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** Vice President Scientific Affairs MicroVention
Current Clinical Trial Data to Support Safety and Effectiveness	**Stacey Pugh** Vice President and General Manager Medtronic Neurovascular
Recommendations and Conclusion	**John Allison, RAC** Vice President, Regulatory and Clinical Affairs 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

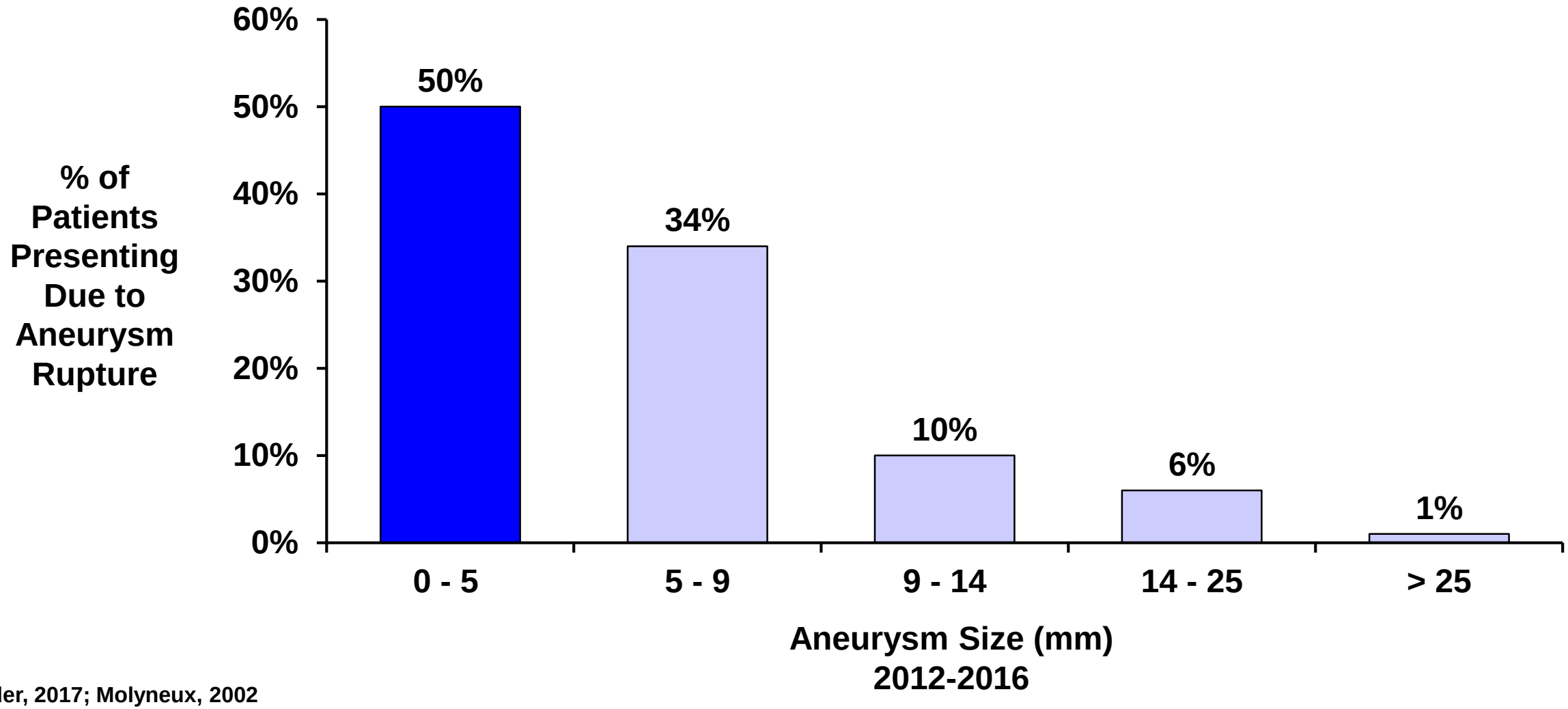
- Large, retrospective and prospective, cohort study
  - 60 centers in USA, Canada and Europe
- Patients evaluated in 3 non-randomized cohorts
  - Observation, surgical, and endovascular treatment
- 2 groups broadly defined for observation
  - Group 1 without history of SAH
  - Group 2 with history of 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

