# General Issues: Meeting to Discuss the Evaluation of Safety and Effectiveness of Endovascular Medical Devices Intended to Treat Intracranial Aneurysms

Neurological Devices Panel

March 1, 2018

# Introduction

**Jacques Dion, MD**

Vice President Scientific Affairs

MicroVention

# Unified Industry Presentation

BALT

Medtronic

phenox
German engineering - cathlab inspired

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# Presentation Focus to Advance Aneurysm Treatment and Patient Care

- Target aneurysm treatment populations and challenges associated with natural history data
  - All aneurysms, including small aneurysms, present risks to patients and should be considered for treatment
- How to use current safety and effectiveness data to evaluate new device technology
- Recommendations and post-marketing studies

# Agenda

| | |
|---|---|
| **Aneurysm Disease Background** | **Jacques Dion, MD**<br>Vice President Scientific Affairs<br>MicroVention |
| **Current Clinical Trial Data to Support Safety and Effectiveness** | **Stacey Pugh**<br>Vice President and General Manager<br>Medtronic Neurovascular |
| **Recommendations and Conclusion** | **John Allison, RAC**<br>Vice President, Regulatory and Clinical Affairs<br>Stryker Neurovascular |

# Aneurysm Disease Background

**Jacques Dion, MD**

Vice President Scientific Affairs

MicroVention

# Significant Consequences of Intracranial Aneurysms (IAs)

- 2–5% of adults have an IA[1]
- Screening for IAs not standard practice
- Majority of IAs asymptomatic and undiagnosed prior to rupture
- Ruptures typically occur suddenly and often lead to cerebral bleeding or subarachnoid hemorrhage (SAH)
- SAH is a devastating disease[2]
  - ~45% of events are fatal
  - ~50% of survivors experience significant disability

1) Thompson, 2015; 2) Lantigua, 2015

# Difficult to Predict Risk of Rupture

- Aneurysm rupture attributed to many factors
  - Size, morphology, location, prior history of SAH
- Consistent trends in literature demonstrate increased risk
  - Larger vs. smaller
  - Posterior circulation vs. anterior circulation
- Severity and consequences associated with rupture independent of size and location

# Reliable Conclusions Challenging to Draw from Natural History Studies

- International Study Unruptured Intracranial Aneurysms (ISUIA)
  - Initial report published 1998
  - Post-hoc re-analysis of data 2003
- Two natural history of aneurysm studies in large cohorts in Finland and Japan
- Inconsistency in studies creates uncertainty regarding prevalence

**International Study of Unruptured Intracranial Aneurysms Investigators, 1998 and 2003**
**The UCAS Japan Investigators, 2012; JUVELA, 2000**

# ISUIA Study Design

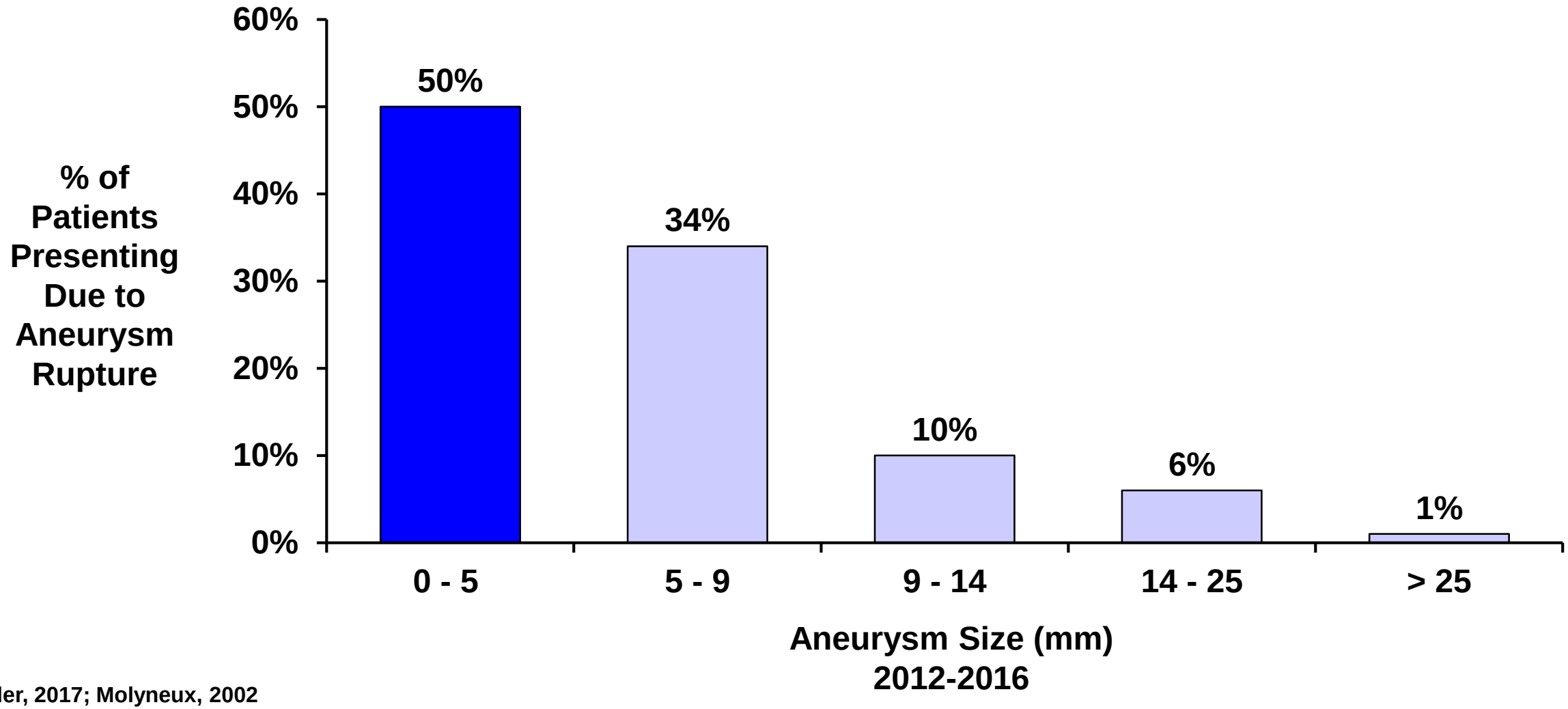
- Large, retrospective and prospective, cohort study
  - 60 centers in USA, Canada and Europe
- Patients evaluated in 3 non-randomized cohorts
  - Observation, surgical, and endovascular treatment
- 2 groups broadly defined for observation
  - Group 1 without history of SAH
  - Group 2 with history of SAH
- Patients followed annually for 4 years with standardized questionnaire
- 1998 retrospective analysis in 1449 patients
  - Group 1 aneurysm < 10 mm had rupture rate of < 0.05%

