Clinical and Statistical Considerations for Clinical Studies Evaluating the Safety and Effectiveness of Intracranial Aneurysm Devices

Neurological Devices Panel Meeting
April 17, 2015

Presentations by: Jeffrey Toy, Ph.D., Samuel Raben, Ph.D., Mohamad Bydon, M.D. and Laura Thompson, Ph.D.

Office of Device Evaluation (ODE) and Office of Science and Biometrics (OSB)
Center for Devices and Radiological Health (CDRH)
U.S. Food and Drug Administration
Morning Session Outline

• Purpose
  - Jeff Toy, Ph.D.

• Device History and Regulatory Background
  - Samuel Raben, Ph.D.

• Clinical pathology of aneurysms and treatment options
  - Mo Bydon, M.D.

• Statistical Considerations
  - Laura Thompson, Ph.D.

• Open Public Hearing
Afternoon Session Outline

• Panel Deliberation
• Panel Questions
  - Jeff Toy, Ph.D.
• Adjournment
The purpose of this panel meeting is to discuss the clinical and statistical considerations for studies evaluating intracranial aneurysm devices.
Focus Areas of the Meeting & Outline of Panel Questions

1. Aneurysm subgroups (e.g. characteristics, location, size, and morphology)
   Questions 1-3

2. Clinical trial designs
   Questions 4-5

3. Safety and effectiveness endpoints, durability of treatment
   Questions 6-8
FDA Panel Team

- Bennett Blumenkopf, M.D. – Neurosurgeon
- Mohammed Bydon, M.D. – Neurosurgeon
- Kuo Chao, M.D. – Interventional Neuroradiologist
- Robert Herrmann, Ph.D. – Biomedical Engineer
- Martin Ho, M.S. – Statistician
- Larry Lo, M.D. – Neurosurgeon
- Sanjay Misra, M.D. – Neurosurgeon
- Samuel Raben, Ph.D. – Mechanical Engineer
- Laura Thompson, Ph.D. – Statistician
- Jeffrey Toy, Ph.D. – Toxicologist
Device History and Regulatory Background

Samuel Raben, Ph.D.
Mechanical Engineer
Division of Neurological and Physical Medicine Devices
Office of Device Evaluation
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Aneurysms develop at vessel weak spots which balloon out and fill with blood

- Aneurysms develop at weak spots on a blood vessel in the brain that balloons out and fills with blood.
  - Ruptures lead to Subarachnoid Hemorrhage (SAH)
- 6% of the population may be harboring an unruptured aneurysm. ¹

¹ www.aans.org
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Intracranial Aneurysms typically occur at branch points in the neurovasculature

- Aneurysms occur more frequently in the anterior circulation.
  - Anterior ~85%–90%
  - Posterior ~10%–15%

- Patient outcomes are influenced by aneurysm location. ²

2. Wiebers 2003 The Lancet
Aneurysms are typically located at branch points

Distribution of Congenital Cerebral Aneurysms

Anterior cerebral 30%
- Distal anterior cerebral 5%
- Anterior communicating 25%

Internal carotid 30%
- Ophthalmic 4%
- Posterior communicating 18%
- Bifurcation 4%
- Anterior choroidal 4%

Middle cerebral 25%

Posterior cerebral 2%
- Posterior communicating and distal posterior cerebral

Basilar 10%
- Bifurcation 7%
- Basilar trunk 3%

Vertebral–posterior inferior cerebellar 3%

Anterior circulation 85%

Posterior circulation 15%
Aneurysms occur in a variety of sizes and morphologies

- Saccular aneurysm protrude from a side wall.
  - Most common type
- Fusiform is a dilation of the vessel.
- Dissection is the result of a tear between the vessel wall layers.
Aneurysms occur in a variety of sizes and morphologies

- Aneurysms sizes can vary
- Small aneurysms occur most frequently

<table>
<thead>
<tr>
<th>Size</th>
<th>Range</th>
<th>Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small</td>
<td>≤ 5 mm</td>
<td>47%</td>
</tr>
<tr>
<td>Medium</td>
<td>6-10 mm</td>
<td>27%</td>
</tr>
<tr>
<td>Large</td>
<td>11-25 mm</td>
<td>12%</td>
</tr>
<tr>
<td>Giant</td>
<td>≥ 25 mm</td>
<td>14%</td>
</tr>
</tbody>
</table>