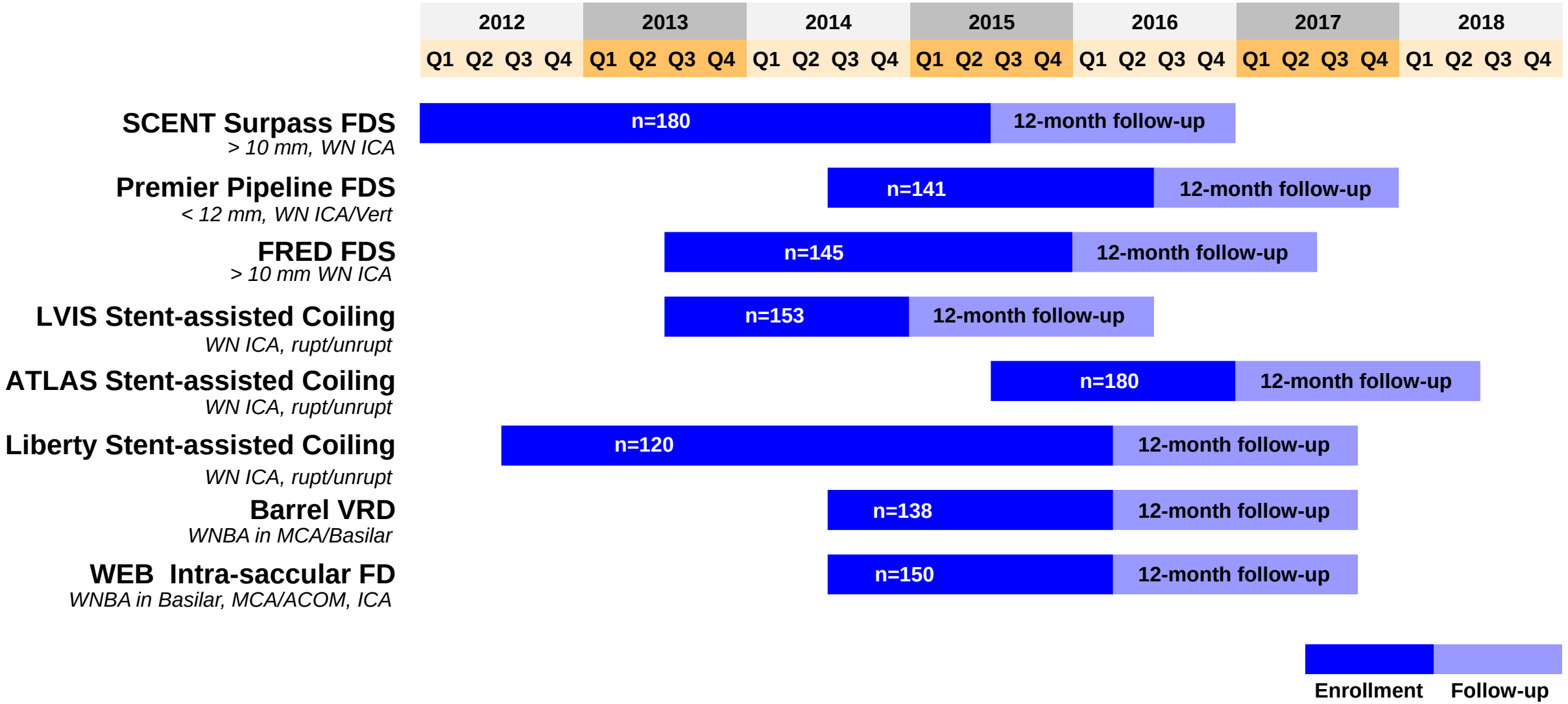
Current Clinical Trial Data to Support Safety and Effectiveness

