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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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NEUROLOGICAL DEVICES PANEL

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March 1, 2018
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, MD 20877

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GREGORY THOMPSON, M.D.	Panel Member
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JAMES GROTTA, M.D.	Panel Member
HUY M. DO, M.D.	Panel Member
BRUCE I. OVBIAGELE, M.D.	Panel Member
ASTERIOS TSIMPAS, M.D.	Panel Member
PHILLIP POSNER, Ph.D.	Patient Representative
ELIJAH WREH, M.S.	Industry Representative
VEVERLY EDWARDS	Consumer Representative
ADEN ASEFA, M.P.H.	Designated Federal Officer

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M E E T I N G

(8:04 a.m.)

DR. JENSEN: Thank you. Good morning, I would like to call this meeting of the March 1st, 2018 meeting of the Neurological Devices panel meeting of the Medical Devices Advisory Committee to order. It's now 8:04.

I'm Dr. Mary Jensen, and I'm the Chair of the Panel. I'm an interventional neuroradiologist and a Professor of Radiology, Neurology, and Neurosurgery at the University of Virginia.

I note for the record that the members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

For today's agenda, the Committee will discuss and make recommendations regarding the evaluation of clinical study data to support the safety and effectiveness of intracranial aneurysm treatment devices and factors that can affect clinical outcomes. 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.

Before we begin, I'd like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. And let us begin with Dr. Peña.

DR. PEÑA: Hi, good morning. My name is Carlos Peña. I'm the Director for the Division of Neurological and Physical Medicine Devices in the Office of Device Evaluation at the Center for Devices and Radiological Health at FDA.

DR. TSIMPAS: Good morning, my name is Asterios Tsimpas. I'm a dual-trained neurosurgeon in cerebrovascular and endovascular neurosurgery. I work for Advocate

Health Care in Chicago, and I'm a clinical assistant professor at the University of Illinois.

DR. GROTTA: Good morning, my name is Jim Grotta. I'm a vascular neurologist from Houston, Texas, where I've been running the stroke program since 1979 and now operate the nation's first mobile stroke unit.

DR. DO: My name is Huy Do. I am an interventional neuroradiologist practicing at the Stanford University Hospitals and Clinic, and I'm a Professor of Radiology and Neurosurgery at Stanford University Medical School.

DR. OVBIAGELE: Good morning, I am Bruce Ovbiagele. I'm a vascular neurologist. I am Professor and Chair of Neurology at the Medical University of South Carolina.

DR. DORSEY: Good morning, my name is Ray Dorsey. I'm a Professor of Neurology at the University of Rochester, active in clinical research.

DR. LYDEN: My name is Pat Lyden. I'm Professor and Chairman of Neurology at Cedars-Sinai Medical Center, where I also direct the comprehensive stroke center.

DR. THOMPSON: Good morning, I'm Greg Thompson. I'm a Professor of Neurosurgery, and I do endovascular and open vascular neurosurgery at the University of Michigan, where I've been for 20 years.

MS. ASEFA: Good morning, my name is Aden Asefa, and I'm the Designated Federal Officer for this meeting.

DR. SELIM: Good morning. I'm Magdy Selim, a vascular neurologist. I'm the chief of the stroke service at Beth Israel Deaconess Medical Center and Professor of Neurology at Harvard Medical School.

DR. CONNOR: Hi. I'm Jason Connor, a biomedical engineer turned biostatistician from ConfluenceStat in Orlando, Florida, and also Associate Professor of Medical Education at the University of Central Florida College of Medicine.

DR. PILITSIS: Hi, I'm Julie Pilitsis. I'm a Professor of Neurosurgery and the Chair of

the Department of Neuroscience and Experimental Therapeutics at Albany Medical College, Albany, New York.

DR. ASHLEY: Hi. I'm William Ashley, and I'm in cerebrovascular and endovascular neurosurgery. I'm the Director of that section at LifeBridge Health in Baltimore.

DR. ERKMEN: Good morning, I'm Kadir Erkmen, and I'm a vascular/endovascular neurosurgeon at Temple University Hospital and a Professor of Neurosurgery at the Lewis Katz School of Medicine.

MS. EDWARDS: Good morning, my name is Veverly Edwards. I'm affiliated with several safe patient projects; one is the Consumers Union Safe Patient Project, and I'm also affiliated with the USA Patient Network.

DR. POSNER: Good morning, I'm Phil Posner, and I'm the Patient Representative. I'm a retired cardiac electrophysiologist and neuroscientist from the University of Florida.

MR. WREH: Good morning, I'm Elijah Wreh. I'm the regulatory affairs manager at Invacare Corporation, and I'm the Industry Representative on this Panel.

DR. JENSEN: Thank you, distinguished Panelists.

To the audience, if you've not already done so, please sign the attendance sheets that are on the table by the doors.

Ms. Asefa, the Designated Federal Officer for this meeting, will now make some introductory remarks.

MS. ASEFA: Good morning. I will now read the Conflict of Interest Statement.

The Food and Drug Administration is convening today's meeting of the Neurological Devices panel meeting of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the Industry Rep, all members and consultants of the Panel are special Government employees or regular Federal employees for other agencies and are subject to Federal conflict of interest

laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that the members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208.

Elijah Wreh is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Invacare, Incorporated.

For the duration of the Neurological Devices panel meeting on March 1st, 2018, Drs. James Grotta and Bruce Ovbiagele have been appointed to serve as Temporary Non-Voting Members, and Dr. Phil Posner has been appointed as Temporary Non-Voting Patient

Representative. For the record, Drs. Grotta, Ovbiagele, and Posner serve as consultants to the Peripheral and Central Nervous System Drugs Advisory Committee in the Center for Drug Evaluation and Research. These individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

The appointments were authorized by Dr. Rachel Sherman, Principal Deputy Commissioner, on February 15th, 2018.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue.

A copy of this statement will be made for review at the registration table during this meeting and will be included as a part of the official transcript.

Before I turn the meeting back over to Dr. Jensen, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated.

Information on purchasing videos of today's meeting can be found on the table outside the room.

The press contact for today's meeting is Stephanie Caccomo.

I would like to remind everyone that the members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until the FDA meeting has concluded.

If you are presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slides, please give your slide presentation to FDA, and please arrange to do so with AnnMarie Williams at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and other electronic devices at this time.

Thank you very much.

Back to Dr. Jensen.

DR. JENSEN: Thank you, Ms. Asefa.

So at this time I would like to welcome Dr. Carlos Peña, Director of the Division of Neurological and Physical Medicine Devices at the Center for Devices and Radiological Health, with a few opening remarks, followed by Lin Zheng, who is the Branch Chief of the Neurointerventional Devices Branch. She will be followed by Samuel Raben, reviewer in the Neurointerventional Devices Branch at the Center for Devices and Radiological Health, along with Dr. Patrick Noonan, medical officer of the Neurointerventional Devices Branch, to present an overview of cerebral aneurysms, following the benefits and risks of aneurysm treatments.

DR. PEÑA: Thank you. Good morning, Panel Chair, the Neurological Devices Panel, patients, industry, societies, clinicians, principal investigators, and the general public. Welcome to this meeting. And thank you for your attendance. It's always helpful to see the turnout at our meetings when you do the calculus of how important and far reaching the impact can be for medical devices in reaching patients and their families.

The purpose of the current meeting today is to hear on a couple -- and you'll hear this a couple times, to make sure everyone is aware of the Agency's objective; it is to seek expert opinion on the scientific and clinical considerations relating to the determination and

evaluation of the possible benefits and risks of endovascular aneurysm treatment devices for marketing approval in the United States. It is intended to be a very simple goal. I'm a little biased, but these factors to assess these treatment devices are important that we discuss here in our open public forum so we can succeed in our call of ensuring that U.S. patients have access to high quality, safe, and effective medical devices of public health importance first in the world. As we look forward to hearing your discussions, the public discussion, and industry and societal discussions, we hope all stakeholders, on behalf of the Agency, have a voice at this public meeting.

When this Panel met last in 2015, we talked about the aspiration of what we would like to see with regard to trial design for aneurysm devices, and we received very important and useful information towards this goal that we continue to review and evaluate today. As we proceed together at this next public meeting, the purpose will be to take another step in evaluating these medical devices and moving both safe and effective products to the marketplace. The discussions and questions you will hear today will help the Agency make appropriate science-based and, I hope, on behalf of the Agency, fair decisions as we go forward.

Last, I would like to thank the Panel for their attendance today, on behalf of the Agency, and share with you that we hope you, the Panel and the attendees, and again, as smart as we think you are, in helping us with this product area. Thank you.

DR. ZHENG: Good morning, my name is Lin Zheng, and I am the Branch Chief of the Neurointerventional Devices Branch in the Division of Neurological and Physical Medicine Devices in the Center for Devices and Radiological Health at FDA. We welcome you to the general issues Neurological Panel of the Medical Devices Advisory Committee meeting to obtain recommendations from the Panel on the evaluation of benefits and risks of endovascular medical devices intended to treat cerebral aneurysms.

Today's FDA presentation will be presented by Dr. Samuel Raben and Dr. Patrick Noonan, and I will present some introductory slides for the meeting agenda today and the purpose for why we are meeting today.

The purpose of today's general issues panel meeting is to obtain Panel feedback on how the clinical data should be evaluated to assess the benefits and risks of new cerebral aneurysm devices once a trial has been completed. We are requesting panel recommendations regarding the importance of certain adverse events and rates and what is considered adequate aneurysm occlusion and length of patient follow-up that should be considered as part of our premarket decision for marketing approval of new cerebral aneurysm treatment devices in the United States.

In addition, we ask the Panel to keep in consideration how to assess the benefits and risks of the new device when there may be limitations in the clinical trial design, such as if a single-arm study was conducted and if a device is determined to be approvable for marketing in the United States, what level of information should be described in the instructions for use and indications for use so that the clinical user is advised of the appropriate patient population indicated for treatment that is supported by valid scientific evidence?

Here is an outline of FDA's presentation: Our short introduction on the purpose of this meeting will be followed by a presentation by Dr. Samuel Raben on cerebral aneurysm overview and aneurysm treatment methods. Dr. Patrick Noonan will close the presentation with factors to consider when evaluating the benefits and risks of different cerebral aneurysm treatments from FDA's perspective.

We would like to remind everyone that in April 2015 we held an Advisory Committee meeting to obtain feedback from the Panel on the clinical trial design for cerebral aneurysm treatment devices, specifically flow diverters. The summary of the panel recommendations

included that randomized controlled trials should always be considered unless it is determined to not be feasible. If performance goal-based single-arm studies are the only option, the pre-specified performance goals should be well justified and matched to the patient population studied.

The Panel also concluded that 1-year patient follow-up data appears reasonable for a premarket decision, but long-term 5-year data may be needed to assess for certain delayed adverse effects.

Furthermore, the Panel recommended that with respect to trial design, for poolability of clinical outcomes, small and medium aneurysms can be grouped together, and large and giant aneurysms can be grouped together.

Also, anterior circulation aneurysms should be evaluated separately from posterior circulation aneurysms with consideration of aneurysms located in perforator-rich regions.

The Panel also recommended that different aneurysm morphologies should be considered when designing clinical trials.

We thank all of you for participating in today's panel meeting, and I will now turn to Dr. Samuel Raben to provide the background on cerebral aneurysms and available treatment methods.

DR. RABEN: Hello, my name is Sam Raben, and I am a lead reviewer and engineer at the FDA in the Office of Device Evaluation. I'm going to discuss aneurysm overview and the different treatment methods for intracranial aneurysms.

Aneurysms can present with different morphologies. The three predominant types of aneurysms are saccular, fusiform, and dissecting.

Saccular aneurysms, sometimes referred to as berry aneurysms due to their appearance, protrude off the vessel side wall. Fusiform aneurysms are a dilation of the vessel on all sides, while dissecting aneurysms occur when blood pools in between the

layers of the vessel wall.

Neck size, or the opening that connects the aneurysm to the parent artery, is also an important feature to consider when determining treatment options. Aneurysms with a neck size greater than 4 mm or a dome-to-neck ratio less than 2 are generally considered to be wide neck. An aneurysm being described as wide neck is an important distinction as it can require different treatment methods than what is used for non-wide neck aneurysms, as these aneurysms are less amenable to surgical clipping and traditional coiling alone.

Intracranial aneurysms typically occur near or at branch points in the neurovasculature. These aneurysms are primarily located in the anterior circulation. The distinction between aneurysm locations is important as literature has shown that anatomical location can influence patient outcomes with worse outcomes being seen for patients with aneurysms located in the posterior circulation. The anterior circulation also includes portions of the internal carotid artery, which has been the focus of previous studies for device approval.

One factor relating to anatomical location for devices that are placed inside the arterial lumen is their interaction with perforators. Perforators are small branches that emerge from the larger parent artery that may be responsible for supplying blood to various portions of the brain. While these perforators exist in both the anterior and posterior circulation, the clinical risks associated with perforator occlusion in the posterior circulation is greater than that in the anterior. This elevated risk may require different considerations when determining treatment.

Aneurysms can also occur in a wide range of sizes. The most frequently diagnosed aneurysms are small to medium. While there is some variation in the literature, for the purposes of discussion today, we have decided to classify the aneurysms in the following size ranges.

Previous studies have shown that there is a correlation between aneurysm size and rupture rate, with giant aneurysms having a higher probability for rupture. Aneurysm size, as well as the associated risk of rupture, is one of the main factors that should be considered when determining the appropriate treatment for different aneurysms and underlying benefits and risks for new treatment devices.

Aneurysm rupture is the primary concern when considering treatment options for intracranial aneurysms. When determining treatment options for a patient, there are a number of risk factors to consider, such as aneurysm characteristics, prior subarachnoid hemorrhage, family history, gender, whether a patient smokes, previously diagnosed aneurysms, can all impact a patient's treatment.

Additionally, aneurysm size can be an important factor when considering rupture risk. Small aneurysms, while more common, have a much lower 5-year rupture risk than large and giant aneurysms.

This next section of the presentation will talk about different aneurysm treatment methods. Before I start, I would like to give a brief overview of the different regulatory pathways to bring a new device to market in the United States.

In bringing a device to market, there are four pathways that require premarket review by FDA: 510(k) or premarket notification, de novo, humanitarian device exemption, and premarket approval.

The 510(k) pathway is available to low- to moderate-risk Class II devices, such as clips, coils, and balloon-assisted coiling catheters, and requires the device demonstrate substantial equivalence to another device with the same intended use and similar technological characteristics that is currently on the market.

The de novo pathway is available for new devices for which a predicate device does not exist, but general and special controls have been found to be sufficient to provide a

reasonable assurance of safety and effectiveness. This is a less common pathway for aneurysm devices.

The HDE regulatory pathway, which was created for products intended for diseases and conditions that affect a small population where it may be difficult to gather enough clinical evidence: HDE marketing applications are supported by performance data (in vivo data, in vitro data, human clinical studies) that demonstrates that the device will not expose the patient to an unreasonable or significant risk of injury or illness, and the probable benefit to health from use of the device outweighs the risk of injury or illness.

Premarket approval is required for the highest-risk devices. These devices typically require clinical data to support a reasonable assurance of both safety and effectiveness for its proposed conditions of use to obtain marketing approval in the United States.

The HDE and PMA pathways have been used more frequently for aneurysm devices.

When treating an unruptured or a ruptured aneurysm, there are three primary treatment approaches: open surgery, endovascular treatment, and medical management and observation. There is some debate clinically whether some aneurysms should be treated or more conservatively managed through observation, especially for very small aneurysms that may have a low risk of rupture during a patient's lifetime.

While open surgery requires removal of part of the skull to expose the brain, endovascular techniques are typically performed by inserting the device through the femoral artery and tracking up through the vasculature into the brain. Surgical clipping can be used to treat both ruptured as well as unruptured aneurysms, and endovascular techniques listed on this slide can also be used to treat both ruptured and unruptured but offer a minimally invasive approach to treating these aneurysms.

While the methods listed here are not the only methods that can be used to treat unruptured or ruptured aneurysms, they will be the focus of today's conversation.

It is also important to mention that while in today's meeting we would like to discuss some of the different clinical considerations regarding the benefit and risk from using these devices, our intention is not to directly compare one device to another.

Traditional coiling is one of the first endovascular approaches developed to treat these aneurysms. These coils are manufactured with a preset shape, similar to a slinky, and are available in framing, filling, and finishing coil types. The framing coils are used to outline the dome of the aneurysm and support the filling and finishing coils. The filling coils and finishing coils are inserted after the framing coil to further occlude and fill the aneurysm sac to promote blood stasis. These coils are typically metallic, made from a platinum alloy.

The benefit to coiling is that it is less invasive than surgical clipping. Clinical studies have reported in the literature that long-term mortality rate is lower with coiling as compared to clipping.

One of the limitations with coiling alone is that it may be difficult to treat wide neck aneurysms because coils may prolapse into the vessel due to the wide neck. In addition, procedurally, it may be difficult and time consuming to coil certain aneurysms such as those that are large and giant in size.

Balloon-assisted coiling is similar to traditional coiling with the exception that a balloon is inflated across the neck of the aneurysm while coils are being inserted into the sac. The coils used in this procedure are the same as those that are used in traditional coiling. Once coiling is completed, the balloon is deflated and removed from the parent artery. The balloon allows for a tighter packing of coils while limiting the possibility of coils prolapsing into the parent artery.

The complication rates for this technique have also been shown to be similar to that of traditional coiling alone, based on published literature. This technique does, however,

have the limitation that it can be difficult to treat aneurysms with it as the neck becomes very wide as this technique does not prevent coil prolapse after the balloon is removed.

In conjunction with these coils, stent-assisted coiling is another endovascular surgical technique developed mainly to treat wide neck cerebral aneurysms by implanting a self-expanding nitinol stent across the neck of the aneurysm in the parent artery to support the coils from herniating out of the sac. Recent developments in stent technology have made it possible to re-sheathe partially deployed stents, which can aid clinicians during deployment.

One risk of these devices is the fact that stent struts may possibly occlude overlapped perforators in the different sections of the vasculature. Also, patients must be prescribed antiplatelet therapy if the device is implanted. There is also an unknown long-term risk due to the limited amount of long-term data available on these permanently implanted devices.

All of the stent-assisted coiling systems currently on the market in the United States have been approved through the HDE regulatory pathway.