# ISUIA (2003) Post-Hoc Re-Analysis Suggest No Risk to Patients with Aneurysms < 7 mm

| 5-Year Cumulative Risk, % | < 7 mm | | 7–12 mm | 13–24 mm | ≥ 25 mm |
|---|---|---|---|---|---|
| | No SAH Separate Aneurysm | SAH Separate Aneurysm | | | |
| Cavernous Carotid Artery (N=210) | 0 | 0 | 0 | 3.0 | 6.4 |
| AC/MC/IC (N=1037) | 0 | 1.5 | 2.6 | 14.5 | 40 |
| Post-PCom (N=445) | 2.5 | 3.4 | 14.5 | 18.4 | 50 |

AC=Anterior communicating or anterior cerebral artery; IC=internal carotid artery (not cavernous carotid artery); MC=middle cerebral artery; Post-PCom=vertebrobasilar, posterior cerebral arterial system, or posterior communicating artery

# Majority of Ruptured Aneurysms Are Small




Bender, 2017; Molyneux, 2002

# ISUIA Study Limitations

- Post-hoc reconstructions of artificial subgroups
- Methodological factors impacting low rate of reported rupture
  - Selection bias
  - Arbitrary assignment of PCom aneurysms to posterior circulation
  - High crossover rate from observation to treatment group
  - Undefined observational periods with no predefined hypotheses, sample size, subgroup definitions
  - Aneurysms < 2 mm excluded

Raymond, 2008

# Goals of Treatment

- Primary goal to prevent rupture and related morbidity and mortality
- Secondary goals
  - Symptom relief due to mass effect
  - Prevent further growth
  - Prevent thrombus formation

# Surgical Clipping High Occlusion Success but Limited to Certain Anatomical Locations

- Current options are surgical or endovascular
  - Surgical clipping associated with high occlusion success, but safety varies according to location
- 1.7 – 2.6% mortality rate[1,2]
- 5 – 10.9% permanent morbidity rate[1,2]
- ISUIA: 2.3 / 12.1%[3]
- Surgical risk related to location[2]:
  - Small (< 10 mm): 4%
  - Large (10 – 24 mm): 12.1%
  - Giant (> 25 mm): 26.5%
  - Anterior vs. posterior: RR = 4.1

1) Kotowski; 2) Raaymakers, 1998; 3) ISUIA, 2003

# Endovascular Treatment Options Evolving

- Progression of endovascular treatment
  - Coiling
  - Stent-assisted coiling
  - Balloon assisted coiling
  - Flow diversion
- Innovative and refined endovascular treatments reduce complications and improve outcomes

Etminan, 2016

# FDA Question 3

*What patient characteristics justify foregoing treatment for an aneurysm that would otherwise be considered for treatment?*

# Factors to Consider for Aneurysm Treatment

- Life expectancy
- Family history of aneurysmal SAH
- Co-morbidities (poorly controlled HTN, PKD, smoking)
- Aneurysmal growth on sequential imaging
- Aneurysm location
- Risk of treatment
- Patient choice