(Wiebers 1998)
Should the role of perforators also be considered

- Perforators are small branches from arteries

- Exist in both the anterior and posterior
  - Posterior perforator occlusion has a higher clinical risk than anterior perforators

- Perforators can be affected by both open surgery and endovascular methods
Aneurysms can present as a ‘Wide-Neck’ aneurysm

- Defined as:
  - Neck $\geq 4$ mm
  - Dome/Neck $< 2$
- Wide neck aneurysms can require different treatment methods.
Approaches employed to treat unruptured intracranial aneurysms

- Open Surgery (Craniotomy)
  - Direct Clipping
- Interventional Treatment
  - Coiling
  - Balloon Assisted Coiling (BAC)
  - Stent Assisted Coiling (SAC)
  - Flow Diversion (FD)
The surgical approach to treatment is with the use of clips

- Placed across the neck of the aneurysm
  - Multiple clips may be used
- Benefits
  - Clips can provide complete and immediate occlusion
- Risk/Limitations
  - Open surgery
  - Not all are surgically accessible
Coiling

• Technology
  • Typically made of metal

• Benefits
  • Less invasive than open surgery

• Risk/Limitations
  • Subsequent rupture
  • Neck size can affect treatment outcome
Balloon Assisted Coiling (BAC)

- Technology
  - Balloon inflating across the neck
  - Utilizes traditional coils
- Benefits
  - Increase coil density with no vessel implant
  - Complication rates similar to traditional coiling
- Risks/Limitations
  - May not work with all neck sizes

Pierot (2012) AJNR
Endoluminal Devices

A portion or all of the device is placed in the arterial lumen. Devices interact with proximal and distal sections of the vessel.

- Stent Assisted Coiling
- Flow Diverters
Stent Assisted Coiling (SAC)

- Technology
  - Self expanding stent with coils
- Benefits
  - Low recurrence rate
  - Treatment of wide-neck aneurysm
- Risks/Limitations
  - Unknown Interaction with perforators
  - Unknown long term risks
- 3 HDE approved devices
Flow Diverters

• Technology
  • High mesh density metal stent

• Benefits
  • Can treat wide-neck aneurysms
  • Nothing is placed inside the dome

• Risks/Limitations
  • Narrow Indication for Use
  • Interaction with perforators still unknown

• 1 FDA approved device
Regulatory Pathways for Devices
## Regulatory Background

### 510(k)
- **Approval Standard:**
  - Substantial equivalence to a predicate device
- General controls
- Special controls may down classify devices from Class III (high risk) to a Class II (lower risk)

### HDE
- **Approval Standard:**
  - Probable benefit outweighs risk from the use of the device
  - Requires local IRB approval
  - Less then 4,000 patients per year

### PMA
- **Approval Standard:**
  - Reasonable assurance of safety & effectiveness
- Requires Clinical Data
- General and special controls alone are insufficient to assure the safety and effectiveness

FDA works with Sponsors to tailor the scientific and clinical evidence to support approving a device for marketing in the U.S. typically along one of three pathways shown above.
### Regulatory Background

<table>
<thead>
<tr>
<th>Clips and Coils</th>
<th>Stent Assisted Coiling</th>
<th>Flow Diversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 510(k) devices</td>
<td>• Currently all SAC systems are HDE</td>
<td>• Only Pipeline Embolization Device has received marketing approval</td>
</tr>
<tr>
<td>• Coils were Class III but were down classified through the use of special controls</td>
<td>• Prospective Observation clinical studies have been performed</td>
<td>• PG based clinical study</td>
</tr>
<tr>
<td>• Literature provides both RCT and PG Studies</td>
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<td></td>
</tr>
</tbody>
</table>

- **Specific Aneurysm Devices** have undergone specific regulatory pathways, but one regulatory pathway does not necessarily signify its approach for all devices.
Measuring Primary Effectiveness

Aneurysm Occlusion
Post-Treatment Grading Scales

- Raymond Scale (Raymond et al. 2003)
- Meyers Scale (Meyers et al. 2009)
- Kamran (Kamran et al. 2010)
- Szikora (Szikora et al. 2010)
  - Divide Effectiveness into parts (Flow Modification/Occlusion)
## Grading Scales