Flow diversion is another endovascular technique that is also designed to treat wide neck aneurysms. For this technique, a high mesh density stent is placed inside the parent artery crossing the neck of the aneurysm. Flow diverters are intended to be used as a standalone device, unlike stent-assisted coiling devices, and its mechanism of action is to divert blood flow from entering the aneurysm sac and results in endothelial growth across the neck of the aneurysm, leading to occlusion. These devices are a similar construction to the stents used in stent-assisted coiling in that they are a self-expanding nitinol stent that can also be re-sheathable.

One potential benefit of this method is that nothing is placed inside the aneurysm sac that could perforate the walls and could cause a rupture. Also, because only one device

is implanted, it may result in shorter procedure times.

Some of the risks associated with flow diverters are the limited information about how these devices may interact with perforators in the neurovasculature. There may be a delayed effect of aneurysm securement until endothelialization takes place, and patients must be put on antiplatelet therapy if the device is implanted.

Currently, the only approved flow diverter on the market is the Pipeline embolization device, approved for a portion of the internal carotid artery.

Intrasaccular flow disruption is a technique that has been recently presented in the clinical literature. This treatment method works by placing a tightly woven mesh into the sac of the aneurysm that blocks blood from entering the neck and promotes endothelial growth across the neck. The meshes of these flow disruption devices are similar to that of flow diverters; however, these devices are placed in the aneurysm sac with no permanent implant left inside the parent vessel.

The possible benefits of this treatment type is that the aneurysm could be treated with a single device, thus potentially reducing procedure times, as well as the device can also be adept at treating wide neck bifurcation aneurysms.

A possible risk of these devices is the predetermined shape of these devices may not align with every aneurysm. Additionally, long-term safety and effectiveness and potential retreatment risks of these devices is currently unknown.

It is important to note that currently there are no intrasaccular flow disruption devices approved by FDA in the United States.

Surgical clipping is an open surgical technique where a clip is placed across the neck of the aneurysm in order to disconnect it from the vasculature. These clips, which are typically made from titanium, use a tiny spring to remain closed once placed on the aneurysm. For large aneurysms, multiple clips may be used to secure the neck.

One benefit of using clips is that they can provide complete and immediate occlusion of the aneurysm. Additionally, clips can be used with both ruptured and unruptured aneurysms.

Conversely, clipping is an open surgical procedure that includes all of the inherent complications, as well as the fact that not all aneurysms are surgically accessible.

In addition to endovascular and open surgical treatments for aneurysms, some clinicians and patients choose a more conservative approach of non-surgical medical management alone. Patients receiving conservative medical management most commonly undergo regularly scheduled follow-up imaging to assess the aneurysm growth and/or any morphological changes. These patients are advised to reduce risks factors that may contribute to rupture, such as elevated blood pressure and smoking.

The benefit of this approach is that patients do not undergo any type of surgical procedure which may carry surgical risks.

The limitation of this approach is that patients are sometimes uncomfortable with the idea of an untreated aneurysm present in their brain. Additionally, all of the risk factors associated with aneurysm rupture are not well understood.

In summary, we have discussed different treatment options for intracranial aneurysms, touching on some of the different benefits and limitations. Treatment options can vary based on different aneurysm characteristics. An understanding of the benefit and risks of these different treatment approaches for both ruptured and unruptured aneurysm is a major focus of this meeting today. We are interested to hear the Panel's recommendation regarding the current clinical landscape and how it can be applied to the premarket review of new aneurysm devices.

With that, I would like to turn the presentation over to Dr. Patrick Noonan.

DR. NOONAN: Hello, my name is Patrick Noonan, and I am an interventional

neuroradiologist practicing in Texas and a medical officer for the FDA. I am going to discuss the factors we consider from a regulatory perspective when assessing whether the benefits of a new device outweighs its risks for the proposed conditions of use of new intracranial aneurysm devices.

For PMA and de novo classifications, FDA utilizes a benefit-risk model for premarket decision making when assessing whether a new device provides a reasonable assurance of safety and effectiveness by weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use. The factors that FDA considers in the benefit-risk assessment are listed here.

When determining the benefits, we consider the type, magnitude, and duration of the benefits. For risks, FDA considers the severity, types, duration, rates, and probability of harmful events. All of these benefit-risk factors can be considered either individually or in aggregate when making a premarket decision on the reasonable assurance of safety and effectiveness of a new device.

Specific to intracranial aneurysm treatment devices, the benefit and risk factors that FDA considers are those such as limitations of the clinical study data based on patient populations studied or those related to trial design, assessing needs of treatment such as ruptured versus unruptured aneurysms, the rates and capture of certain adverse events, aneurysm occlusion status, patient follow-up duration for pre- versus postmarket clinical data collection, and how different device designs and technologies should be applied to the characterization of different aneurysm characteristics.

Thus far, different intracranial aneurysm treatment devices have been regulated through different premarket approval pathways in the U.S., with varying levels of evidence to support their approvals or clearances. The highest reasonable assurance of both safety and effectiveness is provided for the highest-risk medical devices (Class III devices)

regulated under the PMA pathway. PMA approval is typically supported by both preclinical and large, multicenter, prospectively designed pivotal clinical trials with pre-specified hypothesis testing, primary safety and effectiveness endpoints, and a statistically justified sample size. There is only one PMA-approved device for intracranial aneurysms, which is a flow diverter, and that's the Pipeline embolization device.

To support regulatory approvals in the U.S., FDA will consider all valid scientific evidence during the premarket review. This evidence can come from a range of information sources, including clinical data, animal studies, and nonclinical in vitro performance data.

According to the regulations, valid scientific evidence is defined as 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 a reasonable assurance of the safety and effectiveness of a device under its conditions of use.

Here we show different trial designs and the level of uncertainty with each. Real-world clinical experience of marketed devices is another potential source of valuable clinical information. The clinical information gathered from these different trial designs could all be considered valid scientific evidence.

However, based on how the clinical data was collected, there may be varying degrees of uncertainty in the clinical information presented to understand the benefits and risks of a device for its conditions of use, which may also impact whether sufficient safety and effectiveness data exists to support marketing authorization.

Also, please note that when a clinical trial is submitted under an investigational device exemption, or IDE, submission, even though FDA may not agree with the clinical trial design, such as whether the study is a randomized controlled study or a single-arm

performance goal-based study, we cannot disapprove studies based on trial design alone due to the FDA Safety and Innovation Act of July 2012.

If we do have study design issues, we convey these concerns as study design considerations as an attachment to the IDE decision letters, which the sponsor may address during the course of study conduct. If the sponsor completes their study even though there were outstanding FDA concerns regarding the safety design, the FDA is still required to review the data generated from the clinical study, considering the previously conveyed study design considerations, and decide as to whether the data supports a reasonable assurance of safety and effectiveness for a new device. In some cases, we may even hold a panel meeting to publicly discuss this information.

Prior studies for cerebral aneurysm treatment devices published in the literature have chosen to use a primary safety endpoint defined as the rate of neurological deaths and major ipsilateral stroke. Major stroke has been defined as an increase in the National Institutes of Health Stroke Scale score of 4 points or greater compared to baseline. The primary effectiveness endpoint has been defined as the percent of subjects who achieve complete or 100% occlusion of the aneurysm without also incurring significant parent artery stenosis or requiring retreatment of the aneurysm at 1-year follow-up.

Secondary endpoints for clinical trials for aneurysm devices published in the literature include assessment of the modified Rankin score, procedural success for device placement, retreatment or the need for adjunctive device treatment, recurrence of the target aneurysm, procedural time, and radiation exposure.

Although prior clinical studies have focused on the rate of neurological deaths and major strokes as the primary safety events to determine whether a device is considered reasonably safe, additional serious adverse events observed for intracranial aneurysm devices reported in the public literature include, but are not limited to, minor strokes and

transient ischemic attacks, subarachnoid hemorrhage, device migration, dual antiplatelet therapy related adverse events, arterial access site issues, and delayed aneurysm rupture.

We kindly ask the Panel to keep these events in consideration as they debate the Panel questions this afternoon. When assessing these events or additional adverse events that the Panel may recommend, the Panel should also consider and specify what rates of occurrence would be considered acceptable risk for new aneurysm treatment devices.

For effectiveness, the optimal treatment outcome is to achieve 100% aneurysm occlusion. However, sometimes this result may be difficult to achieve based on the device design, patient factors, or aneurysm characteristics. One of the critical questions the FDA faces when assessing benefit is whether an aneurysm with a residual neck or a residual aneurysm is considered an acceptable effectiveness result at a certain time point (for example 1 year) when a premarket decision is made.

In addition, in assessing benefit, we consider the rates of patients with each occlusion type at 1 year post-procedure. There are examples of occlusion types on the slide. This is especially important if there is no concurrent control group to make a direct comparison to an alternative treatment method.

We recommend that the Panel consider the assessment of benefit of new cerebral aneurysm treatment devices because many of the specific questions posed to the Panel this afternoon focus on these points.

As described previously in FDA's assessment of benefit-risk, we also consider the pre- versus postmarket balance in whether premarket clinical data requirements could be minimized and balanced with long-term collection of clinical outcomes postmarket if there are some uncertainties that remain with the premarket data.

Prior FDA decisions for PMAs have been made with 1-year follow-up data, while for HDEs the clinical follow-up has been limited to 6 months. Many of our clinical studies now

consent patients up to 5 years of follow-up in the event that post-approval studies are needed. This avoids the need to enroll more patients in a brand new cohort of patients.

Even though the precedence has been 1 year of follow-up for PMA premarket decisions, FDA is requesting Panel feedback now that additional clinical information is available for different aneurysm treatment devices. One of the questions posed to the Panel concerns whether 1-year follow-up is sufficient, especially taking into consideration the potentially different percentages of patients with different degrees of aneurysm occlusion at 1 year.

After FDA's review of the clinical data, if a device is determined to be approvable for its conditions of use, FDA believes device labeling or instructions for use is important to provide information about the use of the device, including the indicated patient population supported by valid scientific evidence, appropriate warnings, precautions, and/or major contraindications, as well as step-by-step instructions on how to safely use the device. Labeling can also make more transparent the clinical data that was reviewed and what population was studied.

In summation, FDA has presented some of the scientific and clinical factors regarding cerebral aneurysms and their treatment. FDA has provided background on some of the different regulatory pathways for these devices to reach the U.S. market.

Additionally, we have provided information regarding some of the prior benefit-risk considerations we have used for devices in this field.

We look forward to the Panel's recommendations regarding aneurysm treatment devices to support FDA's mission of ensuring U.S. patients have access to high quality, safe, and effective devices of public health importance, first in the world.

Thank you for your attention, and this concludes the FDA's presentation. Does the Panel have any questions for the FDA?

DR. JENSEN: So I would like to thank the FDA for their presentations, and I'd like to invite Dr. Noonan and Dr. Raben to the table in front of us.

And I would now like to invite anybody on the Panel who has a clarifying question that they would like to ask to the FDA. Remember that the Committee is going to be asking questions during the committee deliberations this afternoon, so you have plenty of time to ask questions. Anybody have a clarifying question about anything that was discussed?

MR. WREH: My name is Elijah Wreh, Industry Rep.

I see you -- you know, during your presentation, I noticed you said randomized controlled trial is the lowest level. If you don't mind, could you please deliberate in detail why this is considered the lowest level, because if I remember, I think back in 2015 this was a huge issue of concern from FDA. Thank you.

DR. NOONAN: It's actually the lowest level of uncertainty. It's the highest level of certainty.

DR. JENSEN: Any other questions?

DR. CONNOR: So Jason Connor here.

So is it typically evident which regulatory pathway if a new device maker, a new device comes in, or is there much negotiation or uncertainty about which regulatory pathway a product would have to take?

DR. RABEN: So that will depend on the device, but most often that is a discussion that FDA will have with a sponsor if there is uncertainty. There is a formal pathway, the 513(g) pathway, where sponsors can come in to FDA and provide information about their device and request a designation to be placed in one of the buckets, whether they're a Class II device, whether they are Class III. So there's both a formal process, but oftentimes, sponsors will informally discuss it with FDA through a submission, a Q-submission, to discuss, you know, their proposed device development and things like that. So it's not set

in stone, like there's no, you know, this device will be this. It really depends on what the exact characteristics of the device are. But most commonly for aneurysm devices, they are Class III devices, so they would fall into either that PMA or HDE bucket.

DR. DO: Hi. Huy Do from Stanford.

Can you explain the de novo pathway in more detail for me and maybe for the Panel, and are there any examples in neurological devices that have gone through this pathway, whether it's vascular or not vascular?

DR. RABEN: Sure. So the de novo pathway is available to devices that are low to moderate risk devices, so these would not be your high-risk devices, but it would be a scenario where FDA believed that general and special controls would be appropriate to assure safety and effectiveness for the device.

One example for this would be -- recently, would be the stentriever that received -- initially, the stentrievers for stroke treatment had a tool claim, and then they came in requesting a treatment claim. That was determined to be a de novo device using -- not having a valid predicate since nothing had that treatment indication. However, we believed that general and special controls were sufficient to assure safety and effectiveness. So the first device that received that treatment claim came in as a de novo, and then subsequent devices from other manufacturers could then come in using that as a predicate through the 510(k) pathway.

So the de novo pathway creates a predicate for future devices, and that's important, that's an important distinction, because in the PMA pathway it is an independent submission. You're not relying on what previous devices may or may not have done. You're saying this is our device, and this is the evidence to specifically support our device, where in the 510(k) pathway, you're saying we are substantially equivalent to this other device for the following reasons. And so the de novo pathway allows you to create a de novo 510(k), a

new 510(k) that will stand as a predicate for future devices.

DR. JENSEN: Any other questions from the Panel?

DR. LYDEN: Yeah. Pat Lyden.

So you made a point that you'll be reviewing these devices for use in the United States, but could you review, sort of, how you look at data from outside the United States and how that data could or could not impact your decisions?

DR. RABEN: So the short answer is that we do -- we will review all clinical evidence that is provided to us, whether it be from within the United States or from outside the United States. There have been HDE applications that have provided OUS studies. The only point of caution, I guess I would say, with providing that information is that if FDA has not had any chance to participate in the discussion regarding the collection of that information. There may be concerns that FDA would like to see addressed that may not have been addressed by the OUS data. There is an FDA guidance on the use of OUS data in support of marketing applications, so we are willing to consider all scientific evidence provided. As I mentioned, the only consideration that I would say is that, you know, if this is the first time FDA has seen the data, there may be some considerations.

The other point that I would like to make is that we will ask how that OUS population is applicable to the U.S. population. So if there are differences in the patient population that has been selected from outside the U.S., we may have concerns and questions about how that population that was enrolled is applicable to the U.S. population.

DR. JENSEN: If there have been no other questions, I thank our FDA colleagues for running ahead of schedule, so we will move on with the presentation from the device manufacturers, which we have 40 minutes for.

So I would like to introduce the device manufacturers who will be discussing the evaluation of clinical study data to support safety and effectiveness of intracranial

aneurysm treatment devices and factors that can affect clinical outcomes. As a group, you will have 40 minutes to present, and I welcome Dr. Dion. I believe you will be starting off the presentation, and you may now begin your presentation.

DR. DION: Good morning, my name is Jacques Dion. I'm Vice President of Scientific Affairs at MicroVention.

My colleagues and I are here today representing seven industry-leading companies of neurovascular medical devices to discuss the clinical and regulatory challenges associated with the treatment of intracranial aneurysms. We want to thank the FDA and the Panel for the opportunity to present our unified perspective on the important issues identified by the FDA, which are relevant to the study and approval of new neurovascular device technology.

By way of background, prior to joining MicroVention last summer, I practiced interventional neuroradiology for 34 years.

The FDA has outlined a number of key things and specific questions for discussion today. We would like to present industry's perspective on the following topics:

First, we will discuss target aneurysm treatment populations and the challenges associated with natural history data. Regardless of size, aneurysm ruptures are catastrophic and often lead to increased morbidity and mortality. As such, all aneurysms, including small aneurysms, present risks to patients and should be considered for treatment. Treatment options should be made available so that physicians and their patients can together make the determination of when to treat on an individual basis.

Next, we will discuss the use of current clinical trial data to evaluate the safety and effectiveness of new devices and provide our recommendations, including how single-arm trials with appropriate performance goals can support approval, and the role of postmarket studies. We look forward to the Committee's perspective and guidance so that we can continue to advance aneurysm treatment and ultimately patient care through high quality

clinical evidence.

For our presentation today, I will begin with an overview of the natural history of aneurysms and the devastating impact they have on patients. Then, Stacey Pugh will review the industry's collective thinking on how to utilize current clinical data to support safety and effectiveness of devices to treat aneurysms as well as address FDA's specific questions. Finally, John Allison will provide our recommendations for how best to collect data for future trials and conclude our presentation. Stacey will then return to the podium to help address your questions.

Turning to disease background, the consequences associated with intracranial aneurysms are significant. According to literature, 2 to 5% of adults are currently living with intracranial aneurysms. Unlike other diseases, screening for aneurysms is not standard practice, so the majority of intracranial aneurysms are asymptomatic and often go undiagnosed prior to rupture. Because ruptures occur suddenly, patients are left at risk for cerebral bleeding or subarachnoid hemorrhage. Subarachnoid hemorrhage is a devastating disease with an approximately 45% mortality rate. For those patients who do survive, approximately half experience a significant neurological disability.

Even when detected, predicting the risk of rupture for any aneurysm remains a challenge. What we know is that many factors, such as size, morphology, location, and previous history of subarachnoid hemorrhage, all increase the risk of rupture. And consistent trends in the literature show an increased risk for larger compared to smaller and posterior compared to anterior circulation aneurysms. Despite these predictors, the severity and catastrophic consequences associated with aneurysm rupture are essentially independent of size and location of the aneurysm.

Three observational studies have attempted to characterize the risk of rupture in these patients. However, the variability of the data makes it challenging to draw reliable

conclusions on the benefits of preventive treatment.

The ISUIA study, which represents the most well-known study looking at rupture rates, was originally published in 1998, and subsequently, the data was reanalyzed post hoc in 2003. Additionally, two natural history of aneurysm studies have been conducted on large cohorts outside the U.S., one in Finland and one in Japan. Even though these studies attempt to clarify the risk of rupture in patients with aneurysms, inconsistency in the reports cloud the interpretation of data.

Looking at ISUIA results in more detail, ISUIA was a large retrospective and prospective cohort study done in 60 centers in the U.S., Canada, and Europe. Patients were evaluated in three non-randomized cohorts by observation, surgical, and endovascular treatment. Two groups were broadly defined for observation: one without a history of subarachnoid hemorrhage from a separate aneurysm, so-called Group 1, and in those with such a history, so-called Group 2. Patients were followed annually for 4 years with a standardized questionnaire.