# All Patients Need Treatment Options

- Who and when to treat
- Risks of surgical and endovascular treatments well-described
- Inconsistent literature reports make interpretation of natural history difficult[1]

1) ISUIA

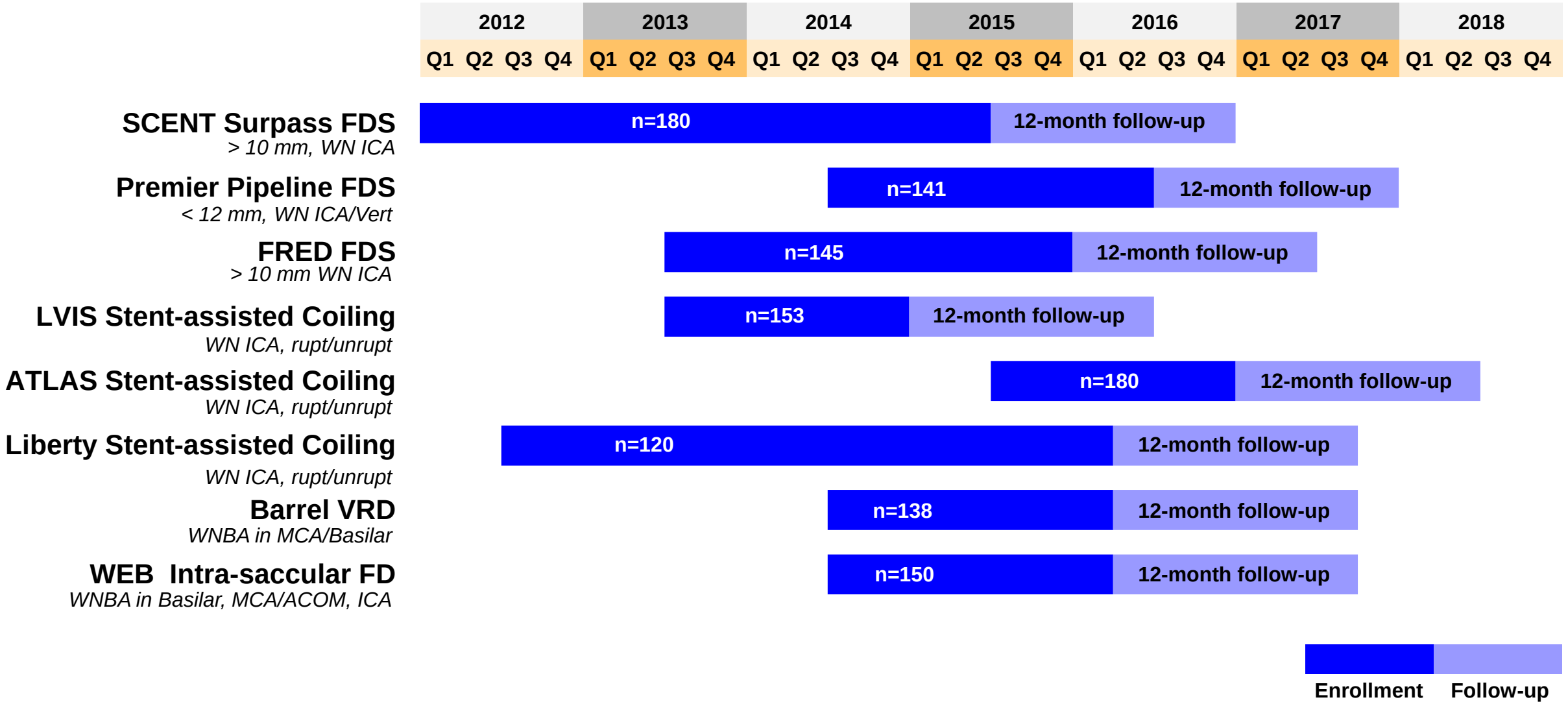
# Current Clinical Trial Data to Support Safety and Effectiveness

**Stacey Pugh**

Vice President and General Manager

Medtronic Neurovascular

# Ongoing IDE Trials for Aneurysm Treatment



# Similar Characteristics Across All 8 Studies

| Operating Characteristics | Common Features |
|---|---|
| Prospective, multi-center, single-arm, PG driven studies | ✓ |
| 12-month primary safety endpoints | ✓ |
| 12-month primary effectiveness endpoints | ✓ |
| Formal hypothesis and predetermined statistical analysis plan | ✓ |
| Core Lab adjudications of imaging endpoints | ✓ |
| Independent DSMB and CEC review | ✓ |

# Industry Perspective on FDA Questions

# FDA Question 2

*Can the mRS at 1 year also be a potential primary safety outcome measure for all endovascular device trials?*

