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**

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

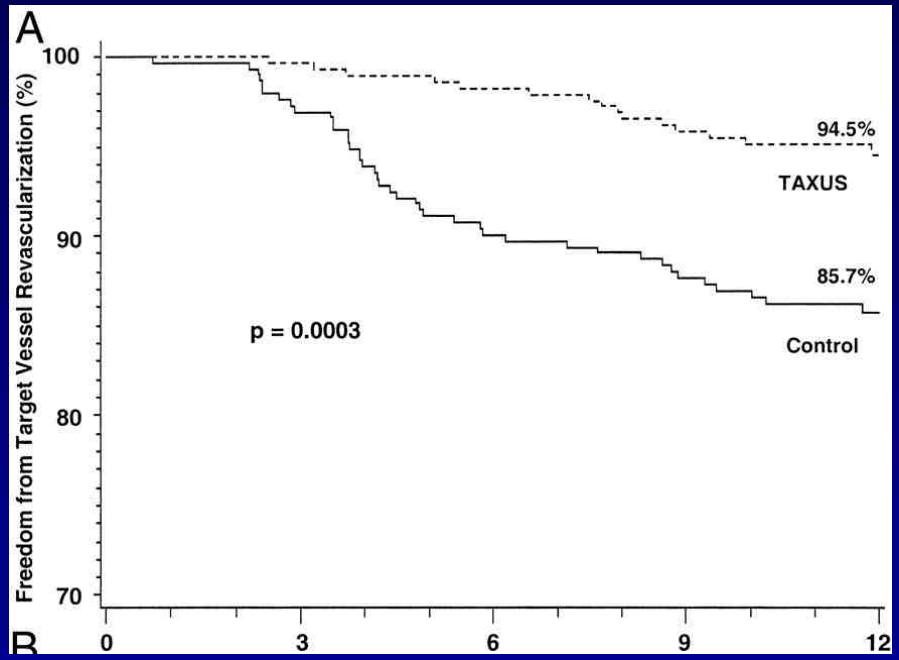
- Stent Thrombosis
  - Different definitions across early DES trials for defining and reporting
  - Misrepresentation of possible device differences
  - Standardized definition from Academic Research Consortium specifies criteria depending on level of certainty