<table>
<thead>
<tr>
<th>Raymond Scale</th>
<th>Meyers Scale</th>
<th>Kamran Scale</th>
<th>Szikora Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Occlusion</td>
<td>Complete Occlusion</td>
<td>Non Residual filling</td>
<td>Flow Modification</td>
</tr>
<tr>
<td>Residual neck</td>
<td>&gt; 90% volumetric occlusion</td>
<td>Residual filling confined to the neck</td>
<td>Complete Stasis</td>
</tr>
<tr>
<td>Residual aneurysm</td>
<td>70-89% occlusion</td>
<td>Residual filling &lt; 50%</td>
<td>Significant Flow Reduction</td>
</tr>
<tr>
<td></td>
<td>50-69% occlusion</td>
<td>Residual filling &gt; 50%</td>
<td>Slow flow</td>
</tr>
<tr>
<td></td>
<td>25%-49% occlusion</td>
<td>No change in endoaneurysmal flow</td>
<td>Aneurysm Occlusion</td>
</tr>
<tr>
<td></td>
<td>&lt;25% occlusion</td>
<td></td>
<td>Complete</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Incomplete</td>
</tr>
</tbody>
</table>
Clinical Background

Mohamad Bydon, M.D.
Medical Officer
Division of Neurological and Physical Medicine Devices
Office of Device Evaluation
Center for Devices and Radiological Health
Introduction

• Review 6 Aneurysm Device Trials
  • 2 Coiling Trials
    ▪ ISAT ¹,²,³
    ▪ ISUIA ⁴,⁵
  • 4 FDA approved trials
    ▪ Pipeline (PMA)
      – Flow diverter
    ▪ Neuroform, Enterprise, LVIS (HDE)
      – Stent assisted coiling

International Subarachnoid Aneurysm Trial (ISAT) ¹,²,³

- Purpose - RCT to compare coils vs. clips
- Multicenter trial
- 2143 patients with ruptured IA
- Primary outcome – modified Rankin score 3-6 (dependency to death)
- Subjects with MRS 3-6 at 1 year
  - 23.7% (coil) vs 30.6% (clip)

ISAT – Safety Results

- Mortality at 1 year
  - 8.1% (coil) vs 10.1% (clip)

- Rebleeding from target aneurysm at 1 yr
  - 26 patients (coil) vs 10 patients (clip)

- Long term follow – up (5 years)
  - Mortality - 11% (coil) vs 14% (clip)
  - Rebleeding – 10 pts (coil) vs 3 pts (clip)
ISAT – Takeaway

• Coiling had lower adverse events
• Clipping had better long term effectiveness
  • Higher recurrence / rebleed rates with coiling
• Critiques
  • Study over 20 years old
    ▪ Began 1994, published 2002
  • 1st generation coiling devices
  • Does not account for morphology
    ▪ i.e. Daughter sac, aneurysm angle
International Study of Unruptured Intracranial Aneurysms (ISUIA) \(^4,5\)

- **Purpose** – Evaluate natural history of Intracranial Aneurysms (IAs)
- **Multicenter, US, Canada, and Europe**
- **4060 patients with aneurysms**
  - 1692 in observation arm
  - 1917 craniotomy for clipping
  - 451 endovascular procedures

\[^4\) Wiebers 1998, \(^5\) Wiebers 2003\]
ISUIA – Natural History

- Size and Location of Aneurysm impact rate of hemorrhage
  - <7mm $\rightarrow$ 0% anterior & 2.5% posterior
  - 7-12mm $\rightarrow$ 2.6% anterior & 14.5% posterior
  - 13-24mm $\rightarrow$ 14.5% anterior & 18.4% posterior
  - >25mm $\rightarrow$ 40% anterior & 50% posterior

- Posterior Communicating (PCOM) categorized in posterior circulation

- Takeaway: poolability of IAs?
  - Statistical presentation

ISUIA – Safety Results

• 1 year follow-up
  • Mortality – 2.3% clipping vs. 3.1% coiling
  • MRS 3-5 – 1.3% clipping vs. 0.8% coiling
    ▪ Sicker patients sent to coiling

• Critiques
  • Not randomized
  • Does not account for morphology
  • Study over 10 years old
ISUIA & ISAT – Relevance to Panel Discussion

- Mortality and morbidity rates
  - 23-30% in ruptured aneurysms (ISAT)
  - 3-4% in unruptured aneurysms (ISUIA)
- Follow-up 1-5 years
- Outcomes differed based on IA size & location
  - Larger IAs more likely to hemorrhage
  - Posterior circulation IAs as well
FDA Approved Aneurysm Devices