# mRS Suitable for Ischemic Stroke but Challenging for Aneurysm Therapy

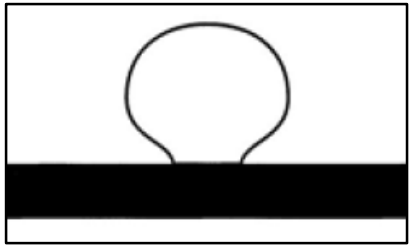
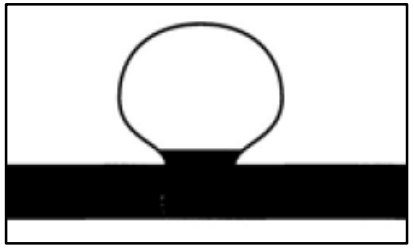
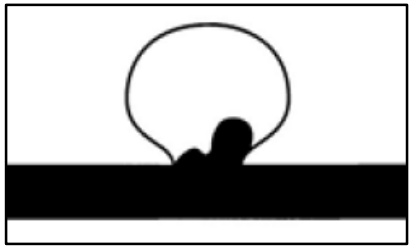
- Challenging in evaluation of ruptured aneurysm treatment due to significant disabilities present at or near time of treatment
  - Pre-rupture: not reflective of disability from rupture
  - Post-treatment: could mask procedure related harm
- Non-specific to cause of functional dependency
- Changes in mRS scores could be due to factors other than aneurysm treatment
- Period of observation for ischemic stroke is 3 months, not 12 months as in aneurysm therapy

# FDA Question 4

*4a: Do you consider the Raymond Classification Scale to be the standard to assess effectiveness for ALL endovascular intracranial aneurysm treatment devices?*

*4b: If the Raymond Classification scale is used, is Raymond II (or higher) classification a satisfactory outcome for aneurysm patients with unruptured aneurysms? And is Raymond II (or higher) classification a satisfactory outcome for aneurysm patients with ruptured aneurysms?*

# Raymond-Roy Classification System Most Established and Reasonable Method to Assess Aneurysm Occlusion

| Raymond Classification | Definition | Example |
|---|---|---|
| Class I | Complete occlusion of aneurysm including neck |  |
| Class II | Persistence of original arterial wall defect without opacification of aneurysmal sac |  |
| Class III | Opacification of aneurysmal sac |  |

# FDA Question 6

*Do aneurysm occlusion assessment recommendations using Raymond differ for endosaccular devices?*

# Evaluation of Occlusion via Raymond-Roy in Aneurysm Treatment Trials

| | Intra-Luminal | Intra-Saccular | | |
|---|---|---|---|---|
| | Flow Diversion | Coiling | Stent-Assisted Coiling or Balloon Assisted Coiling | Intra-Saccular Flow Disruption |
| Raymond I | ✓ | ✓ | ✓ | ✓ |
| Raymond II (Stable) | ✗ | ✓ | ✓ | ✓ |
| Raymond II (Not Stable) | ✗ | ✗ | ✗ | ✗ |
| Raymond III | ✗ | ✗ | ✗ | ✗ |

Mazur, et al. *J NeuroIntervent Surg.* 2016

# Evaluation of Stable Raymond II for Intra-Saccular Technologies

| | Coiling | Stent-Assisted Coiling or Balloon Assisted Coiling | Intra-Saccular Flow Disruption |
|---|---|---|---|
| **Raymond I** | ✓ | ✓ | ✓ |
| **Raymond II (Stable)** | ✓ | ✓ | ✓ |
| **Raymond II (Not Stable)** | ✗ | ✗ | ✗ |
| **Raymond III** | ✗ | ✗ | ✗ |

What is stable Raymond II?

- Defined by serial observations via MRA/DSA required to establish “stability”
- ≥ 6 months apart from first assessment
- Assessments must demonstrate equal or better occlusion of the neck remnant

# Evaluation of Stable Raymond II for Intra-Saccular Technologies

| | Coiling | Stent-Assisted Coiling or Balloon Assisted Coiling | Intra-Saccular Flow Disruption |
|---|---|---|---|
| **Raymond I** | ✓ | ✓ | ✓ |
| **Raymond II (Stable)** | ✓ | ✓ | ✓ |
| **Raymond II (Not Stable)** | ✗ | ✗ | ✗ |
| **Raymond III** | ✗ | ✗ | ✗ |

- Raymond II stable outcomes ONLY acceptable for intra-saccular technology evaluation
- Evaluation must be adjudicated by independent core lab
- Primary effectiveness analysis at 1 year for Raymond II could not occur until 2 stable assessments
- Raymond II occlussions must be followed for 2 years post-efficacy assessment for recurrence or growth