The original 1998 published study in over 1,400 patients determined that Group 1 aneurysms less than 10 mm had a rupture rate of less than 0.5%. And a prospective analysis in over 1,600 patients was published later. The 2003 post hoc analysis of the ISUIA data suggested that Group 1 patients with anterior circulation aneurysms less than 7 mm have a 0% risk of rupture at 5 years.

This conclusion, that patients are at no harm from their smaller aneurysms and that preventive treatment is not warranted, clashes with what we see in everyday practice, as I will show in the following slide.

In his series, Bender showed that from 2012 to 2016, 50% of aneurysms presenting due to rupture were less than 5 mm in size and that 34% were between 5 and 9 mm. Similar results were observed in the ISAT study, where 52% of the ruptured aneurysms were

less than 5 mm.

There are potential limitations to the interpretations of the results of the ISUIA as it relies on post hoc reconstructions of artificial subgroups too small to be reliable for clinical decision making.

Several methodological difficulties and factors with the ISUIA study may also impact a low rate of rupture reported. These include:

- Selection bias as patients evaluated in the observation cohort were selected for observation;
- No treatment by their physicians and therefore were likely low risk for aneurysm rupture;
- The arbitrary assignment of PCOM aneurysms to the posterior circulation, whereas these aneurysms were assigned to the anterior circulation in most other natural history studies;
- High crossover rate from observation to treatment group. Of the 1,692 patients in ISUIA, 534 patients were switched to a therapeutic intervention, surgical or endovascular;
- Undefined observational periods with no predefined hypotheses, sample size, subgroup definitions, and no requirement for repeat imaging; and finally,
- The exclusion of aneurysms less than 2 mm even though these aneurysms can rupture; again, the prevalence rates reported for small aneurysms in the ISUIA study do not align with real-world data.

The primary goal of treatment is to prevent all ruptures and related morbidity and mortality. Secondary goals include symptom relief due to mass effect, prevention of further growth and thrombus formation.

Current treatment options are either surgical or endovascular. Surgical clipping is

associated with high occlusion success, but its safety varies widely according to anatomical location. We agree with FDA that open surgical clipping may be limited with respect to accessibility to treat certain aneurysms based on their location.

In addition, there has been an attrition of neurovascular surgeons due to the success of endovascular therapies and availability of new technologies.

The overall mortality rate associated with surgical clipping is in the range of 1.7 to 2.6%, according to two meta-analyses, and 5 to 10.9% of patients who undergo the surgery will experience a permanent morbidity. The ISUIA prospective treatment arm results were consistent with these meta-analyses. The surgical risk is also directly related to size and location of the aneurysm.

More recently, endovascular treatments have provided physicians a safe and effective option to treat a broader range of aneurysms. The development of endovascular treatments began in the 1990s with coiling. Over time, it was discovered that certain types of aneurysms, specifically wide neck aneurysms, were not successfully treated with simple coiling. Therefore, other technologies were designed to increase feasibility and efficacy of treating challenging aneurysms. These include stent- and balloon-assisted coiling and flow diversion therapy. As endovascular treatments are innovated and refined, we continued to see improvements of not only reduced complications but also improved outcomes.

Before closing, I would like to specifically address FDA's Question Number 3, asking which patient characteristics should be considered when deciding when to treat or not treat an aneurysm.

For the past 3 decades, I've had weekly discussions with patients and their families, trying to answer this exact question. There are many factors I took into consideration when presenting options to my patients, such as life expectancy, family history of aneurysmal subarachnoid hemorrhage, comorbidities, aneurysmal growth on sequential imaging,

aneurysm location, and the risk of treatment. Ultimately, however, the choice to treat or not treat an aneurysm of any size rests with the patient.

In conclusion, treating physicians are often faced with a dilemma of who to treat and when.

The risks of surgical and endovascular treatments have been well described; however, inconsistencies in literature reports cloud the interpretation of the natural history and rupture risk of small aneurysms, as seen in the ISUIA, UCAS, and Juvela studies.

In my experience as a clinician, the option of following the aneurysm rather than treating it is often difficult and sometimes impossible for patients to accept. We believe that all patients, regardless of the size of the aneurysm, need treatment options, and we, as industry, need to continue to push forward to advance the field.

Thank you. I will now turn the presentation over to Stacey Pugh.

MS. PUGH: Good morning. My name is Stacey Pugh, and I am Vice President and General Manager of Medtronic Neurovascular, but I'm here today to speak on behalf of all of the industry partners that were shown before. I'm pleased to be here to share industry's collective thinking on how to utilize current clinical data to support the safety and effectiveness assessment of the devices. We're fortunate to operate in an environment where technology is constantly evolving, and we recognize that innovation also presents complicated regulatory challenges.

Today, there are currently eight ongoing IDE trials for aneurysm treatment. These studies include flow diverters, stents for stent-assisted coiling, and the newer category of intrasaccular flow diverters, which were all described in FDA's opening presentation. All of these device trials have completed their enrollment phase and are in follow-up.

All eight of these studies have many similar characteristics. They are all prospective, multicenter, single-arm, performance goal trials. Performance goals were established

through a comprehensive and systematic review of available literature. All studies have had 12-month primary safety and effectiveness endpoints, which were assessed via a standardized scale. In fact, they're all very similar in design to the PUFS IDE trial, which led to the initial PMA approval in 2011.

Formal hypothesis testing and predetermined statistical analysis plans were based on pre-specified sample sizes, which range from 120 to 180 patients. Study enrollments took between 14 and 43 months, respectively. Both safety and effectiveness data were independently adjudicated to minimize investigator bias and lack of study blinding. Primary effectiveness imaging was assessed independently via core lab, and safety data was adjudicated via independent clinical events committees.

We believe these studies have generated valid scientific evidence that will enable the FDA to evaluate safety and effectiveness of the devices consistent with the requirements of current regulation.

We, as industry, appreciate the opportunity to provide our collective perspective now on the questions posed by the FDA to this Panel. Then, following discussions, we will attempt to address our recommendations related to the analysis of the previously described trials.

The first question we would like to address is FDA Question Number 2. The questions says, "Can the mRS at 1 year also be a potential primary safety outcome measure for all endovascular trials?"

We understand that the modified Rankin Scale is suitable as a primary outcome endpoint for ischemic stroke, but we find it challenging as a recommendation for aneurysm therapy. It's especially challenging in the evaluation of ruptured aneurysm treatment due to significant disabilities which are present at or near the time of treatment. For example, what would we take as a baseline mRS if we're looking at mRS change over time in this type

of patient? If we took a pre-rupture as baseline, this is not reflective of the disability associated with the subarachnoid hemorrhage. In a perfect procedure, you could still have a patient who had significant change in mRS.

On the contrary, were we to take a post-treatment baseline, how would you differentiate disability associated with the rupture from an iatrogenic harm that may have been induced with the procedure or a procedure-related complication? You could mask procedural-related harm.

Because the modified Rankin is not specific to cause of functional dependency and when evaluated at 1 year is not temporally related to the intervention itself, many other things could also affect modified Rankin scores that were not directly associated with interventional treatment.

This issue also exists with the ischemic stroke utilization of the scale, but the period of observation is much more closely related to the intervention itself.

Next, I'd like to address FDA Question Number 4. Question 4a asks, "Do you consider the Raymond classification scale to be the standard to assess effectiveness for all endovascular intracranial aneurysm treatment devices?" And Question 4b says, "If the Raymond scale is utilized, is Raymond II (or higher) a satisfactory outcome for aneurysm treatment with unruptured aneurysms? Secondarily, is Raymond II (or higher) classification a satisfactory outcome for aneurysm patients with ruptured aneurysms?"

We, as industry, do believe that the Raymond-Roy scale is the most appropriate validated scale for consistent assessment of aneurysm occlusion in both ruptured and unruptured intracranial aneurysms at this time. The scale has been routinely applied in the conduct of both existing and historical studies and can be applied to multiple technologies, including both intraluminal and intrasaccular technology. We do believe that there are nuances to the establishment of successful outcome using the scale and that a Raymond I

classification may not always be the best appropriate success criteria.

With regards to Question 6, "Do aneurysm occlusion assessment recommendations using Raymond differ for an endosaccular device versus an intraluminal device?" we believe there are considerations when determining success of treatment via the Raymond-Roy scale. For example, Raymond I is the clearly established criteria for establishing successful treatment with flow diversion, and we believe that should stay. However, with the assessment of intrasaccular therapies, it may be very clinically acceptable to have a stable occlusion with the presence of a small neck remnant, a Raymond II, as long as that neck remnant does not grow or does not have an indication for subsequent treatment.

So we would like to define what we think a clear requirement for success is with a Raymond II occlusion. What is a stable Raymond II? There must be serial observations via MRA or DSA. That second observation establishing stability should be at least 6 months from the first assessment and must demonstrate either equivalent or better occlusion of the neck remnant than the prior assessment. Raymond II stable outcomes are only acceptable for intrasaccular technology evaluation. We recommend that the evaluation must be adjudicated by an independent core lab.

In addition, the primary effectiveness analysis at 1 year must not occur systematically until two stable assessments can be observed within the actual trial design. And we recommend that in postmarket follow-up, the subject with a Raymond II should be followed for at least 2 years post-primary efficacy assessment in order to characterize potential for recurrence or growth.

Next, I would like to answer FDA Question Number 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?"

First, the decision for retreatment must always be made by the treating physician. For the purposes of effectiveness assessment, however, we believe that any worsening or requirement for retreatment should indeed be handled as a treatment failure within the trial.

In the following slide, I would like to review FDA Questions Number 7 and 10. Question 7 states, "What length of follow-up is recommended to assess effectiveness for endovascular aneurysm treatment devices?" And Question 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?"

We would like to propose a follow-up period for observation driven not only by primary efficacy analysis but also by the patient's postmarket occlusion status, which we believe best reflects patient risk. In this scenario, we operate under an assumption that 1 year is broadly applicable timing for the assessment of aneurysm treatment effectiveness that's consistent with the 2015 NDP panel.

If a patient presents at 1 year with a completely occluded aneurysm, a Raymond I occlusion, then the patient should continue to be followed to Year 3 only if treated with a novel technology. However, if a technology is not novel, we believe an occlusion, complete occlusion at 1 year is sufficient for assessment. During a 1-year time period, you should be able to observe a significant percentage of treatment efficacy and safety.

We recommend that subjects who have a stable Raymond II be followed for a period of 3 years to exclude the possibility of recurrence and growth over the long term. Subjects who had an unstable Raymond II, meaning they exhibited growth of a neck remnant, or Raymond III, meaning ineffective treatment, should be followed for a period of 3 years to observe safety and effectiveness associated with retreatment, relevant adverse events associated with persistent risk of rupture.

For the purpose of clarity, we have provided a painful table for you to look at which will clearly allocate patients in such a design to success or failure. Clearly, any patient reporting to the primary effectiveness with a Raymond Grade I without having undergone retreatment would be treated as a study success. As you can see, however, Subjects 4 and 5, with stable or improving Raymond Grade II not requiring retreatment, would also be reported as success in the primary endpoint, again, were this an intrasaccular trial.

On the contrary, as you can see here, Subjects 7 and 9, who did not have stable or progressive occlusion from a Raymond II, would report to the study as a failure.

Lastly, I would like to address Question Number 9. The FDA has asked, "We consider digital subtraction angiography to be the gold standard to assess aneurysm occlusion at follow-up. Can magnetic resonance angiography, or MRA, or CTA serve as a surrogate follow-up examination, and when should this take place?"

We, as industry, agree with the FDA that the DSA is the referenced gold standard for the evaluation of aneurysms after treatment due to its unsurpassed spatial resolution. However, DSA is invasive, and it's not without risks of puncture site and neurologic complications. Study loss to follow-up secondary to subject refusal to undergo DSA is actually common and adversely impacts the sponsor's ability to execute a clinical trial.

MRA offers advantages relative to DSA and may be an appropriate alternative for some treatment technologies. Additionally, MRA has shown positive correlation to DSA with respect to assessing occlusion following flow diversion and coil embolization. In contrast to DSA, noninvasive MRA eliminates risk of cerebral thromboembolism and ionizing radiation. The premarket primary endpoint clinical studies should defer, where possible, to the least burdensome imaging approach for the patient and consistent with standard of care. AHA guidelines state that MRA is a reasonable alternative to DSA for follow-up for treated aneurysms. We acknowledge, however, that technology and imaging-specific

considerations are required for assessing applicability of MRA and endpoint analysis on each trial.

In closing, we believe that the studies conducted will allow for meaningful analysis and determination of safety and effectiveness. We believe those studies can be assessed for effectiveness via the Raymond-Roy scale of aneurysm occlusion, which was a consistent approach applied in the trials.

We've attempted to provide clarity regarding nuances of the scale as it relates to technology and acceptable outcome and to clarify recommendations for subjects reporting to an analysis.

Further, we have attempted to articulate specific challenges for requirement of aneurysm study follow-up imaging.

At this point in time, I would like to turn the presentation over to my colleague, John Allison, to discuss industry's collective thoughts on future opportunities to improve and enhance aneurysm clinical trials. Thank you for your time.

MR. ALLISON: Good morning, my name is John Allison. I'm Vice President of Clinical and Regulatory Affairs for Stryker Neurovascular.

Soon we'll have results from many of the trials just discussed that Stacey showed, and we'll be in a position to establish clinical trial design standards appropriate for this maturing therapeutic area. So to conclude this presentation for the industry partners, I'd like to spend a few moments discussing actionable steps for moving forward.

First of all, we recommend that the current trials with justified performance goals continue through the regulatory review process in order to bring to market important treatment options that advance patient care. As mentioned earlier, these studies present valid scientific evidence that provides reasonable assurance of safety and effectiveness.

Current single-arm studies with performance goals generate sufficient evidence for

approvals. Over time, we are building datasets from which meaningful performance goals can be established for the evaluation and approval of new technology.

Performance goal studies are the most practical and pragmatic approach to understanding the success and failure of new innovative devices. Studies of new endovascular technologies are multicenter and core lab adjudicated, unlike the majority of data that exists today on aneurysm treatment. These well-designed trials enable us to continue to build evidence in an area of high unmet medical need.

To date, there are IDE trials currently generating substantial additional evidence that will allow for performance goal assessment in these high heterogeneous, low volume populations.

And lastly, performance goals serve as the future standard for well-defined, objective performance criteria models that will increase study robustness, answer defined research questions, and standardize new device evaluations.

We, as industry partners, would like to put forth a proposal on how we can continue to generate high quality clinical evidence in this era of emerging and maturing technologies. Our vision is for multiple stakeholders to collaborate on the generation of validated objective performance criteria that can be used in future clinical trials. The clinical trials I just mentioned will provide the data for this effort. We propose appointing an independent third party who will oversee the creation of the OPC model. This would include broad participation from industry partners, medical societies, and the FDA. The published data from current IDE studies can help validate the OPCs by aneurysm type and can help influence evidence-based practice guidance. Additionally, we support pooling patient-level data to better answer questions on aneurysm subgroups.

In summary, these efforts will enable FDA to include OPCs in a future guidance document.

Here's a sample timeline showing now with the trials currently underway. In 2018 we would utilize an independent third party to develop the OPC; followed in 2019 and beyond, there would be stakeholder acceptance of the OPCs, with periodic updates based off of postmarket studies and real-world experience in combination with data from new technology.

By aggregating the data from the 1,400 patients in the eight studies we reviewed momentarily, we will be able to generate a wealth of information that can provide data-driven answers to FDA's questions. Let me show you how we plan to do this.

A multidisciplinary team will be appointed to define research questions and develop a predefined statistical analysis prior to the actual study data integration. From there, we can generate OPCs and examine subgroup data in a variety of ways that can help inform future clinical trial design. This has successfully been done in other therapeutic areas.

In a recent publication by FDA staff, the authors concluded that the development of robust OPCs generally requires relatively mature device technology and the availability of high quality historical clinical evidence. This has been exemplified by the formation of OPCs for several device types, such as ventricular assist devices, endometrial ablation, heart valves, as well as critical limb ischemia laser angioplasty devices.

A similar approach could be applied directly to the neurovascular field. The physician community has already started moving in the direction of proposing OPCs that would be used to evaluate aneurysm devices. Just last year a comprehensive meta-analysis was published which evaluated all relevant literature for wide neck bifurcation aneurysms treated either by conventional surgical clipping or by endovascular treatment. The systemic literature review identified all articles that met pre-specified criteria, which resulted in a dataset that included several thousand treated aneurysms. Safety and effectiveness outcomes were reported for both endovascular and surgical treatment. OPCs were then

calculated based on these outcomes. The authors proposed these literature-derived OPCs could be used in the evaluation of novel wide neck bifurcation devices.

So, in closing, I will summarize the unified perspective we presented today from the seven companies. As you heard, it's important to recognize that aneurysms, regardless of size, warrant consideration for treatment in patients who are at risk of rupture.

In addition, industry provided perspectives and practical solutions to FDA's questions that you will be considering this afternoon.

Further, we believe the eight single-arm performance goal studies that are currently underway can provide reasonable assurance of safety and effectiveness. These IDE studies are near completion, and evidence is maturing to enable us to derive an OPC model.

And moving forward, we'd like to collaborate with FDA and the societies to establish OPCs that can be used to establish clinical trial design standards appropriate for this maturing therapeutic area.

Thank you for your time and attention. And I'd like to call Stacey Pugh back to the lectern to take your questions.

DR. JENSEN: Thank you very much to our industry representatives for that presentation.

Does anyone on the Panel have any brief clarifying questions? I have one I'd like to ask, if that's okay. With regards to the follow-up and MR, can you clarify further whether -- the type of MR, MR with/without contrast, MRI and MRA, MRI potentially to look for unrecognized complications such as intracerebral hemorrhages or unrecognized strokes?

MS. PUGH: So I will attempt to answer that as best as I can, Dr. Jensen. The publications that we referenced in the discussion there speak to the capability to assess occlusion of the aneurysm more specifically. Certainly, MRI post follow-up does get utilized to look for downstream complications, ipsilateral complications, to the procedure. We do

acknowledge, again, when we think about MRA, again, contrast analysis to look at occlusion, that there may be technologies where MRA may be less effective than others, and therefore, the need, when you design a trial, to make a determination of whether MRA is substitutive would likely need to be trial by trial. The references that were provided were specific to coiling and flow diversion therapy.

