

A FDA Staff Discussion on Endovascular Medical Devices Intended to Treat Intracranial Aneurysms

Neurological Devices Advisory Panel Meeting
March 1, 2018

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U.S. Food and Drug Administration (FDA)



Purpose of Current Panel Meeting

The purpose of this panel meeting is to discuss, make recommendations, and advise FDA regarding the evaluation of clinical study data to assess the risks and benefits of intracranial aneurysm treatment devices and factors that can affect clinical outcomes such as aneurysm morphology, size, and location in the neurovasculature.

Additionally, FDA is also convening this committee to seek expert opinion on the scientific and clinical considerations relating to the clinical trial design that may be relevant to the determination of safety and effectiveness for these devices.

Presentation Outline

- Purpose
- Cerebral Aneurysm Overview
- Aneurysm Treatment Methods
- Evaluating the Risks and Benefits of Aneurysm Treatments



April 2015 Advisory Committee Meeting

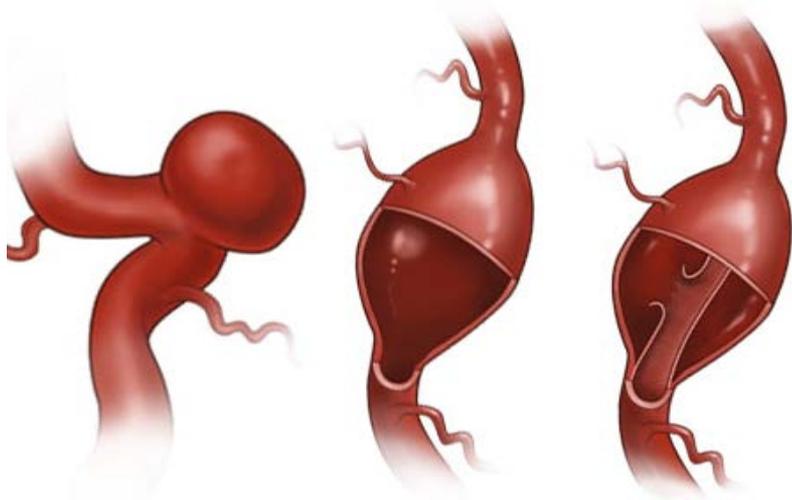
- Purpose was to obtain feedback on clinical and statistical considerations for clinical trial design evaluating intracranial aneurysm devices.
- Summary of Panel recommendations
 - Randomized controlled trials should always be considered, unless determined not to be feasible.
 - If performance goal (PG) based study is the only option, the PGs should be well justified and matched to the patient population studied.
 - One year follow up for these studies is reasonable for a premarket decision and 5 year follow up may be needed for postmarket data collection of long term adverse effects.
 - Aneurysms can be grouped into small/medium and large/giant with respect to risk and benefit profile in addition to considerations for anterior vs. posterior circulation, perforator rich₄ regions, and aneurysm morphology.

Cerebral Aneurysm Overview: Diagnosis and Characteristics

Samuel Raben, PhD
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Morphology of Cerebral Aneurysms

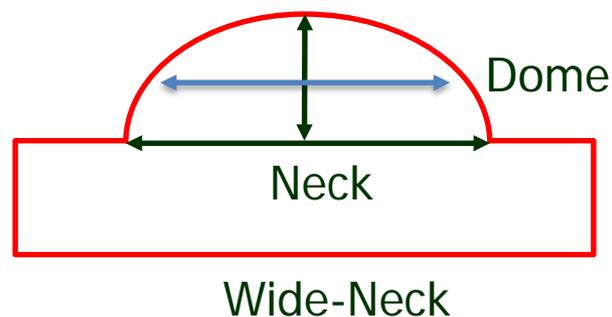
- Saccular aneurysms protrude from a side wall (most common)
- Fusiform is a dilation of the vessel
- Dissection is the result of a tear between the vessel wall layers.
- Wide Neck
 - Defined as neck width ≥ 4 mm or a dome to neck ratio < 2