# FDA Question 8

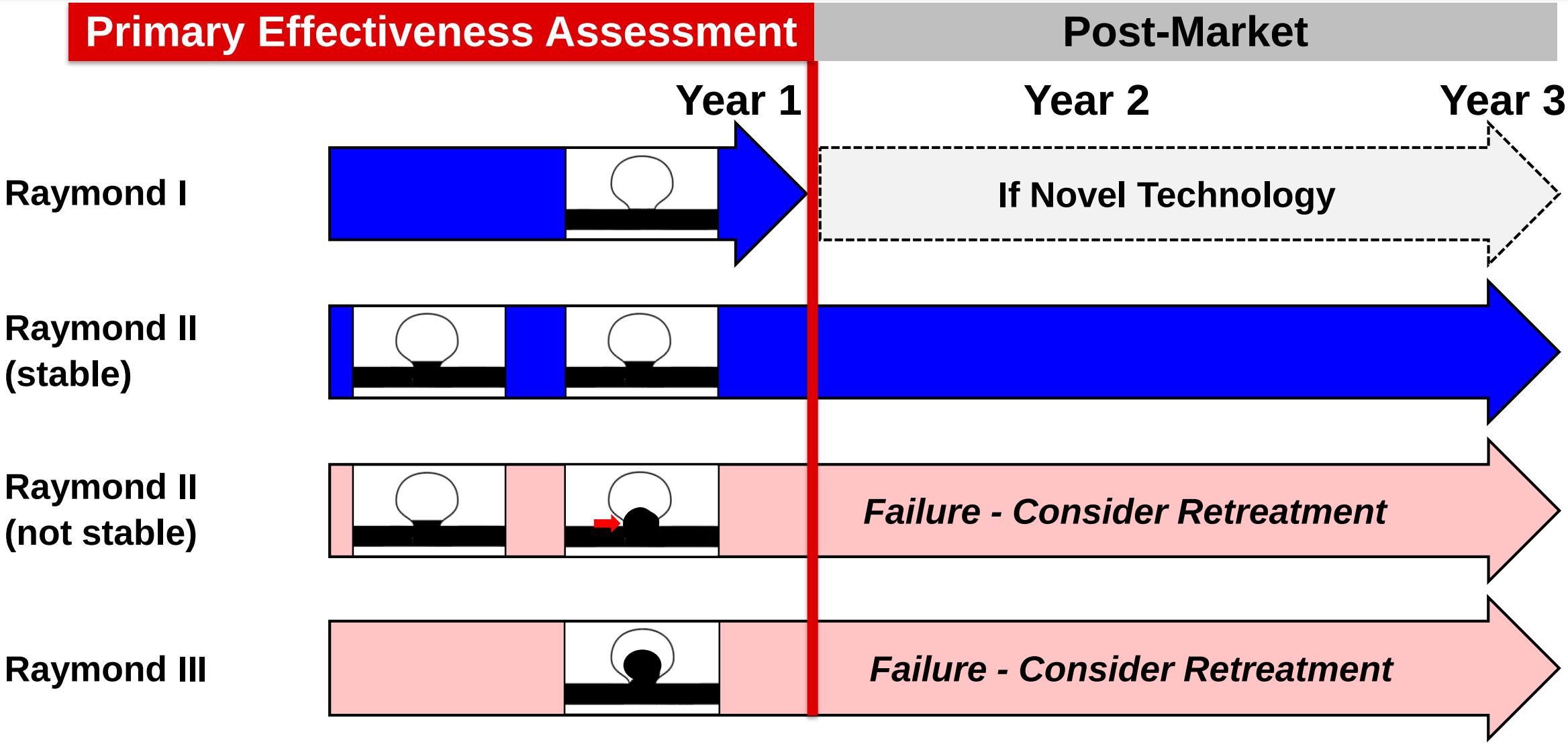
*Does a worsening in the Raymond scale at follow-up imaging warrant retreatment and should FDA consider a worsening of the Raymond scale during 1 year follow-up to represent a failure of treatment?*

# FDA Questions 7 and 10

*7: What length of follow-up is recommended to assess effectiveness for endovascular aneurysm treatment devices?*

*10: What is a sufficient long term follow-up period for a post-approval study where the majority of patients have the following outcomes for ruptured or unruptured aneurysms?*

# Recommendations for Duration of Follow-Up by Raymond-Roy Status



# How Subjects Report to Analysis When "Raymond II – Stable or Improved" Is Acceptable Primary Endpoint Outcome

**Primary Effectiveness Assessment**

| | 6 Months | | 12 Months | Reports to Primary Endpoint as |
|---|---|---|---|---|
| Subject 1 | I | → | I | SUCCESS |
| Subject 2 | II | → | I | SUCCESS |
| Subject 3 | III | → | I | SUCCESS |
| Subject 4 | II | → | II Stable | SUCCESS |
| Subject 5 | III | → | II | SUCCESS |
| Subject 6 | I | → | II | FAILURE |
| Subject 7 | II | → | II Unstable | FAILURE |
| Subject 8 | I | → | III | FAILURE |
| Subject 9 | II | → | III | FAILURE |
| Subject 10 | III | → | III | FAILURE |

# FDA Question 9

*We consider digital subtraction angiography (DSA) to be the gold standard to assess aneurysm occlusion at follow-up. Can magnetic resonance angiography (MRA) or computed tomography angiography (CTA) serve as a surrogate follow-up examination and when should this take place?*