- Coiling Devices
  - 510(k) pathway (Class II devices)
  - substantial equivalence to a currently marketed device

3 Stent Assisted Coiling Devices (Neuroform, Enterprise, LVIS)
  - HDE (Humanitarian Device Exemption)
  - “probable benefit to health from the use of the device outweighs the risk of injury or illness from its use”

- Flow Diverter (Pipeline Embolization Device)
  - PMA (Pre Market Approval)
  - “reasonable assurance of safety and effectiveness”
Indications for Use

• Pipeline (flow-diverter)
  • Currently approved for Large or giant wide neck IAs in ICA from petrous to superior hypophyseal segments

• Neuroform, Enterprise, and LVIS (stents)
  • Concomitant use with embolic coils
  • Wide neck intracranial aneurysms
  • Entire neurovasculature
Pipeline™ for Uncoilable or Failed Aneurysms (PUFS) (P100018)

- Prospective, multi-center, single-arm
- November 2008 – July 2009
- 111 subjects
- Large and giant aneurysms
- Cavernous / paraophthalmic ICA aneurysms (petrous to superior hypophyseal)
- Average aneurysm 18.2mm
- Average neck diameter 8.8mm

See Tables 2-4 in Executive Summary
PUFS Trial Results

• Primary Safety Endpoint
  • Neurologic Death or ipsilateral stroke in 6 subjects (5.6%) at 180 days

• Primary Effectiveness Endpoint
  • 73.6% subjects with complete occlusion at 180 days

• Approval – April 6, 2011
PUFS Trial - Takeaway

- Large trial
  - 111 patients
- Limited anatomical zone
  - Petrous ICA to Superior hypophyseal artery
- Limited aneurysm type
  - Large or giant
- Single arm, prospective
NeuroForm – Stryker Neurvascular HDE (H020002)

- European study
- 31 subjects, 26 underwent treatment
- 18 anterior circulation
- 5 posterior circulation
- 7 PCOMs
- Average dome 7.4mm
- Average neck 4.9mm

See Tables 3, 4 Executive Summary
NeuroForm – Safety and Probable Benefit

• Safety endpoint
  • Mortality - 1 subject (3.4%)
  • Remaining subjects, stable or improved neurologic assessment at 6 months compared to baseline

• Effectiveness endpoint
  • 26 (100%) subjects had > 95% occlusion at 6 months

• Approval – Sept 11, 2002

See Tables 5-6 in Exec Summary
CORDIS Enterprise – Codman & Shurtleff HDE (H060001)

- Multicenter US trial
- 31 subjects, 28 underwent treatment
- Anterior and posterior circulation
  - 19 Anterior circulation
  - 6 Posterior circulation
  - 3 PCOMs
- Size: Dome 8.6mm, Neck 5.3mm

*Table 7 in Executive Summary*
CORDIS Enterprise – Safety

• Safety endpoint (baseline vs 6 months post-procedure)
  • Modified Rankin scale Grade 0 (no disability) to 1
    ▪ Increased from 75.9% to 80.7%
  • NIH Stroke scale (0 = no disability)
    ▪ Mean NIHSS reduced from 1.4 to 0.3
  • 2 patients (7.1%) intracerebral hemorrhage

See Table 8 in Executive Summary
CORDIS Enterprise – Probable Benefit

• Effectiveness endpoint
  • 64% of patients had > 95% occlusion at 6 months

• Approval
  • May 26, 2005

See Table 9 in Executive Summary
LVIS – Microvention HDE H130005

• Low profile Visualized Intraluminal Support device
• Prospective, multi-center US trial
  • 36 subjects, 31 treated
• Location
  • 21 anterior, 5 posterior, 5 PCOMs
• Size: Dome 6.7mm, Neck 4.6mm
See Tables 10-11
LVIS – Safety & Probable Benefit

- **Safety endpoint**
  - Ipsilateral stroke / death within 6 months
  - 0 subjects (0%)

- **Effectiveness endpoints**
  - >90% aneurysm occlusion at 6 months
  - 29 subjects (89.7%) with > 90% aneurysm occlusion at 6 months

