Endovascular trials for stroke

Design considerations

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Overview

- Regulatory pathways
  - » 510(k)
    - de Novo
  - » PMA
- Design considerations
- Guidance links
- Questions

Regulatory Issues

Regulatory Pathway

- 510(k)
  - » Class II
  - » General and Special controls
  - » Predicate
- Clot retrievers cleared under 510(k) pathway
- *De Novo* petition
  - » After NSE
  - » Direct
- PMA
  - » Class III
  - » Independent assurance of safety and effectiveness
- No stroke treatment devices approved under PMA

FDASIA

(Food and Drug Administration Safety and Innovation Act)

- E-copy
- Refuse to Accept (RTA)
- Investigational Device Exemption (IDE)

IDE approval

- Section 520(g)(4)(C) of the FD&C Act now states that FDA shall not disapprove an IDE because:
  - » the investigation may not support a substantial equivalence or *de novo* classification determination or approval of a device;
  - » the investigation may not meet a requirement, including a data requirement, relating to the approval or clearance of a device; or
  - » an additional or different investigation may be necessary to support clearance or approval of the device.

Clinical Study Issues

Design considerations

- Well-defined study population
- Randomized vs. single arm
- Comparators
- Blinding
- Use of ancillary treatments including off-label
- Efficacy endpoints
- Safety analysis
- Statistical analysis plan

Selection of population

- FDA considers subjects to be enrolled
  - » When consent is signed
    - "..prior to initiation of any clinical screening procedures that are performed solely for the purpose of determining eligibility for research."
  - » What if "Standard medical care" not uniform to all centers
  - » What if "Screening procedures" are invasive and risky

Consented/enrolled subjects

- Document all subjects on relevant CRFs until withdrawal/discontinuation.
- Account for all consented subjects
- Document reasons for withdrawal or discontinuation
- Document and follow all adverse events for all enrolled subjects

Selection of population

Definition of eligible strokes

- Baseline NIHSS requirement
  - » Repeat NIHSS prior to investigational treatment if interval between baseline and treatment too long
- Exclude/define those with rapid resolution
  - » Change from initial NIHSS score
  - » Define minimum score at time of treatment
- Exclude/define IV tPA responders

Selection of population

Use of imaging studies

- MRI based selection
  - » Use of methods not cleared/approved for purpose
  - » Use of methods for which evidence of validation cannot be provided.
  - » May lead to results that cannot be used to support a marketing submission

Comparator Issues

- Concurrent
  - » Best medical therapy
  - » Active comparator
    - Superiority vs non-inferiority
  - » Ensure comparable treatment measures
  - » Active sham
- Historical
  - » “Performance goal”

Use of ancillary devices

- Approved/cleared
  - » Interpreted as a failure of the investigational device
  - » Could support adjunctive use
- Unapproved/not cleared
  - » Use interpreted as a failure of the investigational device
  - » Cannot be used to support labeling claims

Endpoints

- Primary
  - » Functional outcome
  - » Surrogates – “tool claim”
    - Reperfusion
    - Cerebral blood flow
- Secondary
  - » Importance when there is only one trial
  - » If clinical relevance not inherent in the primary

Blinding

- Clinical events committee for adjudication of adverse events
- Independent and blinded (if feasible) committee to assess radiologic studies
  - » Eligibility
  - » Endpoints

Analysis methods
Population

- As close to ITT as possible for superiority trials
  - » e.g., inclusion of any subject in whom an attempt to treat was made
  - » PP secondary
- Both ITT and PP for non-inferiority trials.
  - » Ideally the PP population should be primary but this may not be appropriate in all cases.

Analysis methods

Possible Endpoints

- Most commonly the Modified Rankin Scale score
  - » Fixed responder definition
  - » “Shift” analysis: concerns
  - » “Sliding dichotomy”
- NIHSS
- Barthel
- Composite endpoints

Statistical Analysis plan

- Sample size calculations and assumptions
- Analysis plan for primary and secondary endpoints
- Type 1 error and multiplicity
- Interim analyses and early stopping rules
- Assessment of critical covariates
- Missing data handling

Safety

- All adverse events regardless of perceived relationship to the procedure or device
- From time of consent vs. time of initiation of treatment
- Adequate follow-up of AEs occurring in subjects who discontinue/withdraw
- Standardized nomenclature
- Clinical Events Committee

Clinical investigation of medical devices for human subjects

Good clinical practice

- **ANSI/AAMI/ISO 14155:2011**

Thank You!

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E-copy guidance

- http://www.fda.gov/downloads/MedicalDevices

Refuse to Accept 510(k) and PMA

- http://www.fda.gov/downloads/MedicalDevices
- http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313368.pdf

Refuse to accept (IDE)

- http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081027.htm.

Pre-submission - draft

- http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

Design considerations

- **Design Considerations for Pivotal Clinical Investigations for Medical Devices (Draft)**
- http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM267831.pdf

Screening tests

- **Screening Tests Prior to Study Enrollment - Information Sheet**
- **Guidance for Institutional Review Boards and Clinical Investigators**

- http://www.fda.gov/RegulatoryInformation/Guidances/ucm126430.htm