# Alternative Imaging Assessments

- DSA gold standard to assess aneurysm occlusion
  - Invasive and not without risks
- MRA offers advantages compared to DSA[1]
  - May be appropriate alternative to DSA for some treatment technologies
  - MRA positive correlation to DSA with assessing occlusion[2,3]
- Non-invasive MRA eliminates risk of cerebral thromboembolism and ionizing radiation[2]
- AHA Guidelines state MRA is reasonable alternative to DSA for follow-up for treated aneurysms[1]

1) Thompson. *Stroke*, 2015; 2) S.R. Boddu et al. 2014; 3) M.J. van Amerongen et al. 2014

# IDE Studies Conducted Allow Meaningful Analysis of Safety and Effectiveness

- Studies can be assessed for effectiveness via Raymond-Roy scale of aneurysm occlusion
- Provided clarity regarding nuances of this scale as it relates to technology and acceptable outcome
  - Recommendations for subject follow-up and reporting
- Articulate specific challenges for requirement for aneurysm study follow-up imaging

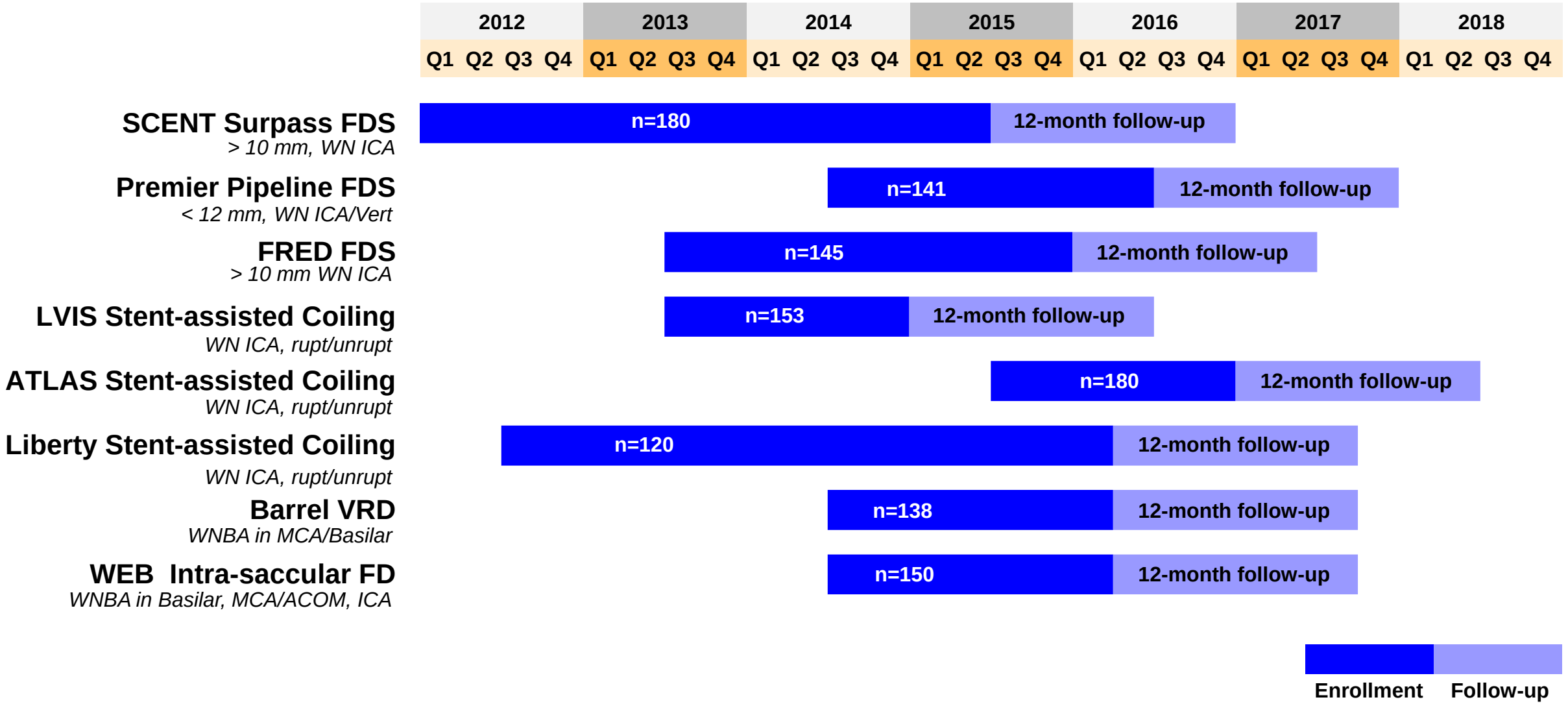
# Recommendations for Current and Future Studies for Aneurysm Treatment and Conclusion