Saccular

Fusiform

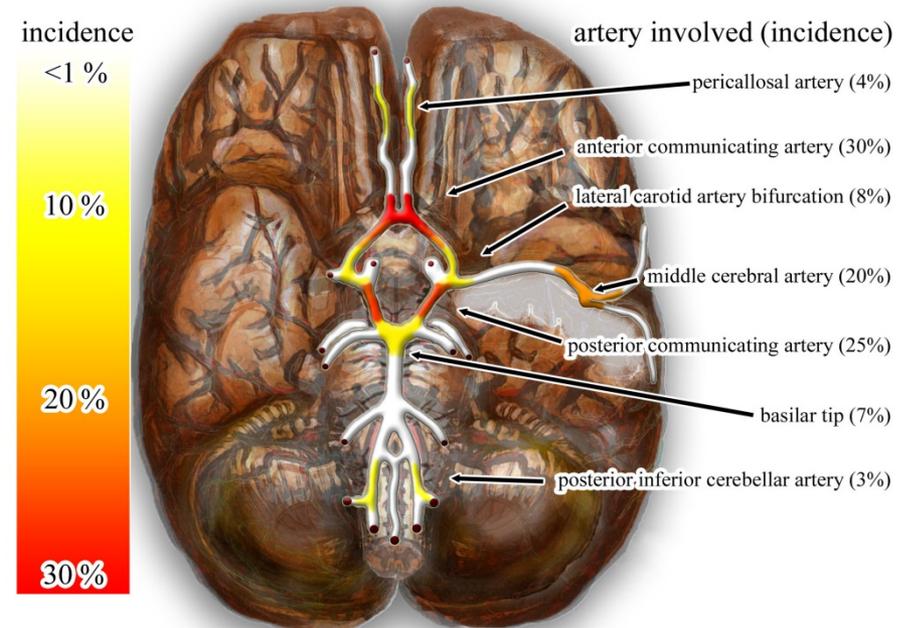
Dissection



Anatomical Locations

- Typically occur at or near vessel branch points or bifurcations
- Aneurysm occur more frequently in the anterior circulation
 - Anterior ~85%–90%
 - Posterior ~10%–15%
- Patient outcomes can be influenced by aneurysm location.

Most common sites of intracranial saccular aneurysms



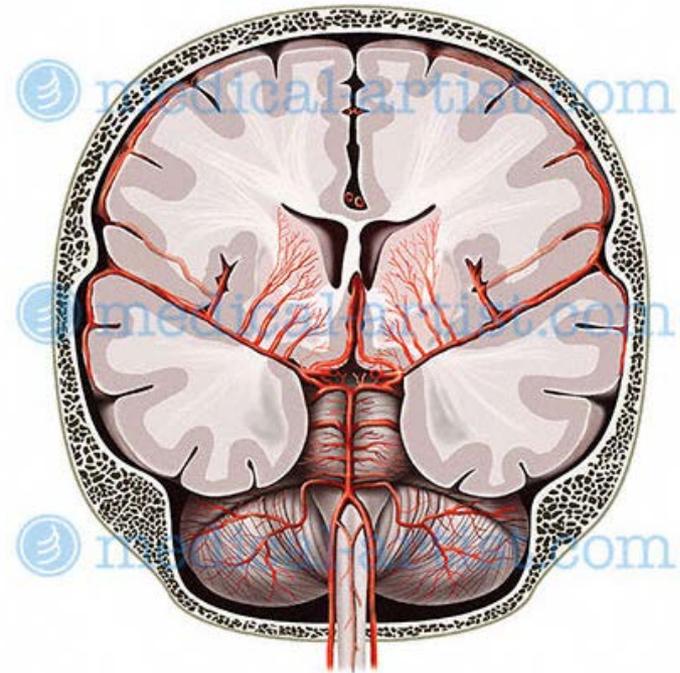
[Wikipedia]

The Role of Perforators in Interventional Treatment

- Perforators are small branches that emerge from large vessels that supply blood to various regions of the brain
- Exist in both the anterior and posterior circulation
- Can be affected by open surgical and endovascular treatment methods
 - Based on the endovascular treatments/device, it may affect the risk of perforator occlusion differently

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Cerebral Aneurysm Size

- Aneurysms sizes can vary
- Small aneurysms occur most frequently

Size	Range	Occurrence (n=1449)
Small	≤ 5 mm	47%
Medium	6-10 mm	27%
Large	11-25 mm	12%
Giant	≥ 25 mm	14%

(Wiebers 1998)

Risk Factors for Aneurysm Rupture

- Difficult to predict the risk of aneurysm rupture.
- Risk factors can include, but not limited to, family history, history of prior subarachnoid hemorrhage (SAH), gender, smoking, location of aneurysm, morphology, and overall size.