- **Approval** – July 25, 2014
HDE Trials - Takeaway

- Smaller trials around 30 subjects each
- Anterior and posterior circulation
- HDE approval requirements
  - Future comparisons to HDE studies a challenge
- Effectiveness
  - > 90 – 95% occlusion at 6 months
- Safety
  - Rates of neurologic death and stroke
Focus Areas of the Meeting & Outline of Panel Questions

1. Aneurysm subgroups (e.g. characteristics, location, and morphology)
   Questions 1-3

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Clinical Regulatory Summary

- 6 Prospective trials
  - ISAT, ISUIA, 4 FDA approved trials
  - Most other trials retrospective
- Coiling vs SAC vs Flow diversion
  - Complexity of the devices increasing
- Anatomical locations differ
  - Pipeline – petrous to superior hypophyseal
  - SAC – entire neurovasculature
- Overall Number of subjects differ
  - Pipeline – 111 subjects
  - SAC – 31 to 36 subjects
Clinical Regulatory Summary Cont.

• 4 devices approved using Performance Goals regardless of the regulatory pathway
  • Rely on existing literature to determine safety / effectiveness goals

• Randomized controlled trials
  • Device is compared to an adequate control (i.e. wide-neck aneurysms – FD vs SAC)

Questions 4, 5 & Stats Presentation
Study Design Considerations

Laura Thompson, Ph.D.
Mathematical Statistician
Division of Biostatistics
Office of Surveillance and Biometrics
Center for Devices and Radiological Health
Outline

1. *(Panel Q’s 1-3)* Combining aneurysm subgroups can make trial sample size feasible.
   - Which aneurysm subgroups are similar when assessing device safety or effectiveness?

2. *(Panel Q’s 4-5)* What trial designs are appropriate for a new aneurysm treatment device?
Advantages/Disadvantages Associated with Trial Designs

1. Controlled Trials (RCT, non-RCT)
2. Single-arm Studies with PG
### Hierarchy of Clinical Trial Designs

<table>
<thead>
<tr>
<th>Clinical Trial Design</th>
<th>Assurance of Effectiveness/Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized Controlled Trial</td>
<td>Highest Assurance</td>
</tr>
<tr>
<td>Non Randomized Controlled Trial</td>
<td></td>
</tr>
<tr>
<td>Single-arm Study</td>
<td>Lower Assurance</td>
</tr>
<tr>
<td>Retrospective Study</td>
<td></td>
</tr>
<tr>
<td>Descriptive Study</td>
<td></td>
</tr>
<tr>
<td>Case Series</td>
<td></td>
</tr>
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</table>
Randomized Controlled Trial

- Treatments randomly assigned to same patient pool
- Patient characteristics likely balanced across groups
- Only systematic difference is treatment.

Single Arm compared to PG

- PG = A minimum threshold from prior studies
- PG should reflect intended patient pop. and med. practice
Non-randomized Controlled Trial

• Alternative approach when randomization not feasible

• Examples
  • Non-randomized concurrent control
  • Historical Control
Advantages/Disadvantages of Trial Designs
Advantages of RCT

• Only systematic difference is treatment applied.
• Can infer causation.
• Confounding probabilistically eliminated.

Disadvantages of RCT

• Requires subjects for two arms.
• Requires consent of enrollees to be randomized to either group.
• Physicians must be willing to treat using either method.
Advantages of Single-arm with PG
• Typically requires fewer subjects than does RCT
• Simple in features

Disadvantages of Single-arm with PG
• No direct control for confounders
• PG may end up being inappropriate for current patient population.
• PG should not be changed after study.
• PG used years ago may not be appropriate now.
Advantages of Non-randomized Controls

- May be more appropriate than using a PG
  - Statistical adjustment (e.g., propensity score method).
- May require fewer concurrent subjects than RCT

Disadvantages of Non-randomized Controls

- Historical control should be recent
- Without randomization, outcome difference can be due to selection mechanism (stat. adjust).
Take Home Message – Trial Design

• Gold standard is RCT
• Other controlled trials may be appropriate.
• Single arm may be appropriate if no good comparators.
• Consider pros and cons to study designs.
How can we power for safety and effectiveness in various subgroups but also keep trial size manageable?

Methods for combining subgroups
Locations/Types of Aneurysms (Possible Subgroups)

**Neurovasculature**
- Anterior circulation
- Posterior circulation

**Perforators**
- Rich area
- Poor area

**Type**
- Aneurysm Dome Size
  - Small
  - Medium
  - Large
  - Giant
- Neck size
  - Wide neck $\geq 4$ mm
  - Not wide neck $< 4$ mm
“Pooling” Scale

**Complete Pooling**
1. Easy, trial not as large
2. Overall statistical test might not represent some subgroups.
3. All HDEs so far.