**John Allison, RAC**

Vice President, Regulatory and Clinical Affairs

Stryker Neurovascular

# Ongoing Multiple Single-Arm IDE Studies



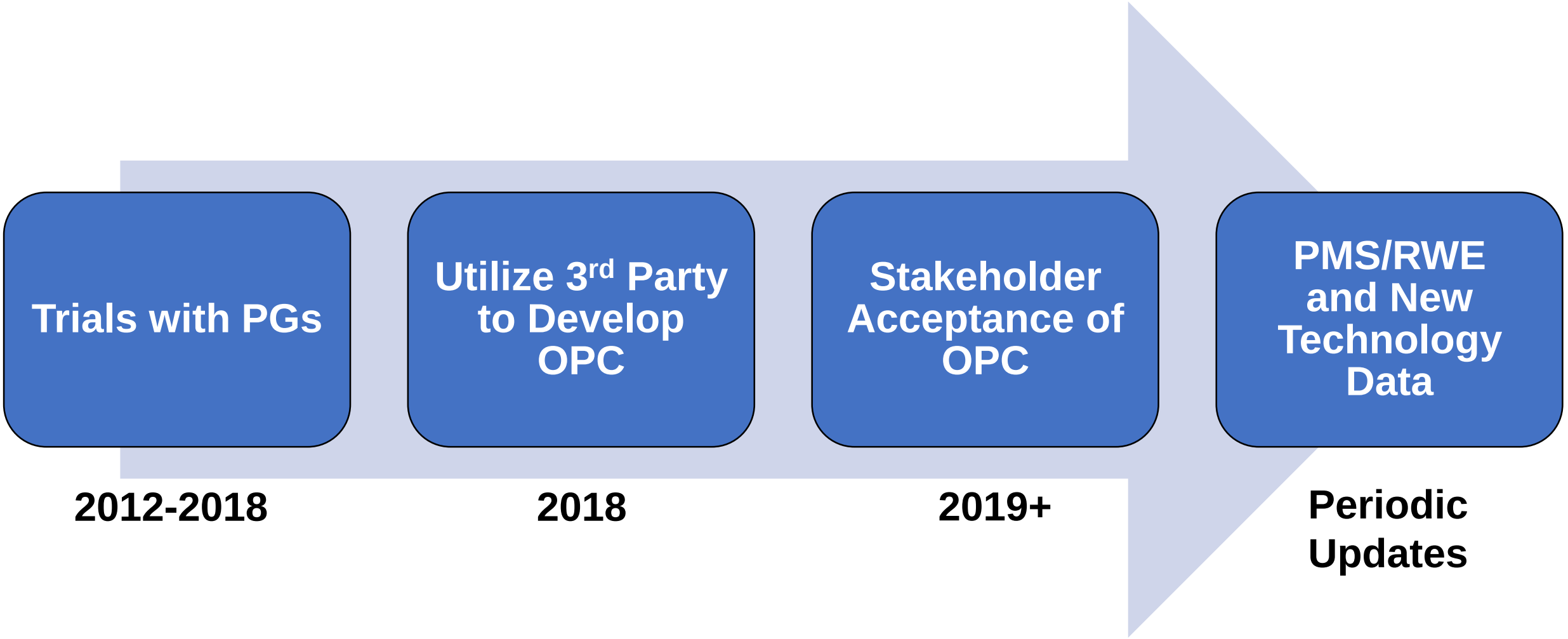
# Current Single-Arm Studies with PGs Generate Sufficient Evidence for Approvals

- Most practical and pragmatic approach to understanding success and failure of innovative devices
- Well-designed, multi-center, and core lab adjudicated
  - Builds evidence in area of high unmet medical need
- Generates sufficient evidence for PG assessment in high heterogeneous, low volume population
- Serves as future standard for well-defined OPC models

