

- Allows for reporting of endpoint events using standard criteria across multiple centers
- Establishes data requirements that allow for determination of endpoint events
- Limits variability and bias
  - Specific criteria > specified data requirements > adjudication by blinded, independent experts
  - Especially important in unblinded trials
  - “Consistency is more important than accuracy for a given case”
Importance of the CEC Process

**Complete Reporting of Events**

- Endpoints frequently misreported or underreported by site investigators
- CEC adjudication corrects for misreporting and can query for missing data elements as needed
- Specified uniform criteria for endpoint definitions allow capture of data elements upfront for detection also of unreported events
Data Triggers

Endpoint Definitions (Criteria) → CRF Design capture elements for all definitions

Suspect events to CEC → Site data and Core lab data
design data queries based on CRF response – “Triggers”

Adjudication
### MI – DES trial
- 55 yo man; 2\textsuperscript{nd} stent for dissection
- DC home after 13 hours
- No events reported
- CKMB at discharge = 13 ng/dl (URL = 4)
- Data query = suspect MI based on CKMB >3 * URL

### Major Bleed – DES trial
- 81 yo woman
- Large hematoma post PCI
- Transfusion and DC next day
- DC Hgb 8.3; baseline = 10.6.
- Major bleed not reported
- Data query based on transfusion and labs
Summary

Clinical events committees and core laboratories are important components of endpoint assessment –

- Standardized definitions for suspected endpoint events
- Capture of all required data elements in CRF design – increases completeness of event reporting
- Reduces variability in data measurements
- Reduces bias in reporting of events as well as supporting data elements
- Improved data quality > ↑ probability of meeting endpoint rate assumptions > ↑ probability of detecting true treatment effect