DR. OVBIAGELE: So I had two questions, and I'm not sure if the first one is better for Dr. Dion, but the first one was just the issue of we heard about the ISUIA design and the population quite well, not so much about the Bender study, which was used as a counterpoint to that particular data. So I wondered if there was any information you could provide about the population and the study design of that particular study. That's one question.

The second question, if I may, is to your presentation and really to the FDA question about mRS at 1 year. And so I guess the question I had is, does industry have an alternative endpoint that you might propose that could be clinically meaningful and functionally relevant as opposed to mRS? Because I do think it's important for that to be a safety, potential safety outcome. So is there an alternative, and if not, is it possible for mRS to be done at 6 months? Because I hear that issue about the proximity to when the event is being done, so could you potentially have a 6-month mRS, so to speak? And it could be done by telephone because, as opposed to the stroke scale, you don't really need a certified rater, so to speak, to examine the patient, and it could be done over the phone. So could you consider that?

MS. PUGH: So can I answer the second question first, because I want to make sure I get it right. Yes, we do believe temporal association was one of the big issues. We do not believe that the Rankin Scale application to a ruptured aneurysm scenario is going to be easily applicable. And so if you're looking for consistency across ruptured and unruptured

aneurysms, I think that study -- where you may actually have the population of both in a study. So we are specifically focused in these trials on unruptured aneurysms, that there are likely technologies coming to the FDA, and subsequently potentially to this Panel, that will include both ruptured and unruptured. And part of our concern was that ruptured scenario, where if you're looking for modified Rankin change from baseline, where do you take a baseline for that patient, right? I mean, either whether you take it immediately post-procedure to account for SAH or whether you take it pre-procedure, the deficit in that may not be attributable to the procedure itself. So that was fundamentally the concern.

These trials have all used an endpoint of stroke and neurologic death as an endpoint, and subsequently defined major stroke because you capture minor and major with a 4-point change in NIH Stroke Scale, and it is challenging to implement those in the acute care setting, no question. That specifically, though, allows a clinical events committee to focus on neurological deficit rather than other things that might affect a Rankin score. So the recommendation would be potentially to tighten or be more consistent, I think, Carlos, with how we're each implementing that stroke and neurologic death endpoint.

On the Bender et al. study -- and, Jacques, please feel free to join me -- that is actually a study that just reports what aneurysms presented to those centers in terms of characteristics.

DR. DION: Correct. The point of the Bender study slide was to contrast the 0% risk of aneurysms of less than 7 mm showed in the ISUIA study with real life evidence. The Bender study is all ruptured aneurysms on presentation, whereas ISUIA was unruptured. So we're not comparing one group to the other. We're just casting doubt or uncertainty, or we're trying to understand the discrepancy between that 0% figure and real life, where all of us see patients presenting with aneurysms at least half the time that are less than 5 mm in size. And it's hard to conceive that none of those patients who present in real life, none

of them are Group 1. I have seen many patients present to me who have one aneurysm, they don't have a family history of aneurysm, and it doesn't line up with the ISUIA. So my purpose was not to bash or criticize the ISUIA study but to raise the point that there are questions of why the differences between ISUIA and Juvela and UCAS exist.

And very short also, the designs between -- the major design differences between the Juvela study, the ISUIA study, and the UCAS study, the populations were different: Finnish, Japanese, American, Canadian, and European. But also, as well, the allocation of aneurysms, as I mentioned, was different. The multiple aneurysms, for instance, in the ISUIA study were all allocated to posterior fossa. The patients in the Finnish study, 80 or 90% of them had a history of subarachnoid hemorrhage in the past, therefore not comparable to Group 1. In the UCAS study, they were Japanese patients. And what emerges from this is, in the larger aneurysms, the numbers are much more consistent in terms of ruptures. More the question arises is why the difference in small aneurysms in Group 1?

MS. PUGH: I think the takeaway for that, for us, is if we look at ISUIA and we look at the output of the 2015 Panel, that perhaps aneurysms under 7 mm are not indicated for treatment. Bender et al. would suggest that 50% of the aneurysms presenting in that study would not have been indicated for treatment had they been detected in advance, and that was the reason for the Bender trial.

DR. JENSEN: Dr. Grotta.

DR. GROTTA: Yes, thank you. Would it be possible for you to bring up that awful -- that you alluded to, awful --

MS. PUGH: My bad chart.

DR. GROTTA: -- chart?

MS. PUGH: Yes, we can do that.

DR. GROTTA: Which I really --

MS. PUGH: Could you bring up the patient allocation chart?

DR. GROTTA: I applaud the chart. I think it made things very helpful, but --

MS. PUGH: Yeah, this was an attempt at clarity to make sure that --

DR. GROTTA: Right.

MS. PUGH: Yeah.

DR. GROTTA: Right. So do you think, just looking at Subject 6 and 7, is there evidence that an MR angio would be able to detect the difference of a I going to a II and a II going to an unstable II?

MS. PUGH: For coiling, we believe that there is. For flow diversion, again, I is the only acceptable outcome, and it's a very binary failure, but we do believe there's references, and we'd be happy to get those to the Committee, that speak to the capability to do that with coiling or intrasaccular technology. There may have to be an evaluation of the specific technology to make sure that artifact does not become an issue and obscure neck assessment by MRA.

DR. GROTTA: Okay. And a second question with regards to this on Subject 3. So my understanding is, is that if someone, if you try to coil an aneurysm or whatever and there's a lot of dye around the coils, wouldn't that be a failure, right, de novo right from the start? I mean, as opposed to just seeing some dye intercalated within the coils? I mean, I think there's literature to distinguish between different grades of III, and I would think that some III's would be a failure right from the start.

MS. PUGH: You know, I think -- remember that these trials include a provision such that any retreatment that would be required, to your point -- I think the case you're describing where you might assess I have an incomplete treatment and this aneurysm persists at risk for rupture, if a physician felt like that needed to be retreated, that would

indeed warrant -- that is, by definition, failure for the patient in the trial. The reason that you saw us go more general there and allow for the fact that you might have a III at 6 months and a I at a year, if you think about flow diversion technology, a patient may be incompletely occluded at 6 months and progress to a 1-year endpoint. The same with intrasaccular flow diverters, that you might see incomplete occlusion partially that progresses to complete occlusion over time.

DR. GROTTA: Thank you.

MS. PUGH: Yes.

DR. ERKMEN: Can you go back to that same slide? The question I had was on Patient 5, Subject 5. If you go from a III to a II, we don't know at that time point if it's a stable II or a progressing II. So would that patient require longer-term follow-up --

MS. PUGH: Yes, they would.

DR. ERKMEN: -- to call it a success?

MS. PUGH: Yes, they would. You have to have two serial assessments, and that is actually a lack of clarity on the chart, so thank you for calling that out. But part of the criteria that we tried to describe was that for a stable II assessment to occur, for a patient to report a success, you need to have two assessments of at least a Raymond II that's shown to be stable or improving. So thank you for calling that out for clarity.

DR. ERKMEN: Thank you.

DR. JENSEN: So Dr. Connor and then Dr. Pilitsis.

DR. CONNOR: Yeah, I had a follow-up to that. In particular, given how long it takes to enroll many of these studies and what you're calling a stable II, so what if you have -- so you mentioned, you know, if you're a II, you're going to keep following that patient. You know, if you're an early patient into the study, you may have that patient's follow-up before the last patient in plus 12 months.

MS. PUGH: Absolutely.

DR. CONNOR: So if you identify those patients who met that definition at 12 months but then it is evident that that patient is an unstable II by the time you submit the PMA, is that patient a failure, or do you count them a success even though you know he's a clinical failure by the time you submit the PMA?

MS. PUGH: I know what Carlos is going to tell me to do with that patient, I mean, but per the primary endpoint, you're right, you have a 12-month analysis. If, by design, we're suggesting that you have to have a longitudinal analysis here, that patient would then show that you had a recanalization over time. Again, I do believe that is something that has to be considered with a technology like that, and if you do have follow-up data that reports a patient as a failure over time, I'm sure that, you know, whether it's per protocol or -- subsequent analysis would need to be conducted.

DR. CONNOR: Right. I mean, because I mean these are important issues, and it's why the whole Vioxx can of worms existed, right? It's like when you declare your data cutoff, and at some point you have to --

MS. PUGH: Exactly.

DR. CONNOR: -- declare a data cutoff, but it seems fair to use all available data, and appreciating that, you know, the last patient and you're going to have 12 months, with the first patient in, you may have 3, even 4 years of data points.

MS. PUGH: Yeah. Unfortunately, within these trials, multiple times we have multiple-year data on many cohorts when you submit 1-year data.

DR. CONNOR: Right.

DR. PILITSIS: In regard to Question 9, did you have any comment on CTA?

MS. PUGH: We find the literature supportive of CTA in those cases to be less robust, and therefore, we did not come forth with the recommendation that CTA would be

acceptable at this time.

DR. PILITSIS: And my second question is, on Dr. Dion's first slide, he says all treatments should be considered -- all aneurysms should be considered for treatment, and I understand there's conflicting literature. Are there guidelines by any of the physician groups that can come and somehow resolve this conflicting information for us?

DR. DION: The key word on the slide was "considered." Considered includes observation. I don't think there are guidelines. There is confusion in the literature, and I'm sure my colleagues from the medical societies will address that later on today, but to my knowledge, there is no standard or guideline; there is recommendation based on confusing literature reports, and as I said in my concluding slide, it's very difficult to present that to patients. Patients, they've all heard of patients dying of aneurysms, and they're fixated on dying. And so there's the issue of the guidelines and the issue of dealing with a scared patient.

DR. PILITSIS: Thank you.

DR. DION: Thank you.

DR. JENSEN: Okay. All right, we're going to go to Dr. Ashley, Dr. Selim, and Dr. Thompson.

MS. PUGH: I'll try to talk fast.

DR. JENSEN: We'll start out there. Okay.

MS. PUGH: Thank you.

DR. ASHLEY: I have a question about the use of devices that require antiplatelet agents, and is there any consideration to both the assessment of the success in the setting of what kind of antiplatelet therapy they're on, particularly considering testing levels of sensitivity or reactivity, and then how would that affect the follow-up or consideration of follow-up?

MS. PUGH: So I can speak to the clinical trial design. And, Jacques, maybe you should just stay up here with me.

Specific to trial design, some of these trials did indeed account for looking at patients who were therapeutic, determined to be therapeutic at baseline. I'm speaking on specifically the PREMIER flow diverter trial is looking not to include patients who are known to be resistant to antiplatelet therapy at the beginning. We certainly collect that data, and that data is assessed in terms of events. We do see -- and I can speak specifically for the trials I've administered -- you do see modifications to antiplatelet therapy over time when they are tested to maintain therapeutic. You know, can that be analyzed, and I think, do we analyze that? Certainly, within the data, we do it within the safety cohort; the clinical events committees consider that when they look at safety events. But is it absolutely prescribed and standardized how you manage antiplatelet therapy, whether you test and when you test? It has not been the typical approach in all of these studies.

DR. ASHLEY: Thank you. I think one of the parts about that is, particularly when thinking about progression from a stage III to a II, or a II to a I, sometimes there's relationships between, you know, the antiplatelet agent, for example, or --

MS. PUGH: Whether that's -- yeah, whether that's effective.

DR. ASHLEY: -- whether it's all in 1 year and still II or I, etc.

MS. PUGH: I think, to the point that John Allison made, we are now going to have a very large cohort of patients in flow diversion with these trials, and I think it allows us to begin to answer questions more effectively than we've been able to in the single sponsor studies. So I do believe it's an area of inquiry for us, it's very relevant for patients, and we should be able to answer that better very soon.

DR. JENSEN: Dr. Selim.

DR. SELIM: Okay, I want to go back to the issue of the first statement that all

aneurysms should be treated or should be considered for treatment, which means that a lot of unruptured aneurysms would be treated. So you as an industry, have you considered that safety and effectiveness, the assessment of these elements should vary depending on the indication, whether it was ruptured or unruptured?

DR. DION: Let me try to answer your question. My use of the word "considered" meant that that discussion needs to occur with the patient as to treat or not treat. I personally believe that a discussion needs to occur, and the patient who harbors an aneurysm that is less than 7 mm in size should not be told you do not need to be treated. I think the patients need to be shown and explained the data, the confusion about the data, and that's what I meant by considered --

DR. SELIM: No, I'm not questioning that.

DR. DION: Okay.

DR. SELIM: I think what I'm asking is --

DR. DION: I just wanted to be clear on that.

DR. SELIM: -- do you think the effectiveness and safety assessment should vary depending on whether there's a ruptured aneurysm or unruptured aneurysm? Have you considered --

DR. DION: Absolutely. They're two different diseases. Ruptured is a terrible thing with a high recurrence of bleeding rate within the first 2 weeks and 6 months. Unruptured is a difficult thing to assess, and we have to look at the risk of the treatment. Are we proposing a high-risk endovascular treatment for a low-risk aneurysm? Is the patient old? What is the patient's life expectancy? What is the risk-benefit ratio going to be? Is the patient 30 years old and has a 50-year life expectancy with a low risk but a high cumulative risk? Have I clarified that for you? But if not, please --

DR. SELIM: Yeah. I guess what I'm asking, if you as an industry have considered

what these assessments should be. I mean --

DR. DION: Absolutely.

DR. SELIM: Okay.

MS. PUGH: I think all the same endpoints, we believe all the same endpoints and assessment techniques in terms of scales, in terms of definitions of adverse events, are similar. The rates predicated in a trial for those two conditions, in terms of acceptability, would likely need to be different.

DR. SELIM: Okay, thank you.

DR. JENSEN: Dr. Thompson.

DR. THOMPSON: I want to follow up with Dr. Dion as well, about this issue of the size of the aneurysm. I think, in listening to this, one of the concerns I have is the term that was used, "regardless of size." I wonder if you don't agree that although your point is very good about ISUIA, the first ISUIA which suggested that 7 mm less, or 7 mm and less, do not need treatment was basically refuted by subsequent population curves showing that the median size of a ruptured aneurysm is about 7 mm and as many as half are smaller than that.

However, I think you said yourself that size is a matter of importance, and if you look at those same bell population curves, while smaller than 7, it's still significant. Smaller than 4 is a very rare ruptured aneurysm. And while some risk factors can point to possibly the need for use in those patients, I'm somewhat troubled by the use of the term "regardless of size" because it suggests, I think to some, that that is not an issue and it has the potential for perhaps causing indiscriminate use if something like that were to be approved. And so could you comment on that, please?

DR. DION: I'd be happy to. The point of "regardless of size" was specific to real life experience where 50% of aneurysms that present with rupture are less than 5 mm. Again,

to me, intellectually, I have a very difficult time conciliating the 0% with what we see in the emergency room day in and day out. That was simply the point that I was trying to make.

DR. THOMPSON: So you would agree that there is a size of aneurysm at which -- we'll just use 2 as an example -- at which there is a very, very small risk of rupture for unruptured aneurysms?

DR. DION: I would agree that size is absolutely a factor in determining the risk of rupture, and my personal belief is that it is difficult to determine specifically what that risk is, based on the literature that we have today.

DR. THOMPSON: Right.

DR. DION: For those specific aneurysms of less than 7, 5, or 3.

DR. THOMPSON: I think your point is a good one, and I also would grant there are even small, rare -- as we all know -- 2 mm aneurysms, dorsal wall aneurysms that may require further consideration. But I think it's important to not dismiss the size issue, is really my point.

DR. DION: And ISUIA also excluded 2 or less millimeter aneurysms.

DR. JENSEN: So we're going to go with Dr. Lyden, Dr. Dorsey, and then Dr. Posner.

DR. LYDEN: Thank you. Just a couple quick clarifications. You didn't mention, and I just wonder if you have any information or data on the impact of operator skill and volumes on outcomes with these procedures.

MS. PUGH: So this is something we assess in trials and I think is one of the contributory issues when you think about the ability to conduct larger studies in our space. You want to make sure you have adequately trained in volume-based centers to both recruit and treat. That is and will be assessed. Certainly, we look at site-to-treatment interaction as a confounder in a trial, typically, as part of our analyses. I will tell you, in the early flow diversion data, specifically from a retrospective study we conducted called

IntrePED -- and this was, again, just upon flow diversion introduction in the U.S. -- we were able to demonstrate that complication rates went down fourfold with subsequent experience of operator and site. So, you know, I think early technology introduction is certainly something we have to look at. That's part of our commitment in terms of postmarket surveillance of the technology as well. I think we certainly look for treatment center interaction within a trial, and then we attempt to try to characterize that better outside of the study in postmarket surveillance.

DR. LYDEN: Thanks. And then my second question was I couldn't follow your logic with the Rankin. So the Rankin is a disability scale that has nothing to do with stroke. It's invented to measure disability in patients from a wide variety of causes. It's assessed at 3 months or a year after an event. The two correlate well, but they're not perfectly correlated.

MS. PUGH: Um-hum.

DR. LYDEN: And the goal is to assess the impact of a treatment on the proportion of patients that achieve a certain Rankin or a certain distribution of Rankin scores. So I don't understand how that's not possible.

MS. PUGH: I'm not saying it's not possible. I think the question is, is the conclusion valid? So in a patient who has a hemorrhagic stroke, what we're actually looking for is change in Rankin over time, right?

DR. LYDEN: Why?

MS. PUGH: So you want to have a valid --

DR. LYDEN: Why do that and not just do it the way everybody else does it?

MS. PUGH: Well, I think with stroke -- I can speak to the stroke studies. In stroke, you know what a baseline Rankin is, and you set criteria based on that. If I'm studying a rupture population, my ability to assess baseline Rankin, I can ask the family, as I do with a

stroke trial, what was this patient's baseline Rankin score? Depending on severity of subarachnoid hemorrhage, their baseline score may be irrelevant, and it might be irrelevant whether we treated them with an aneurysm therapy or not because their Rankin before the rupture and their Rankin after the rupture may not be the same.

If I use the post-treatment -- let's say a patient has a hemorrhagic rupture. They come into the hospital and they're a Rankin 4, and before that Rankin 4 they had a coiling procedure. If the coiling procedure was irrelevant to their disability and then we look at that as a function of time over 3 months, that's okay. If I say I'm going to take Rankin at the time of hospital discharge for the patient and then look at that over 3 months, I might actually mask a patient who would have had a good Rankin but had an iatrogenic perforation of the vessel during a procedure that harmed the patient. So depending on where you select that time point for a ruptured aneurysm, specifically, we're expressing concern.