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

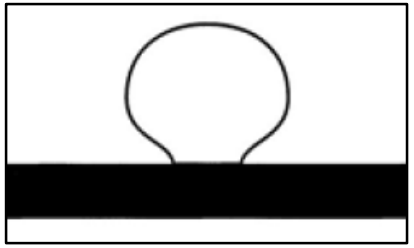
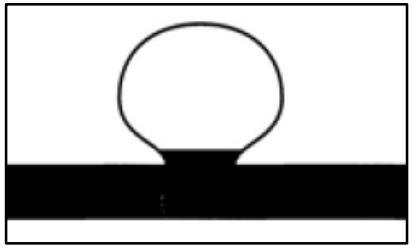
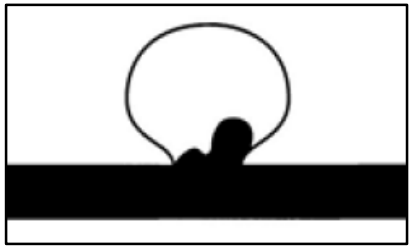
- Challenging in evaluation of ruptured aneurysm treatment due to significant disabilities present at or near time of treatment
  - Pre-rupture: not reflective of disability from rupture
  - Post-treatment: could mask procedure related harm
- Non-specific to cause of functional dependency
- Changes in 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

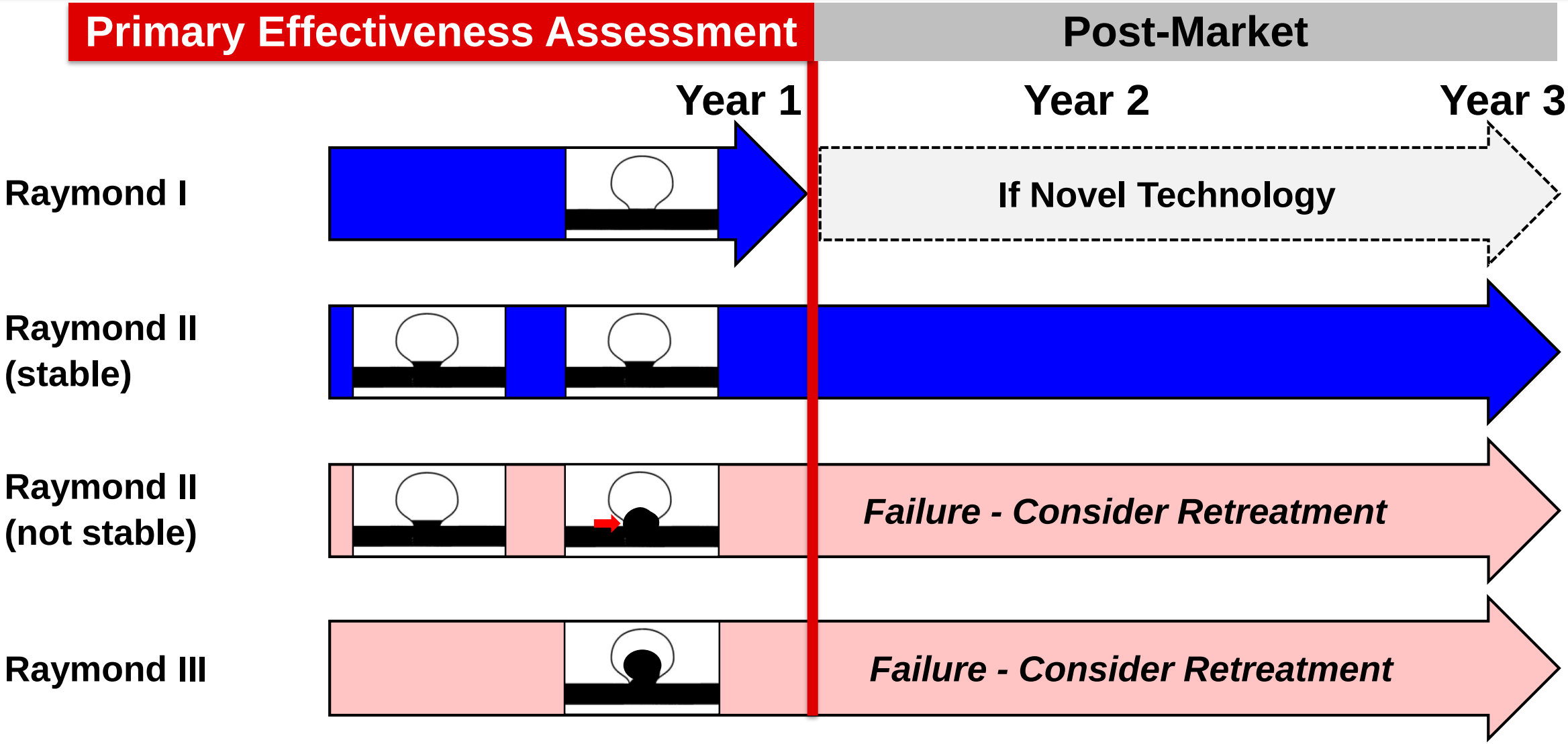
Does a worsening in the Raymond scale at follow-up imaging warrant retreatment and should FDA consider a worsening of the Raymond scale during 1 year follow-up to represent a failure of treatment?

