Clinical Trial Organization

Core Laboratories: A Crucial Component of Clinical Research

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Core Laboratories in Clinical Trials: Provide Reliable Endpoint Measures

- **Primary or secondary endpoint measures:**
  - Efficacy surrogates (LLL, RS)
  - Safety measures (Aortic regurgitation after TAVI)
- **Adjudication of Clinical Events**
  - Revascularization
  - Stent thrombosis
  - Myocardial Infarction
- **Mechanistic insights of performance**
  - IVUS/OCT
  - ECHO

Core Laboratories in Clinical Trials: Standardize Data Collection and Endpoints

- Independent Core Laboratory ensures standardized, reproducible and unbiased evaluation of endpoints
- Definitions: Standard well accepted/consensus
- Measurements: Systematic and validated
- Methodology: Accepted and validated for reproducible endpoints
- Understanding the patho-biology of endpoints
  - Impact of timing of event assessment
  - Impact of intervening test measures on clinical endpoints

Core Laboratories in Clinical Trials: Standardize Data Collection and Endpoints

- CRF Design
  - Design of CRF (endpoint measures) tailored to protocol and knowledge of software capabilities for valid reproducible analysis
  - CRF programming requires validation and build in cross checks
  - Data entry requires 100% QC if single entry, less if double entry
- Site training
  - > 50% of endpoint measurement variability can come from differences in site acquisition
  - Provide detailed, but easy to use instructions to the sites to acquire samples/media in a standard manner to ensure data consistency and quality

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Core Laboratories in Clinical Trials: Standardize Data Collection and Endpoints

- Core Lab analysis
  - Trained personnel with current training records, daily feedback, weekly training sessions, and annual training updates
  - Establish a standard process for the Core lab cycle: receiving, labeling, analyzing, reviewing, managing data, and communicating with data management group and sponsor
  - QC of analysis varies: US standard is 100% review of technical aspects of analysis
  - Validation with measurement accuracy and precision of quantitative and qualitative measures
  - Process, validations, analysis must be detailed in SOPs and maintained current

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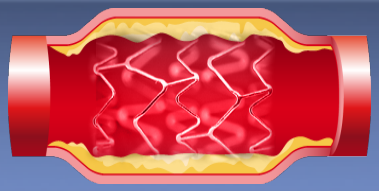

Angiographic Core Laboratory PCI/Stent Trials

- Independent Adjudication of all Revascularizations
  - TLR vs TVR vs Non TVR
  - Thrombosis
- Surrogate measures of device efficacy
  - Validated surrogate
    - Restenosis
    - LLL
    - Stent versus Lesion/segment
- Identify qualifying angiogram for endpoint measure
    - In case of multiple follow-up angiograms, identify which angiogram is used for endpoint measurement

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ECHO Core Laboratory Guidance for Industry and FDA: Heart Valve IDE and PMA Applications

- ISO 5840:2005 annex H provides information regarding the echocardiography protocol (recording studies, data collection, and core laboratory calculations and analysis).
- In addition FDA recommends:
  - An echocardiography core laboratory for the central review of all echocardiographic data.
  - A supervising director experienced in valve echocardiography.
  - Use of a written echocardiography protocol
  - Blinded interpretation of the echocardiograms

The core laboratory interpretation of echocardiograms takes precedence over site reads

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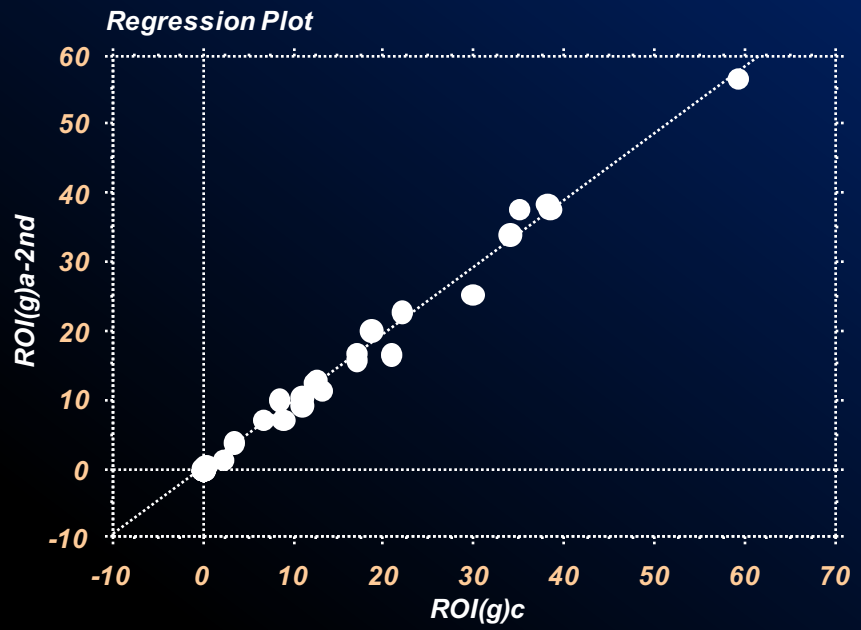
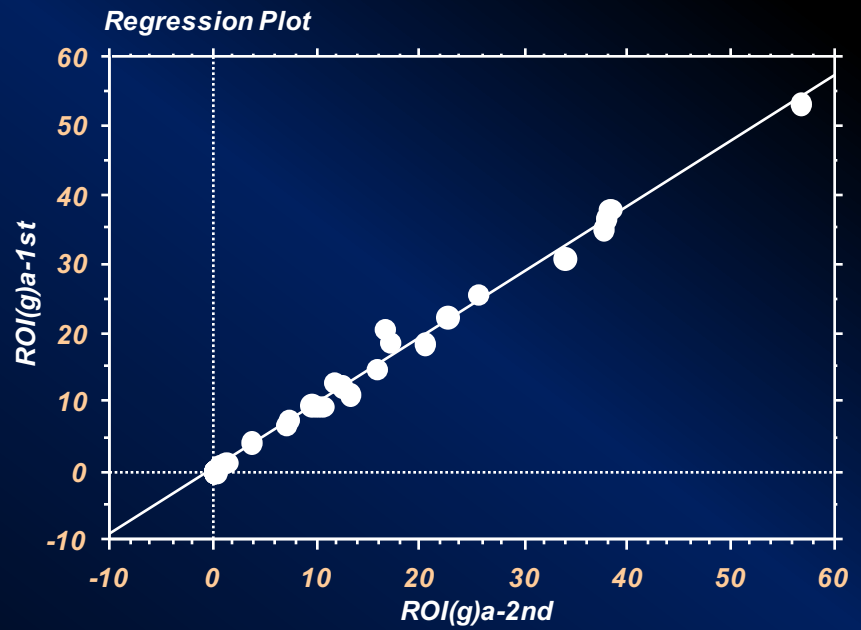
MRI Core Laboratory