**“Partial” Pooling**

**Each Subgroup is Analyzed separately**
1. May need larger sample size.
2. May need longer trial
3. May be burdensome.
**Partially Pooling Subgroups**

1. Subgroups not completely pooled.

2. Each subgroup powered for significance, often with smaller sample size than for separate analyses.
   - Subgroups leverage information from other subgroups, increasing precision.
   - Subgroups must be considered “similar” on the endpoint.
Request for Panel Input

• Which subgroups can be considered similar on each endpoint (and how similar they are expected to be)?
Hypothetical Similarity Spectrum
Dome Size

Low Occlusion Rate

Giant/Large Aneurysms

Large Aneurysm

Medium Aneurysms

Small/Med Aneurysms

Small Aneurysm

High Occlusion Rate
Hypothetical Similarity Spectrum

- Giant/Large Posterior
- Medium Posterior
- Small Posterior
- Can Borrow?
- Low Occlusion Rate
- High Occlusion Rate
- Giant/Large Anterior
- Medium Anterior
- Small Anterior
Hierarchical Modelling: partially pooling subgroups

• The more similar an endpoint is across subgroups, the more info. can be leveraged/borrowed.

• Subgroups at a lower level of the hierarchy borrow more info. than subgroups at higher levels.
Hypothetical Hierarchical Structure for Occlusion Rate
Hypothetical Example

• Primary Endpoint: 100% occlusion

• Single-arm study with PG = 60%

• If LCL on the proportion of aneurysms with 100% occlusion > 60%, study meets primary endpoint.

• 80% power, 5% significance level.
# Assumed Occlusion Rates

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Assumed Occlusion Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wide-neck, G/L</td>
<td>70%</td>
</tr>
<tr>
<td>Wide-neck, Med</td>
<td>75%</td>
</tr>
<tr>
<td>Wide-neck, Small</td>
<td>80%</td>
</tr>
<tr>
<td>Not Wide-neck, G/L</td>
<td>75%</td>
</tr>
<tr>
<td>Not Wide-neck, Med</td>
<td>80%</td>
</tr>
<tr>
<td>Not Wide-neck, Small</td>
<td>85%</td>
</tr>
<tr>
<td>All groups pooled</td>
<td>79%</td>
</tr>
</tbody>
</table>
# Sample Sizes for 80% Power

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sample Size Complete Pooling</th>
<th>Sample Size Hierarchical Model</th>
<th>Sample Size Separate Analyses</th>
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</thead>
<tbody>
<tr>
<td>Wide-neck, G/L</td>
<td>60</td>
<td>150</td>
<td>150</td>
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<tr>
<td>Wide-neck, Med</td>
<td>25</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>Wide-neck, Small</td>
<td>15</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Not Wide-neck, G/L</td>
<td>25</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>Not Wide-neck, Med</td>
<td>15</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Not Wide-neck, Small</td>
<td>10</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>64</td>
<td>150</td>
<td>369</td>
</tr>
</tbody>
</table>
Hierarchical Modeling with Adaptive Design

- Extent of borrowing is data-driven.
- Borrowing may be different than anticipated at design stage.

- Adaptive design is recommended
  - Interim looks to adapt sample size based on actual borrowing
  - CDRH Bayesian Guidance (2010)
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   Questions 1-3

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Summary of Requested Panel Input

- Potential study designs for aneurysm devices include RCT, non-RCT, single-arm with PG

- What are the most appropriate
  - Comparators?
  - PGs?
Summary of Requested Panel Input

• Powering each subgroup separately likely requires borrowing information across subgroups to gain efficiency.

• Which aneurysm locations and types yield similar effectiveness and safety outcomes?
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Thank You

Questions?
Afternoon Session Outline

- Panel Deliberation
- Panel Questions
- Adjournment
Safety and Compatibility of Passive Implants in Magnetic Resonance (MR) Environment

MR Conditional Definition

• Definition of MR Conditional (Per ASTM 2503-13: Section 3.1.11): An item with demonstrated safety in the MR environment within defined conditions.