DR. LYDEN: So that just -- I'm sorry, but that's not any different than ischemic stroke. A patient comes, they have a baseline Rankin at home, before their ischemic stroke, of 0 or 1 or 2. They have a massive stroke, they come and they get treated, and we see them 3 months or 12 months later. The two scenarios are the same.

MS. PUGH: We assume that the rupture of the aneurysm is the impending impact on disability there. Certainly, clearance of the vessel is a driver of a change in disability assessment. I think what we are suggesting -- and again, I want to make sure that I'm caveating that we believe this challenge exists predominantly for ruptured aneurysms. The successful occlusion or exclusion of that aneurysm may not be the driving factor of that patient being a Rankin 0 before and being a Rankin 4 at 9 months or 3 months or 12 months. I think that's the concern. We're looking for the capability to assess what was the positive or negative impact of the intervention, and we believe the subarachnoid

hemorrhage clouds the capability to look at that in both directions.

DR. LYDEN: Okay.

DR. JENSEN: So, to clarify, in an unruptured aneurysm patient who starts at a Rankin of 0, a normal patient --

MS. PUGH: Um-hum.

DR. JENSEN: -- you would not be against obtaining a Rankin after the treatment at a certain time point?

MS. PUGH: I think you see us collecting Rankins as secondary endpoints in these trials today. The challenge that we think we have, especially as you get into more novel technology and small sample sizes, we measure stroke Rankin for primary endpoint at 3 months after the intervention as a measure of did you induce -- improve or induce disability. When you look at 12 months, we're just calling out the fact that we actually believe stroke or neurologic death may be more specific to assessing the impact of the intervention than Rankin. Can it be done in that population? Absolutely.

DR. LYDEN: Okay. So, yeah, a quick final question. So you sort of painted a picture that we don't really understand the natural history of these aneurysms, so the ISUIA study and others, you feel we don't really know. So in the slide that you showed about the ongoing studies, if I did the math right, I counted over 1,200 patients enrolled in a relatively short amount of time, which implies that if half of them had been randomized to no treatment, we'd have a very robust collection today of natural history versus intervention. So I'm just curious why not, if your feeling is the natural history data is so poor, why didn't we do it or why shouldn't we be doing it that way?

MS. PUGH: Well, so first off, that's not necessarily a homogenous population, large and giant aneurysms and small aneurysms. I think we would struggle greatly with ascribing a large and giant aneurysm population with a 40 to 50% 5-year mortality to a 5-year

observation study. So I think there are obvious populations and cohorts here.

If we talk more specifically to small aneurysms, there have been attempts to do that. There's a study called the TEAM study that was run by Jean Raymond et al., and the goal was to randomize patients who were thought to be at lower risk, so sub-7 mm, to observation or intervention and longitudinally follow those. You have to have equipoise both on the part of the patient and the physicians to do that. That trial was actually closed due to abysmal enrollment; there were 80 patients enrolled over a 2½ year period. If you look at the overall sample size for that trial, it would have taken decades.

Again, I think, if I think pragmatically about the discussion, you're going to be consenting a patient to observation who is characteristically similar to 50% of patients who show up ruptured in the U.S. hospitals today, and I think, you know, if equipoise exists, they weren't able to achieve it in a previous attempt.

I don't know, Jacques, if you have other --

DR. JENSEN: Dr. Dorsey and then Dr. Grotta.

DR. DORSEY: Ms. Pugh, thank you very much for the presentation. I have an easy question for you. What does OPC stand for?

MS. PUGH: We thought about this. Objective performance criteria.

Actually, John, I think we have a slide prepared. Did we prepare the slide for what is the difference between a performance goal and an OPC?

MR. ALLISON: Yeah. These are the trials we took you through today at a high level, are all performance goal. They're based on literature. The literature that we used today for aneurysms is not really high quality studies; you know, it's registries, it's observational studies, and so forth. OPCs, or objective performance criteria, is really taking PGs to the next level where you do large meta-analysis from higher quality studies, which these eight studies are all core lab adjudicated, and be able to pool that data all the way down at the

patient-level data so you could do subgroup analysis to really get a better fine-tuning around the response for treatment at the specific aneurysm type level, which is one thing that we believe we lack.

DR. DORSEY: Thank you. And then a second question just to follow up from Dr. Lyden. For ruptured aneurysms, you've indicated that you don't like the idea about using the modified Rankin as a safety outcome measure at 1 year. Did you have an alternative in mind?

MS. PUGH: Again, we believe stroke and neurologic death, given that -- let me give you an example. In my stroke studies, in looking at this, you have certain patient populations or you're going to have certain patients who have a change in Rankin from 3 months to 12 months, not because they had a decline in neurologic status but because they fell and broke their leg and they're non-weight bearing and that patient has a different modified Rankin score. We think safety is the most sensitive measure to look at in the aneurysm population, and so there's a concern about fidelity. When you have a larger study or you're able to randomize, some of that usually comes out in the wash. When we're talking about single patient studies of 150 patients, a few patients reporting maybe declined or artificially improved could sway an outcome, and we're concerned about not the utility, can it be applied; we were concerned about the sensitivity.

DR. DORSEY: Thank you.

DR. JENSEN: So Dr. Grotta -- I'm sorry, it's really Dr. Posner next and then Dr. Grotta. Didn't you have something you wanted to say, Dr. Posner?

DR. POSNER: Just one about size and real-life data versus the large study. And as an ex-cardiologist, I think about mitral valve prolapse, and initially, mitral valve prolapse was treated incredibly aggressively for arrhythmias because those were the only ones you saw were people that came in with arrhythmias. Then we did full cross-sectional studies and

found out that it's less than a tenth of a percent of the population, and now it's not treated aggressively. And I think some of the things you're saying in real life may be you're seeing the patients that have had ruptures. You're not seeing all the ones that haven't.

As a patient also, the watchful waiting, I think it's important how you sell that to the patient or explain it to the patient. If you explain it to the patient that watchful waiting is going to include reduction of risk factors, like smoking and hypertension and also looking at changes in the size over periods of time, you'll get much more agreement from patients in watchful waiting than just saying, well, we can just watch it and see what happens and it may rupture, because in our small coronaries we don't treat small coronaries because there are minimal numbers of ruptures that take place, and you do watchful waiting, which is aggressive, and you do treat risk factors. So I just throw that out to muddle the waters a little bit more.

MS. PUGH: So, first, I don't think anybody's arguing that you arbitrarily treat all aneurysms first, irrespective of size or directed only by size. Certainly, there's multiple risk factors associated with these patients, and we believe a comprehensive assessment has to be made. What we hear, and what we found in going back and trying to investigate and understand what were the issues with the execution of that TEAM trial where they tried to do this, this condition, when it occurs, is immediate and carries a 75% morbidity/mortality; 50% of patients don't make it to the hospital, and the other half who survive are disabled. And so I think it's good to understand if the surrogate that you're talking about in your trial has the ability to detect worsening and therefore modify treatment. Observation in aneurysms may not be that sensitive unfortunately. So those are the things we think are considerations here. I do believe that the societies and the medical community, they're going to be probably far more appropriate to discuss this question than us as sponsors.

DR. JENSEN: Dr. Grotta.

DR. GROTTA: Yeah. Dr. Jensen, I'd like to expand on Dr. Lyden's comments with regards to the Rankin score, but I don't know if you want to just save that for the afternoon or --

DR. JENSEN: I think we can save that for the afternoon.

DR. GROTTA: Okay.

DR. JENSEN: Is that okay? And Dr. Connor. These are really supposed to be more clarifying questions, and we're getting into a lot of conversation that we'll have again this afternoon. So other Panelists, you'll have plenty of time, but we're so ahead of schedule that we've got time now, too.

So Dr. Connor.

DR. CONNOR: On your Slide 21 that we saw before, that kind of shows, I think, the eight current studies.

MS. PUGH: Yes.

DR. CONNOR: Do you have a slide that shows the performance goals, because it sounds like all eight of these have --

MS. PUGH: So we do. Actually, can you bring up the slide that has the primary endpoints? Primary -- I'm sorry, these are actually the endpoints. This doesn't have the specific performance goal, and I apologize. We can get that for you this afternoon because we do have it. The respective performance goals in terms of success criteria are going to be slightly different between the flow diverter trials, as they relate to the original study, stent-assisted coiling, and the intrasaccular bifurcation devices. So we can get that, and that way the group will have that this afternoon.

DR. CONNOR: Okay. And I assume all those performance goals were negotiated/agreed upon with the Agency before study initiation?

MS. PUGH: Absolutely. I mean, those are based -- they're in the trial proposal;

they're based on best available literature at the time. One of the considerations, I know, that has come up for us is that literature, when you look at the duration it takes to enroll some of these studies, new information may become available. So while we had set performance goals, we have at times needed to go back and evaluate and make sure the performance goal was most reflective of contemporaneous practice. But the methodology, I think, around what is relevant literature and how that would be looked at, at this point in time, was very consistent and specified.

DR. CONNOR: Okay, right. Yeah. And I think, I mean, one of the challenges -- and I think Slide 41 maybe said something about heterogeneous patient populations, and I think the concern, right, is that it's a heterogeneous patient population. But if you enroll the easy patients or the lower-risk patients, you can gain that performance goal. And then that's what we even see in health metrics and healthcare systems, is that some high-risk patients have trouble getting treated, even -- like not just for aneurysms but for other things, because no one wants to do hard cases because your numbers go down. Here, if you do easier cases, it gets easier to meet those performance goals. So sometimes I think even having patient-specific performance goals, and there's a way to account for that, is maybe more fair. That way --

MS. PUGH: Propensity scoring --

DR. CONNOR: Right.

MS. PUGH: -- or risk matching.

DR. CONNOR: Yeah.

MS. PUGH: Again, given the quality of the data that we have today, I 100% agree with you. And it's part of our proposal going forward. Because of heterogeneity, we believe pooling this data is going to make the capability to assess that based on the subgroups by location or risk factors by comorbidity much more possible. Unfortunately,

much of these performance goals were driven off of, you know, either single-center, multicenter, non-core lab adjudicated presentation of outcomes, and it's not good, but it is what we have in the aneurysm space today.

DR. CONNOR: All right, thanks.

MS. PUGH: So, absolutely, we acknowledge those limitations.

DR. JENSEN: So I have a couple clarifying questions. In terms of the timeline that you showed of imaging and the fact that you at least seem to be interested in enrolling ruptured aneurysm patients, do you feel that having the first imaging endpoint be at 6 months is too long, considering that ruptured aneurysms that are coiled or treated endovascularly will recur earlier and rupture earlier? Is that left up to the clinician taking care of the patient, if they want to image the patient earlier, or is that a consideration in your plan?

MS. PUGH: It's not a topic that we, as a collective industry partnership, spoke about, Dr. Jensen. It's a very relevant topic, I think, for the future. I'm going to actually ask Dr. Dion to join me because it absolutely is a consideration, especially, as I mentioned, the potential for patients being included who are both ruptured and non-ruptured.

DR. DION: I think the standard that was established a long time ago, that we follow for whatever reason, has been 6 months, and sometimes people do, additionally, a year, 18 months, or 2 years. I agree with your comment that if a ruptured aneurysm is treated, in particular in a smoker, the risk of early recurrence is higher. I don't know what the answer is as to do we need to modify our research protocols to include a 3-month imaging screening to pick up these patients. I think it's potentially a good idea. It may be difficult to apply in real life because it's my belief that most people don't do that, so it may be difficult to impose that in the protocol, but it's certainly a good idea.

DR. JENSEN: And so another question is, when do you determine what the first score

is? Because I can guarantee you, you know, every coiled aneurysm is a 2 or a 3 because the patients are heparinized. If you're going to put a stent in, they're on aspirin and Plavix, you know, so you're really not starting at -- you're going to find that a lot of people are already Raymond II's or III's, and quite frankly, if a flow diverter patient is a I at the very beginning, that concerns me because you know those often go on to thrombus. So how are we doing that, sort of, first number? Does it really matter? Is there a timeline where you're going to look at what the first number is after some of the confounding factors like aspirin and Plavix and heparin are eliminated?

MS. PUGH: So can I ask a clarifying question to that, Dr. Jensen? Are you speaking more specifically to the recommendation about a Raymond II? And we talked about the need for serial assessments 6 months apart. When is that first assessment; is that your question?

DR. JENSEN: So the first assessment, I guess, is at 6 months, and I'm just sort of wondering, when we're starting from ground zero, does that really matter what that number is? Because, again, it's going to be primarily a 2 or a 3. Just clinically, from my experience, none of the aneurysms are occluded right off the bat, right? We're just going to go with whatever it was that the patient began with, and that's not really important. Really, the important number is the 6-month number.

MS. PUGH: Yes. I think when we think about those assessments, again, I think in a Raymond II recommendation, we would say if it's an intrasaccular technology and there is a neck remnant present, the physician doesn't believe it warrants retreatment at 6 months, you look at that, it's stable. I consider it to be truly a Raymond II. We would want to know that you had at least 6 months documenting that that neck remnant was not going to grow. So I think, to your point, that first assessment could not happen prior to 6 months. It could be, by design, a sponsor could say I'm going to do the first assessment at 12 months and my

primary endpoint will be at 18 months. If that's a technology that that's going to have that condition happen a lot, I think it's a trial design consideration. What we were trying to establish is that that is a deviation from the current recommendation that Raymond II is acceptable for intrasaccular, and we were trying to find some balance around how we would define that that was reasonable and could be controlled within a study.

DR. JENSEN: Anybody else have any questions? Yes.

MR. WREH: I have two questions, and I would like to hear from Dr. Dion on these questions. The first one, as you know, medical device labeling is a benchmark for FDA when approving products, so can you provide specific details on how you use device labeling? What do you consider in terms of, you know, size, anatomical sites, location, morphology, and etc. when you do your device labeling? My second question for you is why are you recommending 2 years post-approval study follow-up?

MS. PUGH: Again, we believe in a scenario where you have a neck remnant, we believe a scenario like that warrants longer observation of the patient to be able to assess for -- the real question is, is long-term stability something that's other than absolute perfect occlusion? We also believe, in the postmarket setting on novel technology, that 2 years is appropriate in a postmarket setting for follow-up because the technology is new. That is done in some technologies today, some not. For the original flow diverter approval, we did 5-year follow-up. So, one, for the fact that you have anything other than an absolute perfect occlusion and exclusion of the aneurysm from the circulation; two, because we believe longer-term follow-up is warranted in these patients if technologies are novel. I think, on labeling -- I don't know, Jacques, if you want to take that or if it's more of a methodological -- certainly we report, you know, what size of aneurysms were treated, you know, whether these are ruptured or unruptured aneurysms. Breaking down indication statements to specific locations, it has its challenges. As the FDA has pointed out to us, we

as sponsors may not always have defined the anatomical location exactly the same, and I think that can present challenges both to the Agency and to clinicians who talk about that. But the data results are presented, the size of the aneurysm treated, you know, duration of follow-up, serial occlusion rates, stroke and neurologic death rates, I think all of the relevant data is indeed in the current labeling on these trials. That's certainly more consistent with the PMA technologies. Coiling has a very broad indication that is historical, so specificity on that would not be present in some of the 510(k) products.

Any other questions?

DR. JENSEN: I have one other question. In a trial design, are you designing the trial to try to capture, sort of, equal cohorts of all different sizes of aneurysms? I mean, in my experience, most of the unruptured aneurysms that are found incidentally are usually small ones and so -- and we've had this conversation about, you know, whether or not it's appropriate to treat them. So let's just take -- I'm not picking on anybody, but let's just say a risk rate of complication with a flow diverter is 5%; we'll just say that.

MS. PUGH: Um-hum.

DR. JENSEN: And let's say that this patient has a 2 or 3 mm aneurysm, and if we use ISUIA calculations, or different calculations, on what the risk is for a 60-year-old patient over 5 years is like, you know, 1%. So now you're looking at the patient has to live 25 years in order to reach the same risk rate of using a flow diverter, which would be in a patient who got a 10 mm aneurysm and their risk of rupture is much higher and you're willing to accept that 5% rate. So how are you going to sort of make sure that -- or is it do you need to make sure that when you're studying these patients that you're not basically having a cohort of all patients that have really the smallest risk of rupture based upon size, patient age, you know, no risk factors, etc., versus those that are, you know, larger and truly there's a risk-benefit ratio treatment?

MS. PUGH: I think I can tell you that most of the trials that have been conducted and I think -- please correct me, anyone, if I'm wrong -- have not been done for specific permuted block, you know, or dynamic randomization or minimization. These trials are incredibly challenging sometimes to a crew, and so I can give you an example. There's the historic PUFS study. Whether it's one of my competitors who's bringing another flow diverter to market or whether it's me bringing a next-generation technology to market, for me to attempt to enroll that cohort and match the exact distribution of aneurysms that were in the original trial is going to be incredibly difficult. We don't disagree that you need to be able to assess does the patient respond both in effectiveness and in safety, by location or by size, differently.

And so while we may not be forcibly controlling it here, I think we certainly do that analysis to determine did aneurysm location or did aneurysm size affect response to therapy or safety profile? And the Agency is looking at that. Again, how effectively you can really interrogate that in relatively smaller trials is challenging. I think, in the future, the larger aggregate bodies of data will help guide us as to whether or not differential OPCs need to be put in place for different aneurysm sizes or locations. We know anterior/posterior, you know, they have dramatically different risks both of not treating the patient and of treating. So I think there are clear understandings today, but no doubt, it's an issue of analysis for us when we look at the datasets.

(Pause.)

MS. PUGH: Okay, thank you very much.

DR. JENSEN: And thank you very much.

So it's now, what, 10:17, and we're going to break early. We'll take a 15-minute break. Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any members of the audience, and we will resume in 15 minutes and

start off with the presentations from the professional organizations.

(Off the record at 10:18 a.m.)

(On the record at 10:41 a.m.)

DR. JENSEN: Okay. Welcome back, everybody. So we're now going to move on with the presentations from the professional organizations. First, I would like to invite the American Association of Neurological Surgeons to the podium, and they will be followed by the Society of Vascular and Interventional Neurology. The final presentation is from the Society for Neurointerventional Surgery.

I will remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

You will each have 15 minutes to present, and this must be the Society of Neurointerventional Surgery, or are you actually delaying AANS?

DR. ARTHUR: So what we've done is the societies involved have all collaborated so that we didn't have repetitive stuff, so if it's okay, we've got it all in one presentation, and we're going to have a couple of different speakers come up.