Inter-reader



Y = -.006 + .978 * X; R^2 = .99

Intra-reader



Y = .318 + .955 * X; R^2 = .992

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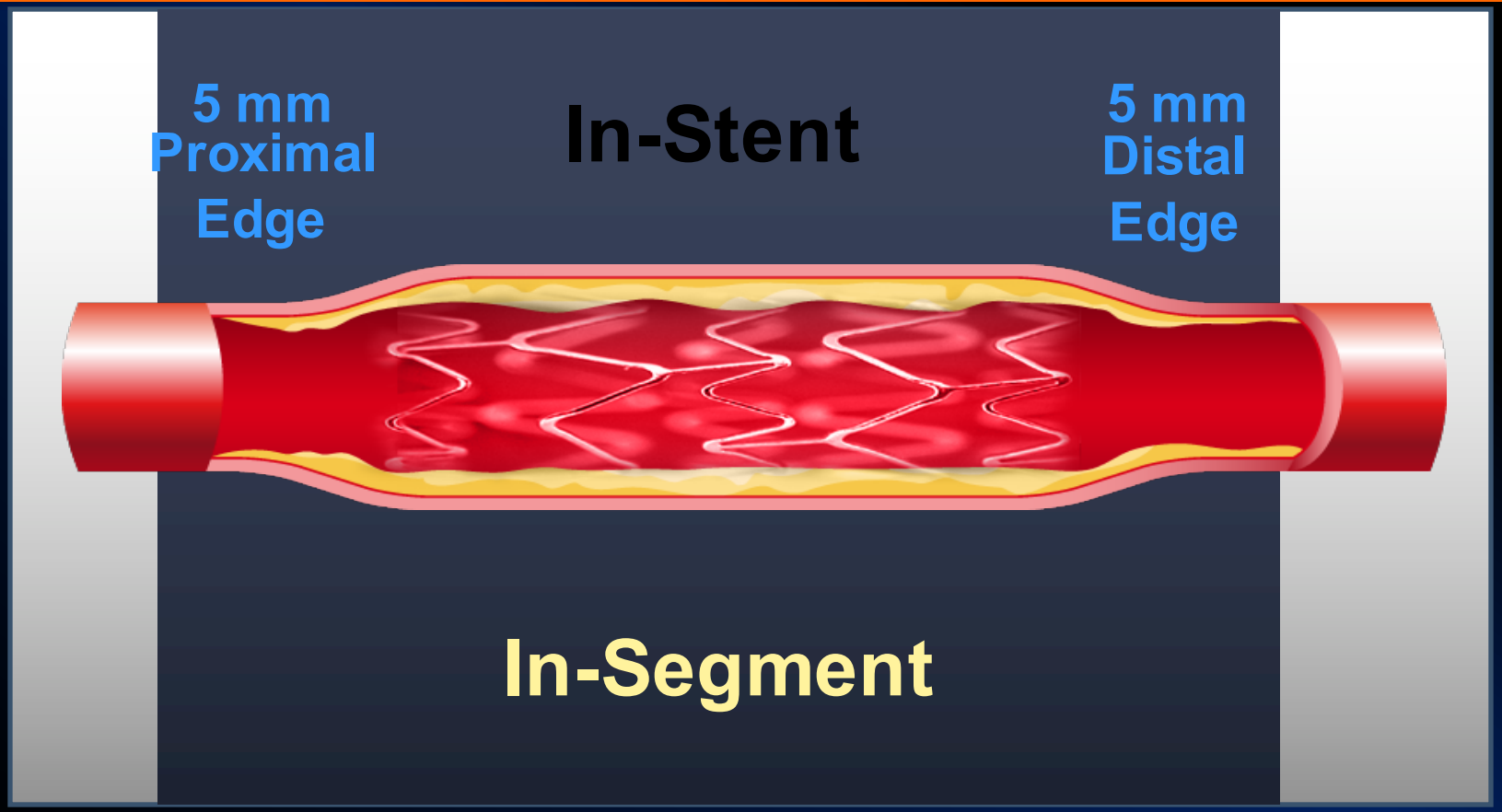
Conclusions

- **Central Laboratories**
  - Important component of most clinical trials
  - Provides independent unbiased analysis
  - Laboratory qualifications and validation ensures consistent reproducible results
  - Assists in the accurate and independent adjudication of clinical events

QCA Method for DES Analysis



All quantitative measurements are performed: (1) in-stent: within the stented segment, (2) in-segment: spanning the stented segment plus the 5 mm proximal and distal peri-stent areas, and (3) in the 5 mm proximal and distal "peri-stent" areas immediately adjacent to the stent

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