• The conditions are supported by non-clinical test methods below or equivalent methods:
  • Magnetically Induced Displacement Force
  • Magnetically Induced Torque
  • Heating by Radio Frequency Fields
  • Image Artifact
Section X.1 - MRI Safety Information

Non-clinical testing has demonstrated that the `<device name>` is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of `<field strength(s)>` T or less
- Maximum spatial gradient field of `<maximum for which device is safe>` gauss/cm (`<maximum for which device is safe>` T/m)
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of `<2 W/kg (Normal Operating Mode)>` or `<4 W/kg (First Level Controlled Operating Mode)>`
- Additional brief instructions essential to safe use in the MR environment, such as, positional requirements (e.g., device must remain outside the scanner bore) or restrictions on coil type (e.g., head transmit/receive coil only; quadrature body coil only). For more complicated instructions, include the following text here `<“Follow the additional MRI safety instructions as specified in Section X.2”>` and list the additional conditions in Section X.2

Under the scan conditions defined above, the `<device name>` is expected to produce a maximum temperature rise of ____ °C after 15 minutes of continuous scanning.

In non-clinical testing, the image artifact caused by the device extends approximately ____ mm from the `<device name>` when imaged with a `<gradient echo or spin echo>` pulse sequence and a ____ Tesla MRI system.

Section X.2 – Additional MRI Safety Instructions

- e.g., Positional requirements requiring more than a few words to describe
- e.g., Restrictions on coil type requiring more than a few words to describe
MRI Conditional Label Takeaway

Devices can be safely scanned under the tested conditions. MR compatibility for other scanning conditions are unknown.

Using an endpoint based on MR imaging could potentially limit the pool of investigational sites for a study. Some sites may not have the capability to conduct MR imaging using tested conditions.
MR Conditional Definition

• Definition of MR Conditional (Per ASTM 2503-13: Section 3.1.11): An item with demonstrated safety in the MR environment within defined conditions.

• The conditions are supported by non-clinical test methods below or equivalent methods:
  • Magnetically Induced Displacement Force
    ▪ ASTM F2052-14, Standard Test Method for Measurement of Magnetically Induced Displacement Force on Medical Devices in the Magnetic Resonance Environment
  • Magnetically Induced Torque
    ▪ ASTM F2213-06 (Reapproved 2011), Standard Test Method for Measurement of Magnetically Induced Torque on Medical Devices in the Magnetic Resonance Environment
  • Heating by Radio Frequency Fields
  • Image Artifact
Panel Questions
Studying Aneurysm Devices in the Intracranial Neurovasculature

The benefits and risks of treating unruptured aneurysms depend on multiple factors such as, aneurysm size. One approach to studying devices to treat unruptured aneurysms is divide the intracranial aneurysms into different subgroups. Approaches to dividing the intracranial neurovasculature include: (1) the separation of aneurysm based on their location in the neurovasculature such as the intracranial anterior circulation and intracranial posterior circulation, (2) the separation of aneurysms based on the surrounding perforator status such as, perforator rich and perforator poor regions, or (3) some combination of both.

Additional considerations include: aneurysm size, neck size (wide-neck versus non wide-neck), morphology (saccular, fusiform, dissecting), and any additional subgroups formed from a combination of the above.
Studying Aneurysm Devices in the Intracranial Neurovasculature

Additional considerations include: aneurysm size, neck size (wide-neck versus non wide-neck), morphology (saccular, fusiform, dissecting), and any additional subgroups formed from a combination of the above.

Questions #1
Please discuss what aspects of these aneurysm subgroups and any additional grouping of the characteristics should be considered when designing clinical trials of aneurysm treatment.
Studying Aneurysm Devices in the Intracranial Neurovasculature

There are several methods for analyzing a study outcome when the study includes aneurysms in different locations and with different characteristics. Pooling aneurysms across all such subgroups as though the subgroups were immaterial to the endpoint outcome, is a simple method, but may not provide sufficient information on different success rates or adverse event rates across subgroups. Conversely, powering each subgroup separately may require an impractically large trial size. An option in between (hierarchical modeling) acknowledges that aneurysms occur in different subgroups, but accounts for them within one analysis that leverages information across subgroups.
Studying Aneurysm Devices in the Intracranial Neurovasculature

**Question to the Panel #2**
From a safety perspective does the panel believe that the adverse event rates for the follow groups are similar?
- Anterior circulation aneurysms versus posterior circulation aneurysms
- Small versus medium versus large versus giant
- Perforator rich versus perforator poor
- Any other similar/dissimilar groups

