FDA Perspectives of Clinical Trials in Interventional Cardiology: US FDA

Angela Smith
Acting Chief
Interventional Cardiology Devices Branch
ODE/CDRH
US Food and Drug Administration

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Objectives

- Provide background on US medical device regulation
- Discuss FDA Perspectives of Interventional Cardiology Clinical Trials
  - Drug Eluting Stents (DES)
  - Cardiac Occluders

US Regulation of Medical Devices

- Risk based classification
- Defines level of oversight
- Class I, II and III devices
- Regulatory submissions
  - Premarket notification [510(k)]
  - Premarket Approval (PMA)
  - Investigational Device Exemption (IDE)
  - Humanitarian Device Exemption (HDE)

Device Classification

- Class I: common, low risk devices
  - General controls
  - Most exempt from premarket submission
- Class II: more complex, higher risk
  - General and special controls
  - Premarket Notification [510(k)]
- Class III: most complex, highest risk
  - General controls and premarket approval
  - Most require Premarket Application [PMA]

Drug Eluting Stents

Study Objectives

- Determine safety and effectiveness endpoint rates (Death, MI, Revascularization)
- Evaluate impact of stent thrombosis
- Assess adjunctive antiplatelet therapy (APT)

Study Design

- Randomized Controlled Trial for new DES
- Non-randomized design can potentially be used to expand original indications:
  - Additional stent diameters
  - Additional stent lengths
  - Direct stenting
  - Chronic total occlusions
- Other indications likely to require some randomization: AMI and LM & 3VD disease

RCT Designs

- Superiority Study
  - DES vs. BMS
  - Investigational DES vs. approved DES
  - Superiority margin should be clinically meaningful
- Non-inferiority Study
  - compared to DES
  - “Delta” for equivalency should be clinically meaningful
  - Care should be taken to avoid “outcome drift” in successive non-inferiority studies

Endpoints for DES Trials

- Clinical Endpoints (device oriented):
  - Composite endpoint allows for assessment of safety with a reasonable sample size
  - Cardiac death + target vessel MI + TLR at 12 months
  - While not powered for individual components, FDA looks closely at each outcome independently

Endpoints for DES Trials

- Imaging Endpoints
  - % Diameter Stenosis
  - Late Lumen Loss
  - Provide quantitative data on stent performance
  - Provide greater sensitivity of outcomes
  - Utilized in addition to clinical endpoints
- Angio/IVUS captured in separate study or after 12-month clinical visit due to impact on revascularization rates

Endpoints for DES Trials

- Use of Multiple Endpoints
  - Composite/co-primary clinical and imaging endpoints
  - Adjustment for correlation between endpoints
  - Preservation of type I error
  - Study success = meeting both endpoints
- Additional Evaluations:
  - Angio
  - IVUS

  - stent apposition
  - peri-stent phenomena
  - stent fractures

Sample Size Considerations

- Dependent on technology (i.e., novel vs. generational)
- Driven by safety
- For NME: Ability to detect catastrophic events that occur at a 1% rate with an upper 95% CI of 1.4% with 2000 patients
- Not all patients need to be part of randomized trial
- Smaller sample size may be appropriate if evaluating less novel technology

Post Approval Studies

- Assessment of unanticipated risks or rare occurrences in real-world patient populations
- Follow-up up to 5 years post-implant
- Evaluate Stent Thrombosis
  - Detect a 1% increased rate in each 12 month period with 95% confidence for on-label patients
- Evaluate cardiac death plus MI
  - On-label patients pooled with pre-approval pivotal cohort
- Evaluate use outside of labeled indication

DES Draft Guidance

- US FDA has published a draft guidance and a companion document for evaluation of DES:

  http://www.fda.gov/cdrh/ode/guidance/6255.pdf

  http://www.fda.gov/cdrh/ode/guidance/6255comp.pdf

- Currently open for comments
- Workshop to be held on April 29 to obtain comment and discussion

Cardiac Occluders

Cardiac Occluders

- US Approved Devices:
  - PDA (1)
  - ASD (2)
  - VSD [muscular only] (2)
  - PFO (none)
- 2 approved ASD: non-randomized studies with surgical control
- Now randomization to approved device would be appropriate

Trial Design Considerations

- Evaluate both pediatric and adult populations
- Each patient population has unique profile for interpretation of results
- Challenges with designing and completing trials for PFO (stroke)
  - Off-label use
  - Lack of consistently accepted medical therapy
  - Definitions for TIA and stroke
  - Risks not well characterized

Trial designs for PFO occluders

- Prospective, multicenter study
- Patients with at least one stroke/TIA in the presence of PFO
- No other identifiable cause for stroke
- Randomized Control Trial
  - Treatment of index stroke vs. recurrent stroke on meds
  - Randomization: device + meds vs. meds
- Outreach to clinical community to develop clinical studies for new devices, new indications

Conclusions

- US FDA uses a risk-based classification for medical devices
- RCT needed for novel DES
- Other study designs may be appropriate to expand indications
- There are challenges with designing and completing cardiac occluder studies, but RCT are necessary
- FDA is open to creative trial designs, just interact with us early and often!

Contact Information

Angela Smith
Acting Chief, ICDB
240-276-4188
angela.smith@fda.hhs.gov