Rupture Rate over 5 years (n=4060)				
	<7mm	7-12mm	13-24mm	≥ 25mm
Anterior Circulation ICA, AComm, ACA, or MCA	0%	2.6%	14.5%	40%
Posterior Circulation/Posterior Communicating Artery	2.5%	14.5%	18.4%	40%

Wiebers, 2003



Aneurysm Treatment Methods

Regulatory Pathways

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 four pathways shown.

Premarket Notification (510(k))

- Clearance Standard:
 - Substantial equivalence to a predicate device
- General controls
- Special controls

De Novo

- Granting Standard:
 - Reasonable assurance of safety & effectiveness
- General controls
- Special controls

Humanitarian Device Exemption (HDE)

- Approval Standard:
 - Probable benefit outweighs risk from the use of the device
- Requires local IRB approval
- Less than or equal to 8,000 patients per year

Premarket Approval (PMA)

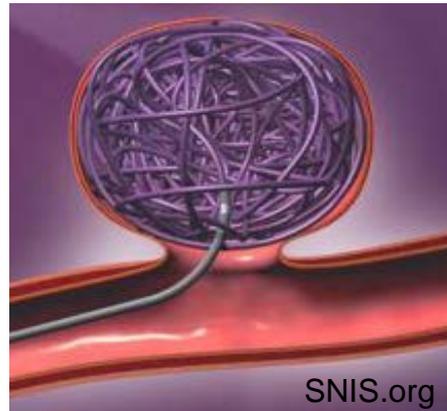
- Approval Standard:
 - Reasonable assurance of safety & effectiveness
- General and special controls alone are insufficient to assure the safety and effectiveness

Cerebral Aneurysm Treatments



- Endovascular Treatment
 - Coiling
 - Balloon Assisted Coiling (BAC)
 - Stent Assisted Coiling (SAC)
 - Flow Diversion (FD)
 - Intracranial Flow Disruption
- Open Surgery (Craniotomy)
 - Direct Clipping
- Medical Management
 - Observation

Neurovascular Embolization Coiling



- Technology
 - Typically made of metal
 - Consists of framing, filler, and finishing coils to pack the aneurysm sac
- Possible Benefits
 - Less invasive than open surgery
 - Controlled filling of the aneurysm sac and may be more amenable to treat various aneurysm shapes
- Possible Risks/Limitations
 - Not suitable to treat wide-neck aneurysms
 - Longer procedural time to fill aneurysm sac with multiple coils

Balloon Assisted Coiling (BAC)

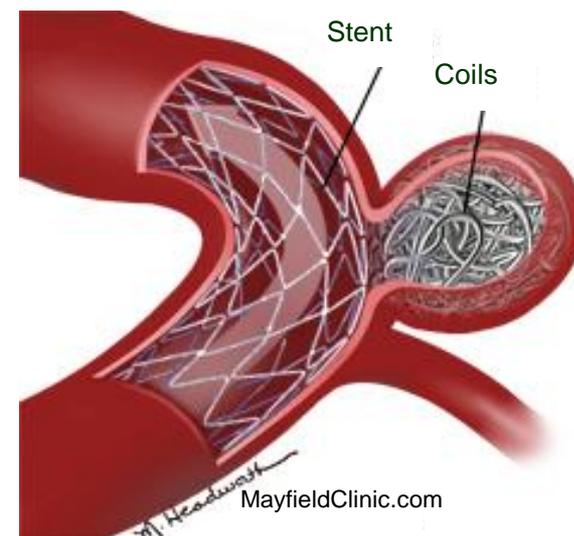


- Technology
 - Balloon catheter inflating across the aneurysm neck
 - Procedural use with traditional neurovascular embolization coils
- Possible Benefits
 - Increase coil density with no vessel implant
 - Complication rates similar to traditional coiling
- Possible Risks/Limitations
 - May not work with all aneurysm neck sizes (i.e., wide-neck aneurysms)