DR. JENSEN: That's fine. Please proceed.

DR. ARTHUR: So our first speaker will be Italo Linfante, who is the President of SVIN. I will follow him from SNIS. Bob Harbaugh is going to have a very quick presentation from the American Association of Neurological Surgeons, then David Fiorella, and then J Mocco. And then we'll all be available for questions.

So Dr. Linfante.

DR. LINFANTE: Good morning, thank you very much. It's an honor to be here. I speak on behalf of the Society of Vascular and Interventional Neurology. I'm going to touch base on some of the points that already been discussed and add some more, perhaps, fuel

to the fire.

So the incidence of subarachnoid hemorrhage, as you know, is 9.7 per 100,000. Median mortality rate in the U.S. is 40% and is much higher in developing countries. Fifteen percent die before reaching the hospital; two-thirds of survivors have permanent neurological disabilities. And it's a disease that affects a patient in their productive life. The median age of subarachnoid hemorrhage is 50 years old.

We discussed about unruptured aneurysm; estimated 1 in 50 people harbor an unruptured cerebral aneurysm. And we discussed the risk for rupture, unruptured aneurysm to rupture. Dr. Dion and others have touched on several epidemiological studies. I'm not going to go into that; we all know them very well, ISUIA and other ones. They attempted to predict the risk of aneurysmal rupture.

Some factors we know. The risk assessment is very complex because of many factors taken into consideration when we discuss these issues with patients. Definitely, we know previous subarachnoid hemorrhage. Location, someone mentioned before posterior circulation are most likely to rupture than anterior circulation. Also, morphology: irregular shape, daughter sacs; enlargement on follow-up imaging. Also, we take a look at a patient's features: age, race. Women have a high incidence of ruptured aneurysm. Smoking, family history for ruptured aneurysms. Smoking is a very strong predictor for rupture, risk for rupture; cigarette smoking was about 3.

And then we'll touch briefly based on size. So size, we know that definitely size is a powerful independent predictor for rupture, in the sense of larger unruptured aneurysms have a greater risk for rupture. The question is what about small unruptured aneurysms? And based on the discussion, I'm going to add some more data to the discussion. Still now, defining a critical size threshold to define small aneurysms at risk for ruptures remains difficult.

Multiple high variability among the studies. ISUIA was mentioned. In the 7 to 12 mm group, the risk for anterior circulation was 0.52% in a 5-year. Posterior circulation, as we know, is higher. It's 2.9. However, if you look at Juvela's paper in the Finnish study, in patient unruptured aneurysm less than 10 mm, the rupture rate is -- risk for rupture is 0.9% to 2.3% per year.

If you look on the side, which is the reality that we work every day, all of us, all studies of subarachnoid hemorrhage have shown that the vast majority of aneurysms that rupture, so patients that present with ruptured aneurysms, are small.

The ISAT, as you all know very well, is a multicenter, prospective, randomized controlled trial with patients presented with aneurysmal subarachnoid hemorrhage. In the study it was 2,143 patients with ruptured intracranial aneurysms. They were randomly assigned to microsurgical clipping versus endovascular embolization.

In ISAT -- 2,143 patients with ruptured intracranial aneurysms -- 95% of the aneurysms were less than 10 mm in size. And 54% -- which is 1,157 -- were less than 5 mm in size. So those were considered to be zero risk for rupture, if you look at the ISUIA data.

And there are several data in the literature, the CLARITY, started from France: 782 ruptured aneurysms, 90% were less than 10 mm. PRESAT: 534 ruptured aneurysms, 86% were less than 10 mm. Ohashi et al.: 280 ruptured aneurysms, 74% were less than 10 mm. And then recently, Lin Zao et al. from China: 1,256 aneurysms, 47.1% were between 2 and 5 mm, and 40% were almost between 5 to 10 mm.

So the dilemma that we have, all of us -- and we'll try to briefly address it in this brief communication. Let's say this patient, 63-year-old woman, 5 mm anterior communicating aneurysm, regular in shape, according to ISUIA, we shouldn't treat this aneurysm because her risk for rupture is low. However, this patient is a 63-year-old women who developed the worst headache of her life with nausea and vomiting, sent to the emergency room with

poor responsiveness, intubated, with a large subarachnoid hemorrhage. And this is the aneurysm. The aneurysm was treated by balloon-assisted followed by stenting with a new generation of Beta Stent, and it worked very well. Follow-up angiography 6 months, the patient did very well.

In summary -- I promised I was going to be short -- subarachnoid hemorrhage is a devastating disease, can affect patients of all ages. I'll remind, the median age is 50.

Although size is directly related to rupture risk, most ruptured aneurysms are small, and there's no question about that.

It is very difficult to predict the rupture risk of a given aneurysm in a given patient.

Treatment decisions are complex and multifactorial and patient-specific. I think a one-size-fits-all that we're trying to do with our epidemiological studies for aneurysms, aneurysmal subarachnoid hemorrhage, with regards to the risk for rupture might not be appropriate.

And I think the best approach is treatment decisions made by the patient in consultation with their physician after careful evaluation of all risk factors.

Definitely, there's a challenging task for the FDA.

Physicians appreciate and share the need for proof of safety and effectiveness of devices used to treat cerebral aneurysms.

And thanks to innovation and the FDA, endovascular approach has definitely revolutionized the treatment of ruptured and unruptured cerebral aneurysms.

Endovascular technology and innovation is expanding, and so we need to expand the armamentarium of devices which will allow aneurysms to be treated as safely and effectively as possible.

And I conclude with a very brief case. It's a 16 -- one of our patients, a 16-year-old woman with seizures, presenting with this giant dissecting aneurysm starting from the ICA,

sinus cavernous to the middle cerebral artery, high risk of rupture, high risk of mortality, very high risk for any type of treatment, open or endovascular. But with the technology we have nowadays, we're able to reconstruct the aneurysm, and this is the results of 3-year follow-up angiography, and this is the patient 5 years later. She works for the American Heart Association as an advocate for aneurysmal awareness and aneurysmal survivors.

And I want to thank you with that.

DR. ARTHUR: Thank you. My name is Adam Arthur, and I'm a neurosurgeon in Memphis, Tennessee, at the University of Tennessee and Semmes-Murphey Clinic. I want to talk a little bit about trial design for aneurysm devices. We're blessed to have neurovascular intervention largely based in the U.S., and we'd like to see U.S. patients having access to the safest and most effective treatment options.

Neuroendovascular therapies are evolving at an exponential pace. That's a PubMed search just looking for endovascular by year, and you can see what's happening there, and this growth has come with a strong foundation of evidence. We understand that there's a tremendous challenge here in being confronted with an increasing number of new devices, but there's a real opportunity if we can be efficient to study these devices carefully and ensure that stroke, which maims and kills more Americans than any other disease, results in some better outcomes and more patients living their lives.

As vascular neurosurgeons, we're interventionalists. We see more and more a bimodal distribution of patients that are either healthy and anxious -- they've been told they have an aneurysm, and they know that there's a bomb that could go off in their head, and as Dr. Thompson mentioned, one of our jobs in clinic is to try to reassure them and then talk about the risks versus the benefits of different treatment options -- or then on the other side, there's the patient who suffered a catastrophic hemorrhagic stroke. And, of course, when we look at trials for approval, indications for use are not the same as

treatment recommendations. The treatment decision is really made by the patient, who should have the power in this, with ideally good consultation.

I'm a very interested person in clinical trial design; I have a master's in public health, and I love randomized controlled trials. They're just not always feasible. One of the differences that Dr. Lyden pointed out between ischemic stroke and hemorrhagic stroke really has to do with incidence of disease. There are many fewer patients with aneurysms than suffer ischemic strokes in the United States, and then we've got a decentralization of care with many more centers where neuroendovascular therapy is offered than even 5 or 10 years ago. This can make it very difficult to force enrollment in clinical trials. And if you're going to look at a non-inferiority trial for a second device, we have one device approved but if you were to come up with another flow diverter and you wanted an RCT, you're looking at a 500-patient study which would take years and years to complete in a situation where using the existing approved device, there are textbooks and papers and symposia proliferating.

Another problem with RCTs being applied as a blunt instrument for all approval trials is that there are situations where there is no FDA-cleared device for the same indication. Aneurysms are heterogeneous, and they're not all something that can be treated with the same device or the same approach.

And then finally, as I mentioned, at the end of the day, patients and subjects are two different populations, and not every patient wants to enroll in a trial, and it's difficult, as a physician, to compel or force patients to enroll in a randomized trial, particularly when they're dealing perhaps with a family history of subarachnoid hemorrhage, a medium aneurysm, something that has a poor aspect ratio. We've tried, and I believe this will be spoken to later, but we've tried to do randomized trials. TEAM was mentioned, COCOA, the LARGE trial. And some of these physician-led efforts with multi-industry funding have failed

due to a lack of equipoise and an inability to enroll.

I think I was going backwards, sorry.

I think, for a new device performing a similar function in a well-defined disease state, we can use the existing literature to come up with objective performance criteria, and that would be a way to allow us to get therapies to the U.S. where otherwise we see a situation where these devices are available to residents of many of the other western countries but not available in the United States. And then, of course, that provides a little bit of a disincentive to the companies to even participate in the U.S. neuroendovascular market, particularly with orphan disease states or smaller diseases such as AVMs, dural AV fistulas.

So the alternative that I think has already been discussed today is the development of literature-based objective performance criteria and objective performance goals. This is a paper that Dr. Fiorella and I worked on for an approval trial. Essentially, we created a methodology for defining an objective performance goal. We then went through a careful scientific process. We submitted that methodology and the results to peer review, and after peer review, it was published in the literature. I believe this is a little bit of sunshine as the best disinfectant kind of approach; there's no reason why this can't be something that is obvious and open for everyone to criticize or understand, particularly in a disease like this where there's a lower incidence and a lot of variabilities.

As we move forward, I think we have the prospect of an improved objective performance criteria. This is already resulting in much better data for the evaluation of true safety and efficacy for endovascular therapy than exists for open surgical clipping. It bears mentioning that when we looked at the review done by Sam earlier in the day, many of the studies involved were single-center, self-adjudicated studies of clipping with no follow-up, and that's not something that we would accept for evaluating an endovascular therapy.

As far as the duration of follow-up, I think if a given aneurysm treatment can

demonstrate adequate occlusion, Raymond I or II that's stable for a cohort of patients at 1 year, and there are significant safety or architectural advantages over coiling, the likelihood of significant aneurysm regrowth is low. And in addition, the prospect, particularly for new kinds of technology, a new therapy like in this case, flow diversion, for following that cohort of patients for 5 years is very feasible, where you could then look at postmarket approval studies.

As far as worsening in Raymond grade, which was asked in the questions, I think it's important again to make it clear that worsening in Raymond scale, perhaps from a Raymond I to a Raymond II with a small sub-millimeter neck remnant, does not in and of itself constitute a treatment failure and mandate that the patient undergo an additional procedure. That's not what we see clinically, and therefore, it shouldn't be extended into a trial situation.

Finally, I do think that postmarket surveillance studies are a way to allow us to treat patients better and enrich underrepresented subsets so that we can see better what therapies are effective and what therapies are safe, going forward, in a segment that's technologically advancing at a very rapid rate.

Dr. Harbaugh is going to be next up.

DR. HARBAUGH: Well, I'd like to thank the FDA Panel for this opportunity. I mean, I think generating reliable evidence for how we best treat our patients is one of the really compelling goals for all of our physicians, and this is something that I've devoted a good deal of my career to. I serve as the Director of the Neurosciences Institute and Chair of Neurosurgery at Penn State, a former Chair of the CV Section, and I also serve as the Chair of our National Neurosurgical Quality Improvement and Outcomes organization, the NeuroPoint Alliance.

So who and how to treat unruptured intracranial aneurysms: We've gone over all of

this, and I'm not going to repeat it in the interest of time. These are just a number of key findings in various studies of the factors that go into a determination of treatment assignment. And, once again, all of these things have been discussed, and I won't reiterate them.

ISUIA has been discussed in detail. Just 1 point, that the ISUIA data tells us nothing about what would have happened to the aneurysms that were treated if they had been left untreated. So the most parsimonious explanation for low risk of rupture in the untreated aneurysms in ISUIA is that the physicians who evaluated those patients did a very good job of selecting patients for observation who had a low risk of rupture, or if there was anything that indicated that their risk went up, that they would be treated during the follow-up period.

So how do we gather further data on this? You can do a decision analysis based on the data that are already out there, and that's essentially what we do when we see patients in the clinic. But if you want to gather further data, should we do a randomized controlled trial, or should we do an observational database, and is there a way to make an observational database mimic a randomized trial? And I think there is.

So we did a formal decision analysis of unruptured intracranial aneurysms, and you know, our assumptions were patients start out neurologically well at age 40; we use the natural history rupture rate of 1.46, used the ISUIA clipping morbidity and mortality, and assumed that it was 95% effective. We used the ISUIA coiling morbidity and mortality and assumed that it was 75% effective, took actuarial risks for U.S. health statistics, a standard discount rate for later years of life, quality adjusted life-years through a Monte Carlo method, which is a standard method of assigning them.

And the point of this is if you go through this, at 1 year from entry observation was clearly the best choice for these patients. However, if you looked at 5 years from entry,

now coiling was your best choice, and over the lifetime of this 40-year-old cohort, clipping was the best choice. The crossover point for clipping versus coiling didn't occur until 10½ years, which means to find that you'd have to follow these patients out probably 12 to 15 years.

Now, you know, I don't know if the data upon which we based our model was accurate, neither does anybody else, and another important piece to this is these results are going to be very patient and surgeon specific.

So how do we address all of these issues? Well, an RCT, we heard, is Level I evidence, but it's only Level I evidence if it's double-blind, if you have equipoise in the treatment options, if you have a large and representative patient sample, and none of those things apply for these kind of studies. So I would suggest that an RCT for an invasive study of the treatment of unruptured intracranial aneurysms is not a gold standard.

There are problems. You have intention to treat and crossover. The surgeons and the patients are often not representative. Surgical expertise is going to have profound effects on the study outcome. They're expensive. As technology changes, the results may change. And there is a real lack of equipoise here that's going to be a very bad problem.

For instance, let's take these two patients. One is a 40-year old woman who has a positive family history of aneurysm ruptures, she's a cigarette smoker, has a 10 mm irregular basilar apex aneurysm. I've asked a number of my endovascular and surgical colleagues from multiple disciplines how many people would be willing to randomize that patient, and so far, it's about 1% of the respondents have said they would. Everybody would recommend treatment of this patient.

The next patient is a 65-year-old woman, no family history of aneurysm rupture, she's a nonsmoker, she has a regular ophthalmic artery aneurysm 7 mm in size. Would you be willing to randomize that patient? Well, I can tell you, in my clinic, this is someone I

would follow and not treat at all. But if you asked me would I be willing to randomize, the answer is yes.

Now look what we've done. We've taken that group of patients at the highest risk of hemorrhage, and we treat them outside the trial; they are no longer involved. And you take a group where you feel that the risk of rupture is very low and randomize that group, you do not get a result from that study that you can then apply to the target population.

So I think the right way to approach this is a prospective observational database designed correctly so that you can do propensity score analysis. If you think about it, a well-designed randomized controlled trial differs from a prospective observational study in only one design element, and that's the use of randomization to allocate patients to treatment. Randomization is done to ensure that within the trial the confounders will be distributed equally among groups so that you can measure outcomes directly.

Since in an observational study, treatment selection is influenced by these other factors, you need to account for those in some way so that you can compare treatment effects, and that's what propensity score matching does. And the propensity score is really -- it's the probability of treatment assignment due to these baseline covariates. Patients with the same propensity score are going to have the same distribution of covariates, and so you can do a pseudo-randomization, and then you can compare interventions that are being studied. So I think this is a way to go forward. It's not a single-arm study, it's not a randomized trial; it's a pseudo-randomized trial using a registry science approach. And you need to know a number of different things about this to do a good prospective observational database.

But if you can answer these questions: What randomized experiment do we want to model? In this case, observation versus invasive treatment for patients with unruptured intracranial aneurysms. Who are the decision makers for treatment assignment?

Physicians, patients, family members. What are the key covariates that we use to decide treatment assignment? Patient-specific factors that we've talked about. We have physician-specific factors that we haven't talked about much but are important. We have lesion-specific factors that we have talked about. But we know all of these things, and we can get a good propensity score match. We can measure these covariates well. What clinically meaningful outcomes do we want to measure? And I would suggest, you know, mortality, aneurysm rupture, and quality of life and functional health status are pretty obvious, and we can do traditional power calculations to determine how many patients will be needed.

So I think this type of approach, at least in a postmarketing environment, would be very feasible, and it could also be used to determine the use of new devices. A multicenter registry designed to allow propensity score matching for unruptured intracranial aneurysms is very feasible. We can then evaluate patients with the same propensity score who differ only in regard to their treatment assignment. And then by doing this, we can really get a pseudo-randomized study that gives us more information than a single-arm study and avoid some of the problems with equipoise that we have with randomized controlled trials.

So thank you for your attention.

DR. FIORELLA: Thanks a lot for having me. I'm Dave Fiorella. I'm from Stony Brook University. I direct the cerebrovascular center there, and I'm an interventional neuroradiologist. I'm going to talk specifically about endpoints in trials, and these address, sort of, Questions 4 through 6 in the document that you guys handed out to us.

So with respect to trial endpoints for aneurysms, it seems that the -- well, the Raymond scale was created to assess the occlusion of aneurysms that are treated with coil embolization, and the scale is more or less specific for that purpose, and it seems like recently we've really tried to apply this scale to all aneurysm treatments and all aneurysm

devices. And, in particular, since PUFS came out, it seems that we've established complete occlusion, a Raymond scale of Grade I, as really the only accepted primary effectiveness endpoint or the leading primary effectiveness endpoint that we've been looking at.

I don't think a one-size-fits-all scale is appropriate for the assessment of aneurysms that are being treated with endovascular therapies. Aneurysms, as we've seen, are very heterogeneous disease processes with respect to the shape and size of these lesions, their location, whether they're sidewall or bifurcation aneurysms. And then we have different endovascular devices that have different morphologies and completely different mechanisms of action to treat these, and I think we need to take that into account when we're going to establish these angiographic endpoints that are going to be a surrogate for clinical endpoints.