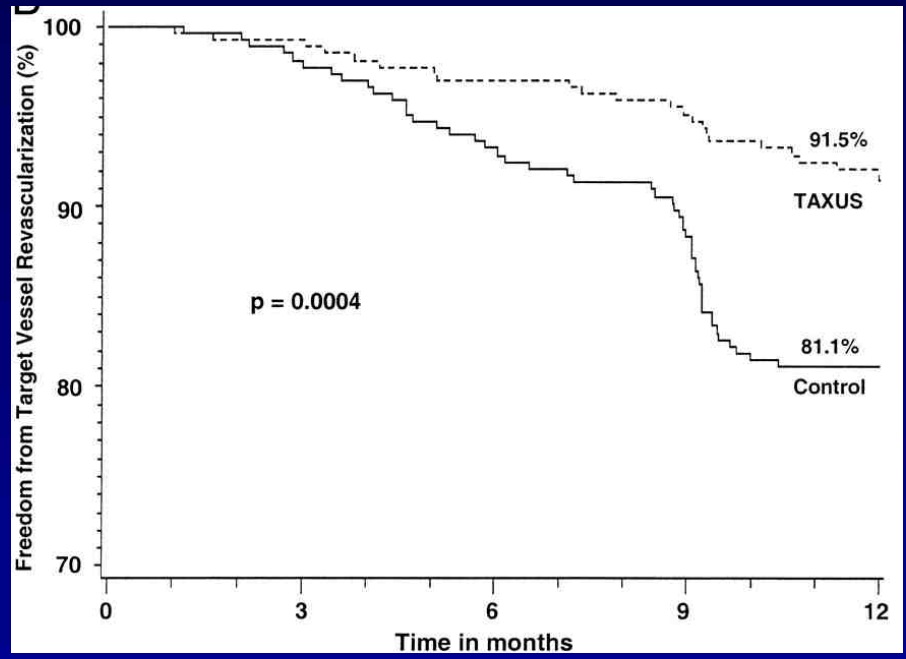
Clinical Trial Endpoints

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



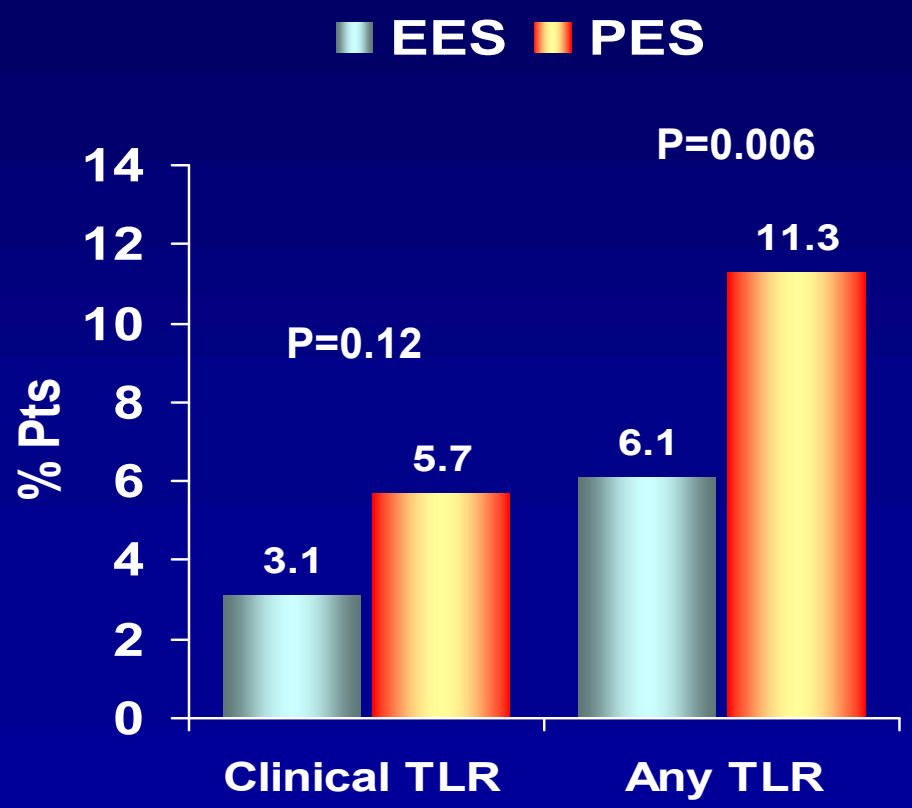


Clinical F/U Only **Routine Angiography**

Pinto, D. S. et al. J Am Coll Cardiol 2006;48:32-36

Clinical Effectiveness
EES vs. PES

SPIRIT III Results - TLR



EES vs. PES

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

G Stone et al. Circulation 2009; 119:680

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

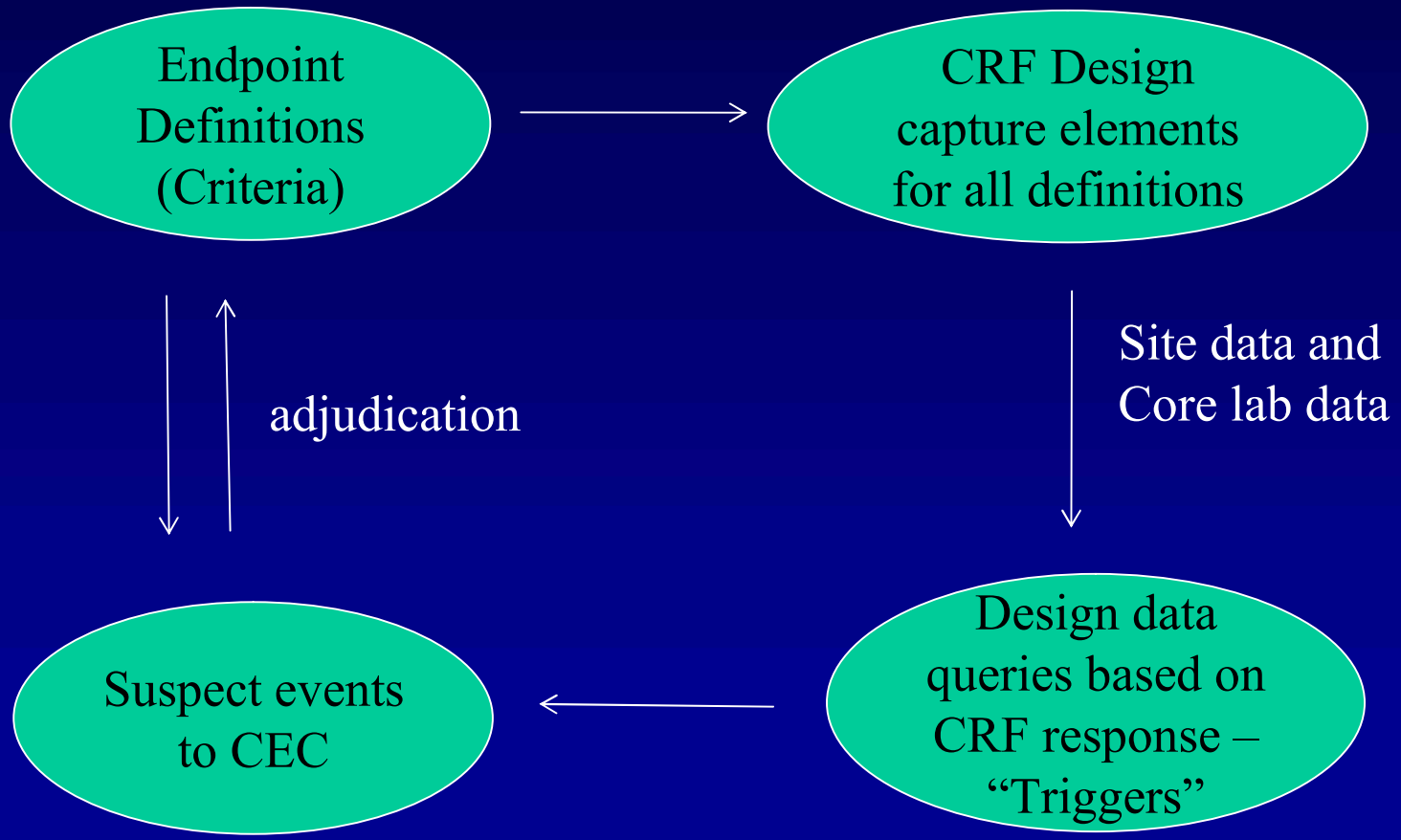
Importance of the CEC Process

- 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



Examples

MI – DES trial

- 55 yo man; 2nd 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