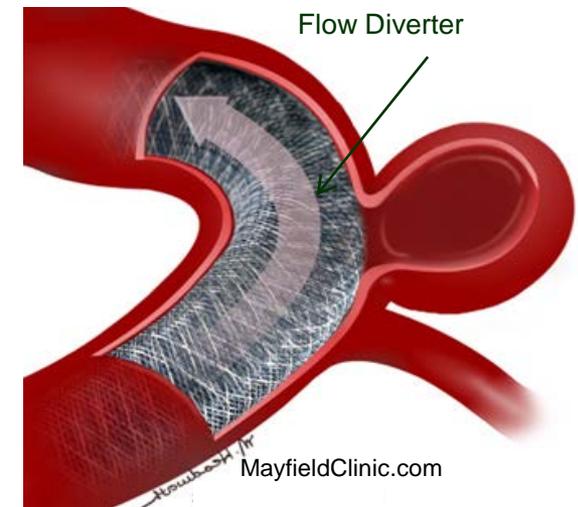
Stent Assisted Coiling (SAC)

- Technology
 - Self expanding stent placed permanently in the vessel to hold neurovascular embolization coils within the aneurysm sac
- Possible Benefits
 - Treatment of wide-neck aneurysms
- Possible Risks/Limitations
 - Unknown long term risks and effectiveness
 - Permanent implant
 - Must be used with antiplatelet therapy



Flow Diverters

- Technology
 - High mesh density metal stent permanently placed in the vessel to divert blood flow from entering the aneurysm sac
- Possible Benefits
 - Can treat wide-neck aneurysms
 - Used as a stand-alone device
 - Shorter procedural time
- Possible Risks/Limitations
 - Narrow approved Indication for Use
 - Interaction with perforators not well understood
 - Delayed effect of aneurysm securement until endothelialization takes place
 - Must be used with antiplatelet therapy



Intrasaccular Flow Disruption



- Technology
 - Devices placed into the aneurysm sac designed to seal the aneurysm neck from blood flow entering the aneurysm and promote thrombosis.
 - Intended to be a stand-alone device
- Possible Benefits
 - No permanent implant in the vessel lumen.
 - Single device implant vs. multiple embolization coils
 - Shorter procedural time
 - Can treat bifurcation and wide-neck aneurysms
- Possible Risks/Limitations
 - May only be suitable to treat a limited subset of aneurysm sizes and types based on device design
 - Long term risks and effectiveness unknown
 - Limited re-treatment options and retreatment risks unknown
- Currently no intrasaccular flow disruption devices on the US market.

Open Surgical Clipping



- Technology
 - Aneurysm clip(s) placed across the neck of the aneurysm
- Possible Benefits
 - Provide complete and immediate occlusion
- Possible Risks/Limitations
 - Open surgical risks and longer hospital stays
 - Not all are surgically accessible

Conservative Medical Management

- **Aneurysm Observation**
 - Regularly scheduled follow up imaging assessments for aneurysm growth or morphological changes
 - Reduction of rupture risk factors
 - Blood pressure control
 - Reduce/eliminate smoking
- **Possible Benefits**
 - No surgical or device-related risks
- **Possible Risks/Limitations**
 - Patient preference
 - Not well understood risk of aneurysm rupture

Summary of Treatment Options

- Different treatment approaches can have different risk benefit profiles
- Treatment options can vary based on aneurysm characteristics (e.g., size, location in the neurovasculature, morphology, wide-neck)
- Understanding the benefits and risk of different treatment options is a major focus of this Advisory Committee meeting, and how the current clinical landscape can be applied to the review of clinical data of new aneurysm devices