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

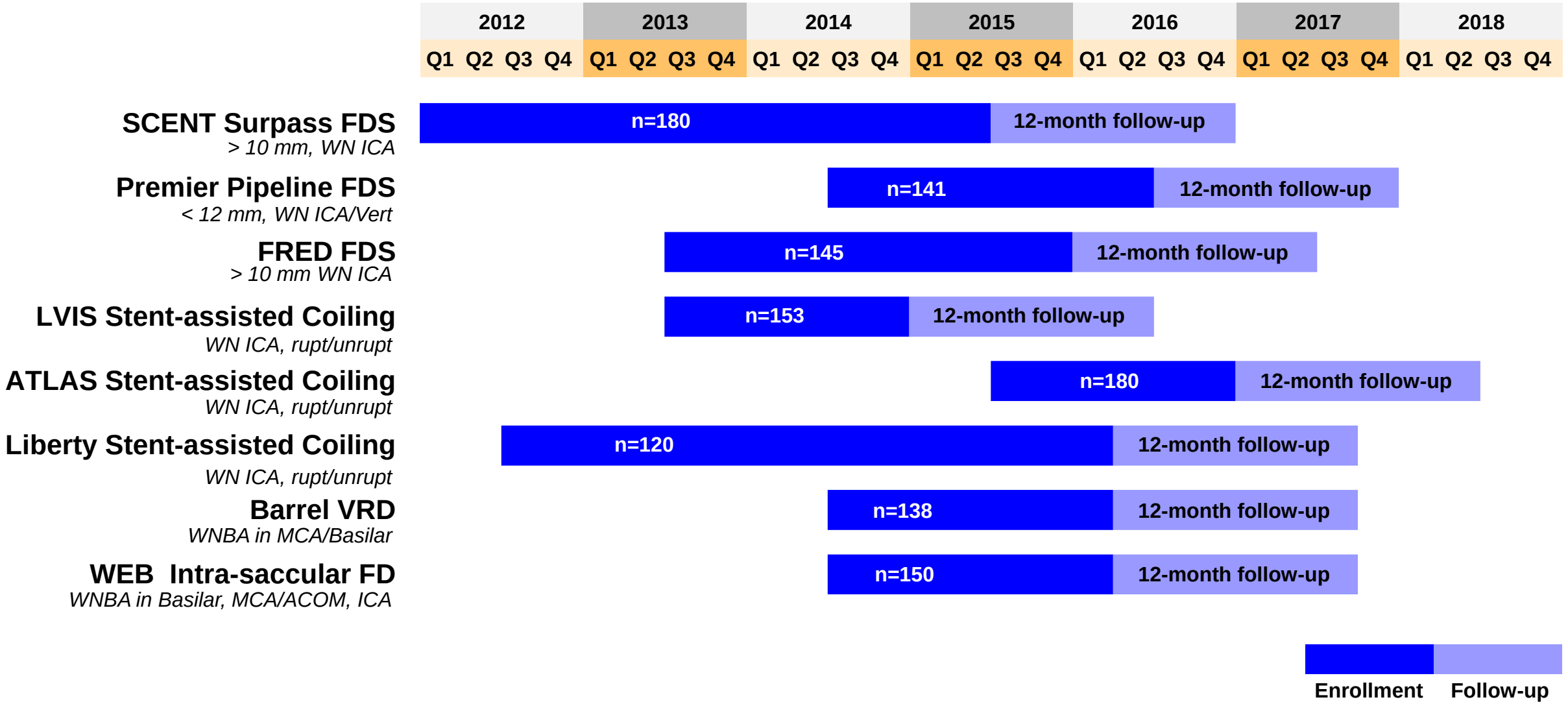
Recommendations for Current and Future Studies for Aneurysm Treatment and Conclusion