**Question to the Panel #3**
From an effectiveness perspective does the panel believe that the occlusion rates for the following groups are similar?
- Small versus medium versus large versus giant
- Wide neck versus non wide neck
- Saccular versus fusiform/dissecting
- Any other similar/dissimilar groups
Clinical Trial Data Analyses and Alternate Measures in Device Study

Single-arm studies using Performance Goals can be useful when an adequate comparative device is not available. Performance Goals are typically derived from published literature or publicly accessible study data. For an RCT, the investigational device and a control device are randomly assigned to patients to provide a head-to-head comparison. This methodology has been used to compare surgical clipping to coiling. FDA is unaware of any published studies at this time where a RCT was used to evaluate an endoluminal neurovascular device.
Question to the Panel #4

a. Please describe under what circumstances a single arm trial with a performance goal would be an appropriate trial design?

In your response, please discuss the best methods for determining a PG for safety and for effectiveness endpoints and how often should a PG be updated to reflect the current practice of medicine as well as new clinical trial information?
Question to the Panel #4

b. Under what circumstances should a performance goal be chosen for a study? In your response, please comment on the clinical and statistical considerations associated with each of the following potential performance goals:

- A single performance goal for effectiveness for patients treated in the intracranial anterior circulation independent of other aneurysm characteristics (e.g., aneurysm size).
- A single performance goal for effectiveness for patients treated in the intracranial posterior circulation independent of other aneurysm characteristics (e.g., aneurysm size).
- A single performance goal for effectiveness that pertains to the complete neurovasculature independent of other aneurysm characteristics (e.g., aneurysm size).
Question to the Panel #5

Please describe under what circumstances a randomized controlled trial would be an appropriate trial? In your response, please discuss what comparators should be considered for endoluminal device trials given the different subgroups discussed in question 1 and if surgery should be considered among the comparators?
Measuring Primary Study Success

There are a number of ways to measure effectiveness of aneurysm treatment in a clinical trial. Some methods look at aneurysm occlusion, such as the Raymond Scale and Meyers Scale, while others focus on occurrence of retreatment (Target Aneurysm Retreatment Rate).
Question to the Panel #6
Please discuss the strengths and limitations of each scale below. In your response, please discuss the utility of using each scale as a primary study endpoint:

- Raymond Scale
- Meyers Scale
- Kamran Scale
- Szikora Scale
- Target Aneurysm Retreatment Rate
Incorporating Secondary Endpoints

Clinical outcome measures provide another method for assessing the safety and effectiveness of a device. FDA has identified the following:

- **Secondary Effectiveness Endpoints:**
  - Retreatment Rate,
  - Recanalization,
  - Change in modified Rankin Scale,
  - Change in Raymond Scale,
  - < 50% Stenosis,
  - Aneurysm occlusions of 90% or 95%,
  - Improvement in symptoms.
Incorporating Secondary Endpoints

- Secondary Safety Endpoints:
  - Death
  - Neurological death
  - Stroke
  - Neurological deficit
  - Transient ischemic attack
  - Aneurysm rupture
  - Neuropsychological effects (dementia)
  - Complications of cerebral angiography
  - Complications of anti-platelet therapy
  - Silent brain imaging changes
Incorporating Secondary Endpoints

Question to the Panel #7

a. Please discuss the relevance of the secondary safety and effectiveness endpoints above.

b. Are there any additional endpoints to consider in evaluating endoluminal aneurysm treatment safety and effectiveness?

c. For a performance goal based study, how should a composite safety endpoint be determined given each safety component has a different severity?
Flow diversion is approved in the U.S. for endovascular treatment of large or giant wide-neck intracranial aneurysms in the internal carotid artery (ICA) from the petrous to the superior hypophyseal segment. One year pre-market follow-up with 5 year post market follow-up is one way to obtain clinical data on long term outcomes.

Question to the Panel #8
Given that the endoluminal occlusion of aneurysm by flow diverters is delayed (which could lead to delayed aneurysm rupture), is one year follow-up premarket sufficient to capture the major adverse events (safety) and demonstrate that the majority of the aneurysm healing has reached steady state (effectiveness)? In your response, please discuss what long term delayed adverse events should be considered when designing a post market study and how long should subjects be followed in order to capture the bulk of these delayed adverse events?
Thank You