Evaluating the Benefits and Risks of Aneurysm Treatments

Patrick Noonan, Jr., MD

Interventional Neuroradiologist, Medical Officer

CDRH/ODE/DNPMD/NIDB



Benefit Risk Assessment

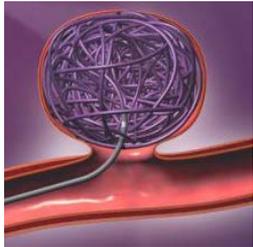
1. The uncertainty in the benefits and the risks;
2. Characterization of the disease;
3. Patient tolerance for risk and perspective on their benefit;
4. The availability of alternative treatments or diagnostics;
5. Any risk mitigation strategies available;
6. The possibility of obtaining post-market data that improves the information about device outcomes; and
7. Whether a device represents a novel technology that addresses an unmet medical need.



Evaluating Potential Benefits and Risks of New Aneurysm Treatment Devices

- Limitations may exist in determining which aneurysms are best treated with each treatment modality based upon the clinical data collected
- Many factors may be considered in evaluating benefit-risk of new devices including:
 - Device designs
 - Limitation of clinical study data
 - Patient population studied (aneurysm characteristics)
 - Ruptured versus unruptured aneurysms
 - Follow up duration
 - Safety and effectiveness endpoints
 - Rate of adverse events and aneurysm occlusion

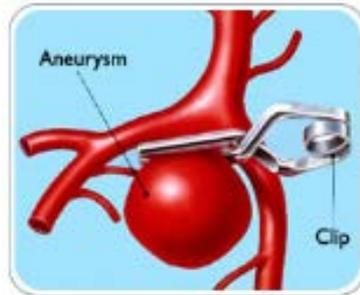
Regulatory Considerations and Levels of Evidence



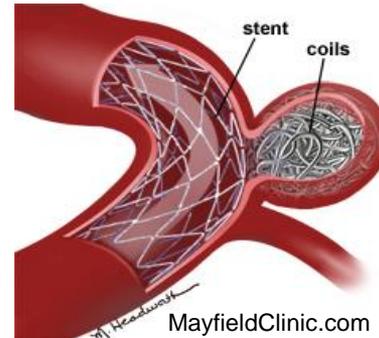
SNIS.org



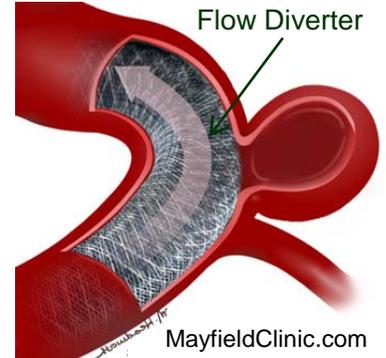
L. Pierot et al. AJNR 2012



universityneurosurgery.com



MayfieldClinic.com



MayfieldClinic.com

Neurovascular Embolization Coils, BAC, Aneurysm Clips

510(k) Pathway – Substantial Equivalence

Numerous Devices Marketed in US

SAC - Humanitarian Device Exemption (HDE) – Safety & Probable Benefit

4 Devices Approved in US

- Neuroform EZ, 3, ATLAS (H020002)
- Enterprise VRD (H060001)
- LVIS (H130005)
- PulseRider (H160002)

Flow Diverter - Premarket Approval (PMA) – Safety & Effectiveness

1 Device Approved in US

- Pipeline & Pipeline Flex Embolization Device (P100018)

Increasing Level of Evidence to Support Marketing Approval in US

Mostly performance standards (e.g., nonclinical in vitro and/or in vivo studies)



Small human safety clinical trials (e.g., ~ 30 subjects)



Well controlled human pivotal clinical trials (e.g., prespecified hypothesis testing, endpoints, multicenter, statistically justified sample size)

Valid Scientific Evidence

Per 21 CFR 860.7(c)(2), “valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.”

A Sample of Clinical Trial Designs

Hierarchy of Clinical Trial Designs

Randomized Controlled Trial	Lowest Level of Uncertainty
Non-Randomized Controlled Trial	
Single-Arm Performance Goal (PG) Study	Highest Level of Uncertainty
Retrospective Study Descriptive Study Case Series	

Study Design Considerations

- July 9, 2012 Revision of FDA Safety and Innovation Act
 - ❖ IDE studies cannot be disapproved based on study design issues.