John Allison, RAC

Vice President, Regulatory and Clinical Affairs

Stryker Neurovascular

Ongoing Multiple Single-Arm IDE Studies



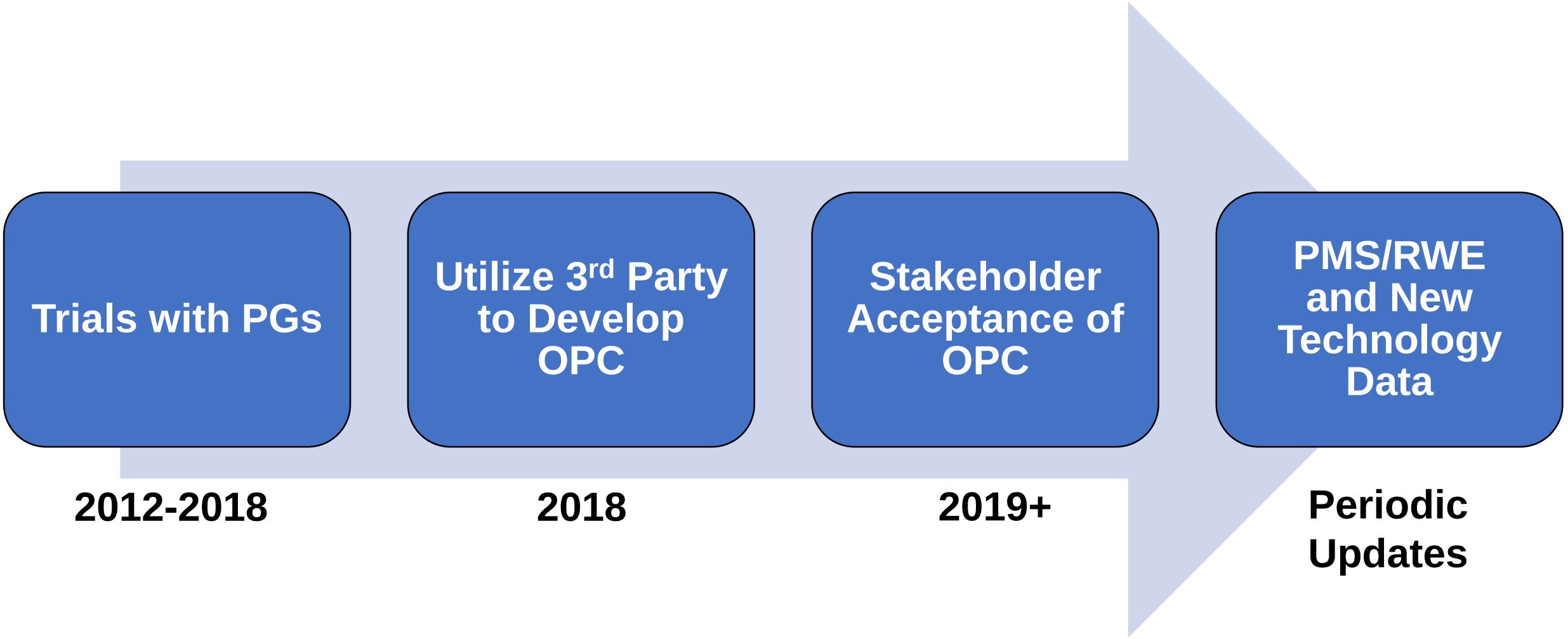
Current Single-Arm Studies with PGs Generate Sufficient Evidence for Approvals