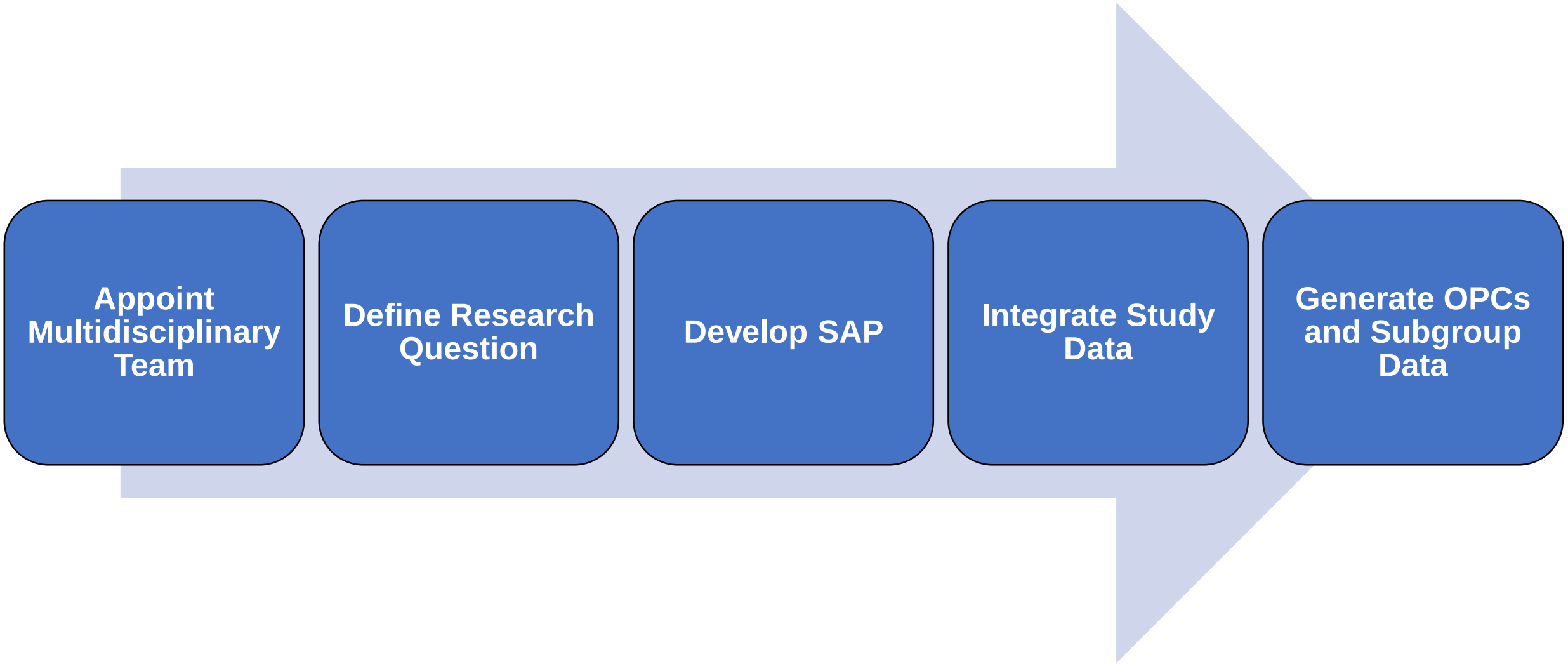
# Unified Industry Proposal to Generate OPCs

- Appointment of independent 3rd party to oversee OPC creation
  - Participation from industry partners, medical societies and FDA
- Published data from current IDE studies to validate OPC(s) per aneurysm type and influence evidence-based guidance
- Pooling patient level data to better answer questions on subgroups
- Enable FDA to include OPC(s) in future guidance document

# Timeline for Generation of OPC



# Implementation of OPC



# OPCs Are Being Used in Other Therapeutic Areas

*"Development of robust OPCs generally requires relatively mature device technology and the availability of high quality historical clinical evidence"*[1]

- Examples of devices with existing OPCs
  - Ventricular assist devices
  - Endometrial ablation
  - Heart valves
  - Critical limb ischemia laser angioplasty devices

[1]Kumar et al, J Vasc Surg 2009

# Efforts to Develop OPCs Already Initiated in Neurovascular Space

- Wide-Neck Bifurcation Aneurysm[1] OPC Publication
  - Meta-analysis of surgical clipping and EVT (coil, stent and coil) strategies for saccular WNBAs (S/M/L), using PRISMA-P* approach
  - Effectiveness: 43 articles (2,794 aneurysms treated) plus CCT WNAD**
  - Safety: 65 articles (5,366 patients treated)
- Literature-derived OPCs could be used in evaluation of novel wide-neck bifurcation devices

***PRISMA-P: Preferred Reporting Items for Systemic Review and Meta-Analysis Protocols**
****CCT WNAD: patient-level dataset from Cerecyte Coil Trial**

**1) Fiorella D, et al. *J Neurointerven Surg.* 2017.**

# Conclusion

- Aneurysms at risk of rupture regardless of size warrant consideration for treatment
- Provided industry perspective and practical solutions
- Current single-arm PG studies can provide reasonable assurance of safety and effectiveness
- Numerous IDE studies near completion and evidence maturing to derive OPC model
- OPCs can establish clinical trial design standards

# General Issues: Meeting to Discuss the Evaluation of Safety and Effectiveness of Endovascular Medical Devices Intended to Treat Intracranial Aneurysms

Neurological Devices Panel

March 1, 2018

# Q&A Slides Shown

# Same Primary Endpoints Across all Studies

| Study | Primary Effectiveness Endpoint: 12 Months 100% occlusion of the aneurysm without clinically significant stenosis or retreatment | Primary Safety Endpoint 12 Months Percent of subjects experiencing neurologic death or major ipsilateral stroke |
|---|---|---|
| SCENT Surpass FDS | ✓ | ✓ |
| Premier Pipeline FDS | ✓ | ✓ |
| FRED FDS | ✓ | ✓ |
| LVIS Stent assisted Coiling | ✓ | ✓ |
| ATLAS Stent assisted Coiling | ✓ | ✓ |
| Liberty Stent assisted Coiling | ✓ | ✓ |
| Barrel VRD | ✓ | ✓ |
| WEB Intrasaccular FD | ✓ | ✓ |