So these effectiveness endpoints have to be appropriately matched to devices and anatomy, and there are some key considerations that differ for different types of therapies. So with regard to coils, coils we place into the aneurysm sac, they're very radiopaque and dense. We can't really see what's going on in the aneurysm sac very well with coils under angiography because of the radiodensity of the materials.

And so we create a picture like this for a Raymond complete occlusion, and what you'll notice is that the aneurysm-parent artery interface, particularly for wide-necked aneurysms, there's a little bit of irregularity there, and that's just the shape of the coil ball as it fits up against the parent artery, but that's still a Raymond Grade I; we look at that as complete occlusion. And the Raymond scale has really been designed and more or less validated over time for coils, so the Raymond scale is very appropriate for coiled aneurysms with or without balloon-assisted therapy or stents.

However, we're starting to see newer innovative devices come out, things that are like coils but not exactly like coils, and I'll use as an example like these intrasaccular braided

devices that we've seen in development. So a device like the WEB. So the WEB is not very radiopaque; we can see it as we deploy it and put it in an aneurysm, but we can still see through it quite well.

And so as you can see here on an angiographic follow-up, we see the aneurysm, what was the aneurysm sac quite well, and if there was any residual filling in there, it would be completely evident. At the base of the aneurysm, though, you see there's a little tiny marker recess, and that marker recess is really just the recess in the device. So a perfectly placed WEB device with an excellent occlusion to the aneurysm is always going to have this little marker recess. And so the Raymond scale wouldn't exactly apply as developed for these types of intrasaccular devices. And so in the WEB trial, we developed the WEB occlusion scale, which is a modification of the Raymond scale, and this was validated on histology and with inter- and intra-observer variability studies, and then the stability of the marker recess was documented in subsequent clinical studies.

And so for braided intrasaccular devices, the Raymond scale is a good starting point because these are intrasaccular implants. However, we have to have some flexibility here; we have to be able to modify these scales as needed for the particular intrasaccular device, and that's not saying modify them without some type of validation, but modify and validate these scales. And as new devices are innovated and come down the pike and we have to evaluate these, we may have to have this type of flexibility with regard to the scales that we're developing to assess these devices and the occlusions.

When we talk about a flow diverter, things are different. So here, we're putting a tube in a vessel; we're going to remodel the vessel and not put anything at all in the aneurysm. And so again, the Raymond scale, which was designed to look at aneurysms that have been packed with radiodense coils, really is not relevant at all for flow diverters. Flow diverters are a totally different type of treatment, and so here, it's really a binary result that

we're looking for, complete occlusion or not.

One thing I'd like to stress is that the best achievable angiographic result is not necessarily the most appropriate angiographic effectiveness endpoint.

The effectiveness endpoints that we choose for success have to be clinically appropriate and match the devices and the anatomy where we're performing the treatment.

So as we talk about, for an intravascular flow diverter, something like Pipeline or Surpass or FRED, these types of devices, complete occlusion is an excellent and appropriate endpoint.

For aneurysm regression to occur, for physiological remodeling and anatomical restoration to occur, that typically requires that the aneurysms have to be completely occluded. Oftentimes we're not placing anything else in the aneurysm sac, so really the only protection that's provided comes from complete cure of the aneurysm after the flow diverter is in place. And complete occlusion, as we've seen, is a pragmatic and safely achievable endpoint in a very high percentage of cases, so we've established this as a good endpoint.

For intrasaccular devices, though, things are different. Here, adequate occlusion, so complete plus near-complete occlusion or a small neck remnant, is perfectly acceptable. And we can base this on excellent data from clinical trials.

So, really, our best trial here for aneurysms is the ISAT trial. The BRAT trial is a very similar trial and has concordant results; it's just much smaller than the ISAT trial. And what ISAT showed us is that the coiling of aneurysms created durably better outcomes in ruptured aneurysms with endovascular therapy than surgical clipping. And this was a large benefit, 6 to 7% absolute benefit for coiling in both studies, and this has been stable in ISAT over 10 years, and in BRAT, now up to 6 years with the same odds ratio.

So if you look at these aneurysms that were treated in ISAT and BRAT, the rate of complete occlusion for endovascular therapy is pretty low; it's only 50%. For surgery, although not as well validated with angiographic follow-up, the rates of complete occlusion were quite a bit higher, 80 to 95%. So we have a therapy that's not giving us perfect occlusion, and that might make us a little bit uncomfortable.

However, if we look at what is the concern about not completely occluding these aneurysms, well, the worry is that we're going to end up with deaths or disability from re-bleeds in the future. Well, it turns out, when we look at the ISAT data, the risk of death or disability from re-bleed is exceedingly low, so six coil patients and only four clip patients over the 10-year-plus follow-up in ISAT had disability or death from rerupture, so extraordinarily low, like 1 in 1,400 or 1 in 2,000 patient-years. So both therapies did very well. And in the BRAT trial, which has results published up to 6 years, there has been no delayed re-bleed in any coiled aneurysm.

So although we have a lower rate of complete occlusion with these technologies, the clinical outcomes are better, and that's really what the most important thing is. And when we look at how the occlusion rates were in these studies, we were achieving these excellent clinical outcomes with, most of the time, complete and near complete occlusions accounting for more than 80% of the cases in these trials.

And, in fact, when you look at the ISAT data, one of the most interesting things is that aneurysm re-bleeding in this population of patients with subarachnoid hemorrhage was really not a major cause of the morbidity and mortality. In fact, in ISAT, you were more than 40 times more likely to die from another cause, typically cancer or cardiovascular disease, than your ruptured aneurysm. And again, only 6 patients died from re-bleed versus 232 from other causes in the ISAT dataset.

What about retreatments? So one of the other worries about residual aneurysms is

they're going to recur, and these residuals are going to grow and get larger. Well, retreatment, it turns out, was not a major cause of death or disability in ISAT or BRAT. So as long as we look at these patients and we follow them, and there does have to be follow-up with these endovascular therapies, there was really no death or disability from retreatment in BRAT through 6 years, and no death or disability from late retreatment in ISAT. So retreatment of these originally treated aneurysms actually is very, very safe for these patients. So we do have to follow them. Occasionally, some of these patients do have to be retreated, but if we look at really what matters is how these patients are doing clinically, they're doing well.

What about complete occlusion? Well, why don't we just go for complete occlusion with everybody? I mean, if the aneurysm is completely occluded, we all feel better about it. Well, as somebody who is in a lot of these trials, there's a lot of pressure on you if you're shooting for an endpoint of complete occlusion, say, to put these extra few coils in there, and a lot of times, as my colleagues will attest to, those last few coils to try to get absolute complete occlusion can be the most hazardous coils that you put into that aneurysm. And being able to accept near complete occlusion or a near excellent or perfect result oftentimes is the best result for the patient. For intrasaccular devices, we may be tempted to put in the largest possible device in the aneurysm to make sure we completely fill it up and get a complete occlusion at that 1-year follow-up. And so when we establish this endpoint of complete occlusion as the only success for these intrasaccular devices, we may be setting up an endpoint for a trial that is going to cause investigators to behave in a way that could make these devices more dangerous. And so, again, I would stress that complete and near complete occlusion may be a safer endpoint.

The other thing is if we place an undue emphasis on complete occlusion and look at these devices with that as the primary endpoint and really the focus of our evaluation, it

could potentially unnecessarily delay or lead to inappropriate non-clearance of devices that are very, very safe and, in fact, quite effective for these patients.

So we know that for aneurysms that are amenable to endovascular therapy. So if we have the tools in our toolbox to treat these cases with endovascular therapy, we know that those therapies provide excellent protection against death and disability and future rerupture. And probably in unruptured aneurysms, you have this great protection against any rupture after the treatment.

So adequate occlusion of aneurysms, as we've seen from the ISAT trial and then the BRAT trial after that, complete and near complete occlusion is fine and effective for endovascular devices. And we know from those two studies that endovascular therapy, if you can have your aneurysm treated with endovascular therapy, you're likely going to do a lot better at most centers than you will with surgical treatment.

So how can FDA improve outcomes for aneurysm patients? Well, you can provide us with access to innovative endovascular therapies that make our treatments less invasive, easier, and safer for the patients and which extend the spectrum of aneurysms that can be treated with minimally invasive therapies. From the data that we have, it looks like the less that we have to treat with open surgery, the better these patients are going to do clinically.

And I love these data. I got this slide from Andy Molyneaux. And so these are the mortality rates from the NHS for subarachnoid hemorrhage, and so you could see they were declining with public health, but then they take a fall off a cliff, and the mortality and morbidity from subarachnoid hemorrhage goes down precipitously. This corresponds to the publication of the ISAT trial. And these are the rates of surgical clipping in the NHS over that same period of time. So you can see the public health impact of this transition that occurred in the UK moving from primarily open surgical procedures to minimally invasive procedures, reducing dramatically the morbidity and mortality related to subarachnoid

hemorrhage. And in the UK now, they have access to many more devices than we have, many different types of devices, and now it's estimated that about 90% of aneurysms in the UK are treated with endovascular therapy versus open surgical clipping.

So I turn it over to J.

DR. MOCCO: Good morning. Thank you to the Panel for inviting us. My name is J Mocco. I'm the Vice Chairman and Professor at Mount Sinai, the Director of the Cerebrovascular Program, and I'm the Chair-Elect of the CV Section of the AANS and CNS. And as my colleagues mentioned, we would like to take the time to make sure we don't overlap and focus on some key questions.

And so I would particularly like to focus on the first three questions that were posed for this Panel, and the first being that, typically, aneurysm device trial primary safety endpoints have focused on death and major ipsilateral stroke by 4 points at the time of stroke event within 1 year after treatment. Additional safety events that are considered in our safety assessment include this list of potential adverse events and safety events that were provided.

And two questions were posed. Please address is the AE list above complete? Again, just for reference, this was the list. If not, what should be added? And secondarily, are there specific rates of AEs that would raise serious concerns about any specific device?

And so to speak to that first, is any AE list complete? Well, there's always an opportunity to come up with other AEs. Our group, the society representatives, briefly met and talked about whether there's an intraprocedural thrombotic event that resolves with some heparinization, whether there's a delayed access site infection that requires a course of Keflex for a few days, or whether you put a flow diverter in a large or a giant aneurysm that creates a cranial nerve deficit, that would certainly be an AE to account for and pay attention to.

However, should the rate of AEs have a threshold which raises concern for safety? Well, the World Health Organization Guidelines for Good Clinical Practice state that an AE is any untoward medical occurrence in a clinical trial subject. It does not necessarily have a causal relationship to the treatment. And that's important. The AE is incredibly critical for clinical trial performance. I consider myself a clinical trialist. I had the good fortune to run four randomized prospective clinical trials and many single-arm studies.

So are there specific rates of AEs that would raise serious concerns? Well, we feel that the answer is no, as a group. What do we mean by that? An AE is a measure of any untoward medical occurrence that occurs in patient populations. There are significant limitations to using AE in this context. Because of this, AEs demonstrate a wide variety of causes. It's often due to a patient's other pre-morbid state and issues, worsening of their diabetes or other things, diseases that they had, changes in medications, new headaches; they can be unrelated to the procedural events and the patient's tolerance of a stressful procedure that's undergone. This doesn't mean that we should not be recording AEs and keeping track of them, but it does not provide an appropriate threshold for evaluating the safety of the new technology.

Additionally, for any of us that have run trials, there is substantial variability in the consistency of reporting AEs. It is a self-reported event that occurs that is then screened by a medical monitor that goes and goes through the medical record, and the variance between medical monitors and their ability to determine and detect AEs within this context has substantial change. There is no fixed denominator.

One of the benefits of clipping of aneurysms is that we developed it as a standard of care before we had many of these rigorous processes for evaluating treatment.

This is a patient that I treated 2 days ago who is going home today, and this was her photo this morning. She has a swollen eye, which will resolve in 3 or 4 days and be fine, but

that would be an AE. She has substantial temporal pain and discomfort that will be resolved in about 2 weeks; that would be recorded as an AE. And she will not be able to open her mouth to get it around a big bagel or a Big Mac sandwich for at least 2 or 3 months until her jaw stretches back out; that would be an AE.

I believe very strongly that clipping is appropriate in many patients. I clip probably 50 patients a year. But to extrapolate from AE records of clinical trials as a serious safety concern, I don't believe that that is appropriate, nor does our group. Rather, safety should be driven by a fixed endpoint, a known denominator, validated assessments such as a modified Rankin at a particular time, such as a stroke event, on an NIH Stroke Scale change of 4 or greater that persists for a particular amount of time.

And that brings us to the next question, Number 2, which is the modified Rankin Scale has often been incorporated as a secondary endpoint. Can it be used as a potential primary outcome? And what magnitude of decline should we look at? And if not, what alternative should we consider?

And simply said, as a group, we felt that for unruptured intracranial aneurysms, the modified Rankin did present a reasonable option, and there are some data to support that and look at it. However, which was spoken to a little bit earlier by the industry group, for subarachnoid hemorrhage, we do not believe that, and I'll come back to that in a second.

If you look at unruptured aneurysms in the ISUIA cohort, prospective data collection on surgical and endovascular treatments, the rate of -- so if you look at their numbers, if you look at the abstract, you'll see the absolute event rate which was based on neuropsychological testing as well. But if you look at the rate of modified Rankin 3 to 5 or surgery-related death, surgery-related death at 1 year, the rate was 6.6% in the coiling arm and 7.1% in the surgery arm of the ISUIA dataset.

Therefore, we would throw out there as a starting point that, also of note, the ISUIA

population was 0 to 2 to be enrolled. So in a patient population that's modified Rankin 0 to 2 to start enrollment, then degrade to dependency or death, a rate that exceeded substantially those established norms such as greater than 10% would raise serious safety concerns for those of us considering what to do for the patient.

In terms of the subarachnoid hemorrhage population, I'd like to speak to why we did not think that the modified Rankin would be an appropriate test. It is completely reasonable, like we do in the stroke population, to pick a fixed denominator time point for assessment, such as at 3 months or 1 year, and collect the population modified Rankin distributions among that group.

But the challenge is, is that the appropriate measure of the technology's success? And this is why we have moved to looking at infarct and strokes instead, because in the subarachnoid population and in a way that we all feel is quite different than the thrombectomy population, there is substantial occurrences that occur after the treatment over the subsequent 2 weeks of hospital care, including hydrocephalus, including vasospasm clinically in up to a third of the patients, including cerebritis and infection and DVTs and PEs and many other things that dramatically complicate and increase the noise in that assessment. Does that make it impossible? No, but it makes the signal-to-noise ratio so challenging that to assess the technology in the patient populations we're talking about, it becomes nearly impossible, and that's where we believe more device-specific assessments are appropriate in that population.

And lastly, considering the AE list above, are there other patient characteristics, such as malignancy, advanced age, and aneurysm size, that would justify forgoing treatment in the aneurysm population? I think this gets to a lot of the discussions that were going before, and I would like to speak to that.

One thing that the group felt reasonably strongly about was that for a patient that

has a very limited life expectancy that wouldn't be able to undergo reasonable follow-up, absolutely. We're not absolutists; we think that this would be a very reasonable exclusion criteria for something like this.

What about age? We all thought 85 was a reasonable number to say this might be if you're over 85. But this is our U.S. government Social Security actuarial life table data, and when you look at a patient who is, for instance, 80 years old, is a female, is otherwise in reasonable health, they have a 10-year approaching life expectancy. So if that patient has an 8 or 9 mm PCOM aneurysm that's got a small neck and is straightforward to treat, and ISUIA tells us that has a 3% per year risk of rupture approximately, why would we not offer that patient a treatment, again, something that potentially has a 4% disability or death rate compared to a cumulative 25% risk over their lifetime? Does that mean the patient should undergo it at 80 years old? Absolutely not. But that decision should be up to that patient when they're appropriately informed by their physician, and that data should be allowed to be considered in the treatment of our patients.

And so as a group, we felt that aneurysm treatment is an extremely complex and nuanced decision that's ultimately driven by patient choice with physician guidance and education. And we feel strongly that we should resist as a group and the Panel should resist creating well-intentioned but inappropriately restrictive external limits on the patient characteristics that are treated, and we should leave the decision making to that relationship between the patient and the physician. And I just want to highlight two things quickly that get to this point of the danger of creating what are reasonable binary decision points that otherwise are not nuanced and applied to each particular patient.

There's been a lot of discussion about ISUIA. This is the *New England Journal* and *Lancet* publications that came out, and this is the table that everyone talks about with 0% in the anterior circulation less than 7 mm, 2.5% in the posterior circulation, and so forth

moving up.

Before going into more detail, I want to make sure it's clear, I am on the ISUIA writing group. I've personally reviewed every rupture angiogram and measured them, as well as over 250 of the total ISUIA datasets. I have published -- led the publication or the last three publications from ISUIA. I know this data as well as anyone except for Dr. Huston, who's read all of the angiograms, okay? And I believe this is an incredibly impactful and important study. I believe that no conversation should be had with a patient about whether they should have treatment or not without referencing this dataset and talking about what it has taught us. However, to take away binary points from this would be a fallacy.

So people have belabored already, very much so, the number of small ruptured aneurysms we've seen. No one has highlighted, but I think this is an important point -- Dr. Carter, when he was at MGH, highlighted how we see smaller ruptured aneurysms in more distal locations, potentially suggesting a relationship between the size of the aneurysm and the size of the parent artery. In fact, this has been validated in some work that we've done, that last ISUIA paper that I highlighted earlier, as well as in the Sapporo study group that found that even in small aneurysms there are metrics that will pull out the likelihood of rupture based on the size of the aneurysm to the parent vessel.

So when we start to say, well, should an aneurysm under 7 mm or should an aneurysm under 5 mm be treated, there are dangers inherent in just that decision as a blanket application. So one question that someone needs to bring up is how reliable are those measurements in the first place? I don't know how many of you are familiar with the methodology of ISUIA. ISUIA was published over '99 and 2001. The methods paper was published in 1995. And the way it was done, the films were cut films for the most part, and a special ruler was created -- this is all in the public literature that you can look up -- that was devised by one of the authors. It was created to evaluate these aneurysms and to

measure them from the cut films.

This is the ruler that's used; this is the one that I used to read the scans in the study. It is a plastic ruler that you put over a cut film, that you measure the AP and biparietal diameters that gives you a scale and you apply to the sliding diagonal lines to get the measurement of the aneurysm.

This measurement was based off of data from 58 neurofibromatosis patients' skull x-rays, as well as then further validated in a 200-patient normal population. And as you can see, although there's great correlation, there are 2 and 3 mm variances across physician-specific measurement throughout the entirety of the cohort, particularly when you're talking between 5 and 10 mm.