- 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

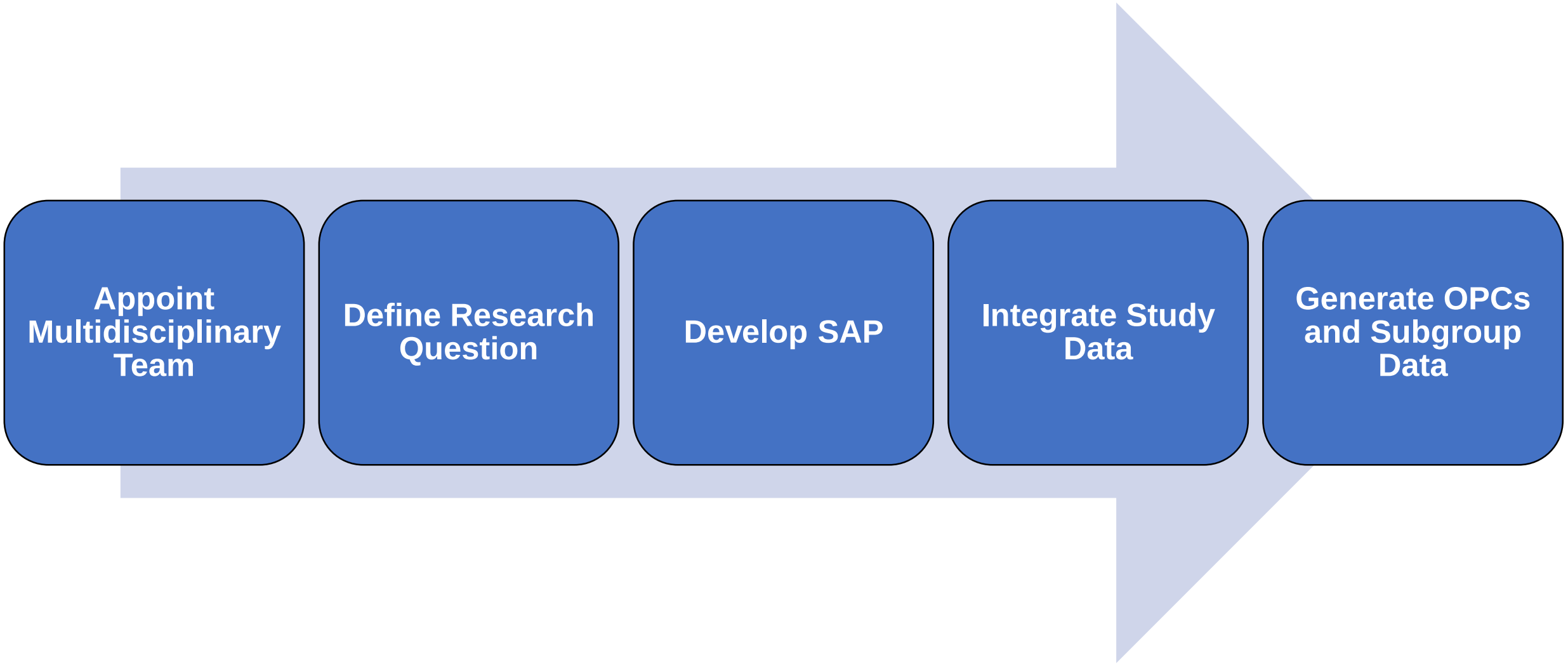
Unified Industry Proposal to Generate OPCs

- 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

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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	✓	✓