Primary Endpoints for Safety and Effectiveness

- **Safety**
 - Rate of neurological deaths and major ipsilateral strokes defined as an increase in the National Institutes of Health Stroke Scale (NIHSS) ≥ 4 points from baseline during the stroke event
- **Effectiveness**
 - Percent of subjects who achieve complete (100%) Raymond I classification without significant artery stenosis ($\geq 50\%$) or retreatment of the target aneurysm

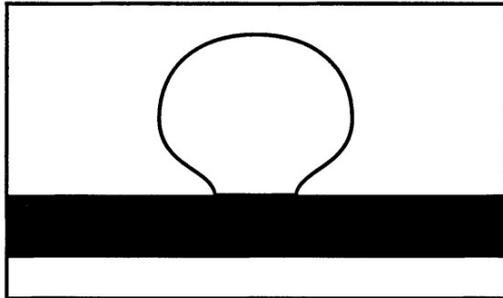
Secondary Endpoints

- Safety/Effectiveness
 - Modified Rankin Scale (mRS)
 - Surgical technical success and device placement
 - Retreatment and use of adjunctive devices
 - Recurrence of target aneurysm
 - Procedural time
 - Radiation exposure

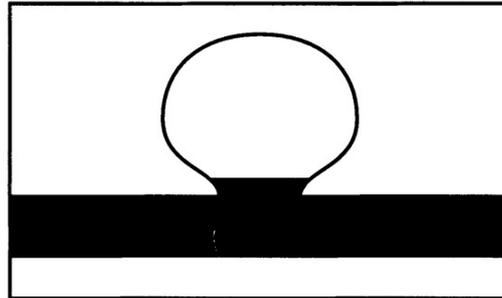
Serious Adverse Events (SAEs) Associated with Aneurysm Treatment Devices

- Minor strokes
- Transient ischemic attacks
- Subarachnoid hemorrhage
- Device migration
- Dual antiplatelet therapy (DAPT) related adverse events
- Access site issues
- Delayed aneurysm rupture

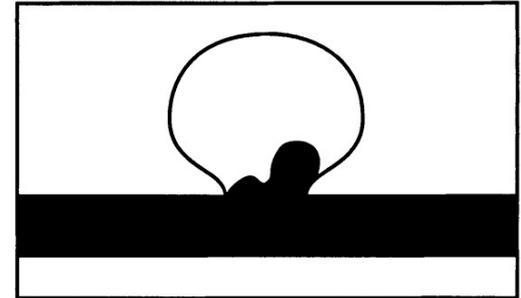
Adequate Aneurysm Occlusion



COMPLETE



RESIDUAL NECK



RESIDUAL ANEURYSM

[R.S. Quadros et al. ANJR 2007]

Follow-Up Duration

Balancing Pre-/Post-Market Review

- Premarket
 - FDA decisions have been made with 1 year follow-up data for PMAs and 6 months follow-up for HDEs
- Postmarket
 - Clinical studies have consented subjects to 5 years of follow-up if post-approval studies or long-term follow-up is needed as a condition of approval of the marketing application

Labeling

- Labeling is important to provide information about the product, including the indicated patient population.
- Labeling may be used to clarify to users the evidence in support of a medical device.
- Labeling can also link to the type of data collected.



Closing Remarks

- The purpose of today's public meeting is to discuss and obtain Panel advice regarding the evaluation of clinical study data to assess the potential benefits and risks of intracranial aneurysm treatment devices and factors that can affect clinical outcomes such as aneurysm morphology, size, and location in the neurovasculature.
- Listen to multiple stakeholders on additional factors important in assessing the benefit/risk relationship for evaluating aneurysm treatment devices.
- Later this afternoon, we look forward to the Panel's recommendations regarding aneurysm treatment devices to support FDA's mission to ensuring U.S. patients have access to high-quality, safe, and effective medical devices of public health importance first in the world.

Thank You

Questions?