The other thing that we -- yeah, the other thing that we don't pick up is aneurysm growth. So we have 5 mm -- we say we have a size, but you have to take into account the aneurysm growth rate series, 1.8% per year.

Here's another series, between 2.6 and 3.5% per year.

Here's a study published in *Stroke* by well-respected authors; over 3% per year of aneurysms that are followed grow. So if you --

(Off microphone comment.)

DR. MOCCO: We're summarizing right now. So if you we look at the patient who is 35 or 40 years old who has a 40- or 50-year life expectancy with a 2 or 3% per year risk of rupture, that needs to be taken into account in this nuanced decision.

So the summary slide is this. We should resist creating well-intentioned but inappropriately restrictive external limits on patient characteristics of the patients that we enroll.

Thank you.

DR. ARTHUR: I know we're over time. We have a statement that's been signed by all

of the societies' representing physicians who treat aneurysms, and we're going to pass that out. Because we're over time, I won't go into this, but we do have -- and I can give you, if you'd like, answers to the other 11 questions that have been agreed to by the societies.

Thank you.

DR. JENSEN: So we're now going to proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel, to present data, information, or views relevant to the meeting agenda.

Ms. Aden Asefa will now read the Open Public Hearing disclosure process statement.

MS. ASEFA: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. PEÑA: Dr. Jensen, it's just Carlos Peña, right here.

DR. JENSEN: Yes.

DR. PEÑA: Just for the record, we might want to make sure that anything handed to the Panel is also made available to the public. So we just want to make sure that that

document that everyone's looking at is also available.

DR. JENSEN: Thank you, Dr. Peña.

Could you please get other copies so that that would be available for the public? Thank you.

Okay. So for the record, we have received six formal requests to speak for today's meeting. Each scheduled speaker will be given 10 minutes to address the Panel. We ask that you speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting. The Panel appreciates that each speaker remains cognizant of their speaking time.

First, I invite Ms. Jill Frebershauser to speak as a patient. Ms. Frebershauser, you have 10 minutes. Thank you.

MS. FREBERSHAUSER: My name is Jill Frebershauser. I am a survivor of an intracranial brain aneurysm. I am also one of the first recipients of a lifesaving device, which is the Pipeline embolization device. I'm also a stroke survivor, and I was one of the first few hundred people to receive the treatment with the ev3 Pipeline embolization device for an intracranial brain aneurysm. It was a wide-necked giant aneurysm behind my left eye, my ICA. The treatment for this was needed because the traditional method of coiling for an aneurysm was not successful for a wide-necked aneurysm like I had, and clipping was also not available.

In July of 2011, I suffered a stroke from -- the aneurysm did not rupture. What it was doing was throwing off blood clots. I received prompt hospital care from St. Agnes in Baltimore. For the next few months, I was told that it was not operable. At the time it was 2011 and they hadn't -- the FDA had just received the device, so the neurologist that I had seen did not know about it.

So for the next couple of months, because I was told that I was unoperable, I went

home and I prepared a will, and I kind of got my affairs in order. I was offered to use a narcotic to keep my anxiety level down, which I declined. I didn't want to spend the rest of -- I'm not sure how long my life would have been under a narcotic.

So I suffered from confusion and numbness. I had vision disturbances. I had many, many, many TIAs during this whole time. I saw very many different neurologists, and I kept hearing, "I'm sorry, there's nothing we can do for you." So I just would go home day after day with the understanding that there was no treatment available for me.

I visited a neurologist in Baltimore who knew of someone that may have a treatment for me, and about 3 days later, Johns Hopkins called me and they said that they had a new treatment available for me and would I be interested, and I said yes, absolutely. And I was in Johns Hopkins in a matter of a week. At the time, there wasn't really a set designated place for the angiogram and for the surgery, so we went down into a basement, and it was dark, and those fluorescent lights were flickering a little bit, and I was very scared, and I received my first angiogram.

So the endovascular surgeon that I had, his name was Dr. Alexander Coon, and at the time there were not very many people, from what I understand, that were doing this procedure. There was a doctor in Chicago and there was one in Baltimore, which I was fortunate enough to live in Baltimore.

So I received one of the first embolization devices. It was made by the Micro Therapeutics d/b/a ev3 Neurovascular. That company, I believe, sold the technology to a different company, so the device that I have in my head, I don't believe, is in use anymore. The device that I have in my head -- I actually have two. Because of the way that my aneurysm was, they put them back to back.

So my experience with this whole thing has been nothing but positive. I received the aneurysm treatment, and I would say, after my first two angiograms, they placed the

Pipeline embolization device in my brain, and about a month later I really do feel that I was -- I felt the difference in the way -- in a way that I could live my life. I felt clearer; I felt like something was happening in there.

So I was placed on 75 mg of Plavix and 25 mg of aspirin before I could receive the surgery. Even though I was terrified, I really believe that my experience was amazing. They would open my femoral artery and move a camera up into my brain from my right side of my leg into my left eye. Then they would inject the dye, and that was just absolutely incredible because you're awake. So when they do that, what you see is fireworks light up in your brain, and I mean it was a little scary, but just to be able to see that was kind of amazing.

So I received the treatment on the day before my 31st birthday, and I was out of the hospital 24 hours later. So here I had a potentially life-threatening disease. I sought treatment, and 24 hours later, I was at home. I mean, how amazing is that, to just go from complete fear to be able to go home and just be comfortable in your space?

I had a lot of work to do because I did -- I was symptomatic. So from the time I received treatment to 18 months, I received complete occulasion [sic]. It was completely dissolved, which was amazing. So after I received the information that my aneurysm was no longer there, I tried to set about putting my life back together. I couldn't walk very well. I could walk, but I had an unsteady gait, and I really took it upon myself to try to heal. So I took a walk around my block for the first time in about a year, and after that, the next day I took another walk, and then I started to run, and slowly over time I was able to heal and to live a perfectly normal life. Two years after my surgery, I ran my first marathon, and I've run three since then.

So I wanted to talk about after-care issues with patients a little bit. I know that I struggled with not really understanding what was happening to me, what symptoms I had

and where my aneurysm was located, what would happen if I received some kind of trauma to that. I wanted to know what symptoms were normal, what kind of healing can I expect, and what kind of quality of life will my life be like. I didn't have a lot of answers to those questions.

After surgery can be just as confusing as before, and I believe that a patient can really benefit from a full understanding of what's happened to them because I don't really think that I had that right off the bat.

I think there are three factors that really have led to my recovery, which I believe has been nothing but remarkable:

- The innovation of biomedical companies;
- The patient care of the doctors and the nurses who continually educate themselves and grow with technological advances; and
- The FDA for being an institution dedicated to providing safe devices and medicines to the patients in need.

There is a human element to my recovery. I know that they talked about keeping your blood pressure down and things like that, and I think I have a glimpse into what it's like to have an aneurysm that's not able to be treated and that one that I was all of sudden given the information that it would be treated. So sometimes I think patients may not take it upon themselves to take better care of themselves, but I think that some of that is because we just don't always know what to do. I mean blood pressure, you know, and --

(Timer.)

MS. FREBERSHAUSER: Okay, so thank you for the time and for the invitation, and I just really appreciate being able to be here today.

(Applause.)

DR. JENSEN: Thank you, Ms. Frebershauser, for sharing your experience with us.

Next, I invite Dr. Michael Russell, who is employed by Azalea Orthopedics, who will be speaking as a patient. Dr. Russell, you have 10 minutes.

DR. RUSSELL: Thank you very much for allowing me to speak this morning. As a way of disclosure, my travel expenses were paid by Stryker Corporation for this conference.

Well, first of all, my name is Mike Russell, and I'm an orthopedic surgeon and spine surgeon from Tyler, Texas. I'm the President of my 24-man group there in Tyler, past President of the Board of Directors of PHA, founder of a hospital there in Tyler. Here's my background. I was a chemical engineer undergrad in my training. I like to fish with my family, and I'm also a pilot, and this is actually where my story starts.

In May of last year I had -- just had the annual on my plane, and I had to replace a cylinder, and so I had to go up and do a test flight to burn in the cylinder, and after about 45 minutes I switched on the air conditioner, which recirculated the air inside the airplane, and after about a couple of minutes I had this weird, sudden feeling that I was passing out and the world was shutting in on me. I even considered pulling the parachute; that plane has a parachute, which is pretty nice. I thought I might have had carbon monoxide poisoning, and I thought there may have been something in the -- the time they worked on the plane that I had inhaled. And so I turned off the autopilot, and I started descending rapidly. Not a very smart thing to do, but I was confused and I was disoriented.

I finally was able to put the plane back onto autopilot and get the plane stabilized, and I called the tower and made an urgent landing. Fortunately, I was able to land the plane without any incident, and it turns out, a good friend of mine, a neurologist who is a pilot, was there when I landed, and he examined me, and he did not think I had carbon monoxide poisoning, but we thought maybe I just inhaled something from the work done.

But 2 days later I had the same symptoms. This time it was associated with the smell of burnt peanut butter. So certainly having an aura associated with it concerned me

greatly. So I immediately went to the hospital where I had a CTA -- excuse me, an MRI, MRA, and a CTA, and this is the CTA showing the aneurysm I had, and that aneurysm is off the right middle cerebral artery, and that small branch off of it is the first branch, the right temporal artery. And as you can see, my neurologist felt that I was probably having some spell from the abnormal flow into the temporal lobe. At least, that was what he felt.

So here I am as a physician and as a patient; what do I do? Well, I'm not going to belabor the epidemiology; you all have been talking about that all morning, but what was clear to me -- and I saw that paper that showed a 0% chance for a 5 mm aneurysm, which is roughly what I had, but clearly that's not true. I mean, if you talk to the neurosurgeons, most of the aneurysms that they see ruptured are 5 mm or thereabouts. So wherever that data came from, that was not true. What was clear to me was that I did not want a subarachnoid hemorrhage because the mortality and morbidity hasn't really improved in the last 10 years. You still have a 50% mortality rate, and you still have a significant chance of being disabled if you have a subarachnoid hemorrhage and you live. And I also knew that it was not zero and that I had a significant chance during my lifetime of having that rupture.

So I talked to my neurosurgery friend, and he obviously felt like he could clip this. He was trained at Barrow's, so there's no problem, but he did admit to me that that small artery off of that he would likely occlude or there would be a good chance that it would occlude, but since it was my non-dominant hemisphere temporal lobe, he wasn't that concerned about it. But my neurointerventional friend was not so -- he disagreed basically, and he felt that that artery needed to be saved, so he recommended a stent-assisted coiling of the aneurysm. However, he said that since that artery was so small, with the current technology at the time, he was afraid that he would be unable to get the stent across it, and so he recommended that we wait until something that had been in Europe for a few years was ready, and he felt, from what he had heard, that the FDA was going to approve it by

late July of last year, so we elected to wait.

So as a patient and as a scientist, what do I do? Obviously, I look at my iPhone and I look up what causes an aneurysm to rupture, and there's a nice little article by CBS News, what causes aneurysms to rupture, and it turns out if I drink a cup of coffee, I double my chance of rupturing my aneurysm. If I exercise or blow my nose, I multiply it by 250%. And as a matter of fact, when I started thinking about it, I'm a runner, and for a couple of months previous to this, if I got my heart rate into the 160s, I would have this surreal feeling of being sort of separated from my body. It's possible that that was, as well, a temporal lobe-type symptom. Drinking Coca-Cola can cause you to increase your risk. Anger can cause your increase for risk. Going to the toilet, constipation, obviously is something to watch. Sex; it turns out if you have sex, you increase your risk by 11 times. And then, of course, startle is something that we all know about; it's 23 times more, according to this article that I read.

So right about this time, I was trying to be relaxed and let my wife drive in Dallas, but she overreacted, and she, you know, pulled -- you know, when someone kind of moved into us, and all of sudden it was, "Oh, my gosh, I'm going to rupture my aneurysm." So, clearly, it was hard to live with it.

Now, what do all of these things have in common? Well, just think of increased blood pressure. I'm an engineer, so if the blood pressure inside the aneurysm is more than the intracerebral pressure, then surely you have a chance of rupture. So I hyper-controlled my blood pressure. The only risk factor I have, other than being 50 years old, is I have mild hypertension. I'm on one medication and have been on one medication for 10 years, but I added a beta blocker so that I could keep my blood pressure to 110 over 70, not real healthy but I was not going to have a ruptured aneurysm. I stopped running, I stopped working out and started gaining weight. I basically changed my lifestyle. I tried to avoid

stress and surprise.

As a matter of fact, I was involved in some transactions for my hospital, and I was on the team to negotiate a merger, and I had to back off. As the president of my organization, there were a couple of really -- going to be contentious meetings I asked my vice president to take over.

Sex; it's hard to have sex without raising your blood pressure, but it can be done, I promise you.

(Laughter.)

DR. RUSSELL: I avoided excessive caffeine and alcohol. So I did all of these things to try to avoid the risk of rupture. By late July, my radiologist called me and said that the -- there was no FDA approval of the stent and no definitive date when to be expected. He gave me the choice to attempt the stent with coiling with current technology. He thought about a 75% chance it would work, and if not, he would abandon the procedure, and he would try later with the new device. But after hearing how that worked, where you pass the first catheter, you pass the guide wire, you pass a larger catheter, then you try to get this larger stent across, it didn't make sense to me. Why would I want -- that was too many passes.

I figured each time there was a little bit higher risk of rupture, so we elected to wait. But I immediately called my congressman and my senator, and within a day I was in a discussion with the FDA on compassionate use of the device. Now, that requires three things. As you know, the physician must request it, the device manufacturer must agree to it, and you must have IRB approval. Well, 1 and 3 were easy, but it turns out that the company was dragging their feet, and I understand there was concern that confusing the FDA with this request when approval was felt to be imminent was not advisable.

So a few weeks went by. Mid-August 2017, I actually got the word that the company

was not going to agree to the procedure. So that's all I had to do. The next day I immediately called the president of the company and got to the right people, and sure enough, they agreed to let me have the device. And here on September 8th, 2017, it is the passing of the stent and the first few coils, as you can see, and this is the post-coiling angiogram.

And now one thing that's really important is that during the procedure, my physician said that the artery actually supplied a major portion of my frontal lobe, meaning not being able to save it was more important than we thought.

So after the procedure, here I am the next week, and that was on a Friday, and on Monday, as you can see, I decreased my surgery schedule; I only had three on Monday and five on Wednesday.

I'm really excited to show this picture about 4 weeks later. My wife and I and a group of friends were celebrating being empty nesters in Napa, where we were there on October 8th, which happens to be the day the fire started, but that's kind of a different story.

Mainly, I agreed to come and share my story to help you see that from a patient's perspective, that waiting for technology that is an upgrade from current technology is difficult and that a randomized controlled trial is impossible because no patient -- as a patient, there's no way that I would allow a craniotomy nor would I wait when technology is available that is safe and effective. I encourage you to adopt quicker and more specific routes to get new technology into the hands of capable physicians.

Thank you very much.

(Applause.)

DR. JENSEN: So thank you for sharing your experience with us.

Next is Dr. Adnan Siddiqui, who will be speaking as a practicing physician.

Dr. Siddiqui, you have 10 minutes.

DR. SIDDIQUI: I'll be sharing my time with Dr. Turk, and so I'll try to do mine in 5 minutes. Thank you very much for the opportunity. I'm happy to see this discussion taking place.

So my perspective is that the GDC coil was approved in 1995, over limited clinical data, as a Class III 510(k) product, and then we did the trials. And by we, I mean the physician community that collectively did the trial, whether it was the ISUIA cohort comparing unruptured aneurysms, clipping versus endovascular, or the ISAT trial, as we have already learned, showing the benefit in the endovascular strategies.

That 510(k) process evolved. From the original helical coils, we started getting more complex coils, soft coils, shaped coils, filling coils, finishing coils.

And then we did the trials to show that there was still a major problem in terms of this complete durable occlusion. There were some studies that suggests 30% recurrence. There were others that suggested 100% recurrence depending on what kind of aneurysm that was being treated.

And that resulted in innovations. The first innovation here among many others was creating a hydrogel on a coil, and the data was somewhat giving us a signal but not quite equivalent efficacy.

There were others that came along on the way that were shown to be not quite effective and disappeared despite regulatory approval. There were bioactive coils and other coils that came and went because the physicians figured out what worked and what did not work.

The Cerecyte coil was another bioactive coil that disappeared from the marketplace based on the clinical trials that we performed post-approval.

Self-expanding stents: Again, trying to improve the availability of endovascular

strategies for more complex aneurysms resulted in devices getting approved. The Neuroform stent was approved for wide neck aneurysms in 2000, and shortly thereafter, the Enterprise stent was approved in 2005 for these wide neck aneurysms that were difficult to treat with coiling alone.

And we learned post-approval that you needed dual antiplatelet therapy for this. We learned post-approval that it might not be a very good idea to use these in acute ruptured situations. So I think the physicians figured out how to use it, and we did the trials with thousands of patients compared to the 30-patient approval studies, which showed that these were very effective devices and could be utilized to great use for treatment of complex aneurysms. We realized what the complications were with these procedures. We standardized these across multiple studies, through multiple institutions and multiple geographies, to really get a good understanding of the 5 to 8% complication rate.

This march of technology, aided by the FDA's focus on safety and efficacy in small, carefully constructed cohorts, was complemented by these randomized trials by the physicians themselves to figure out how to alter clinical practice. And I think that's really important as we think about how we are discussing this today. I think the physicians are the ones who are responsible for modulating clinical practice based on shared data.

The PUFS trial led to approval of the flow diverter Pipeline that we have heard quite a bit about, and that initial trial was a hundred patients, very carefully selected. However, post-approval with a PMA, we did multiple studies, and there's been more patient studies with the Pipeline embolization device than any other endovascular technology that exists. And we were able to, across multiple studies, show that those original results were actually quite realistic and reflected reality in the real world. And these were prospectively collected studies, and then we were able to compare those results with stent coiling, with other flow diversion studies, other flow diverters across the pond, and realize that the

complication rates were about the same; however, the endovascular occlusion was far superior. We also realized that we could use these technologies beyond what the indication was, beyond what the label was, and realize that this technology was effective in sidewall situations, in a variety of different anatomies, and across a variety of different sizes with the PREMIER trial showing an occlusion rate of 83% with a complication rate of 2.1%.

So these technologies continue to evolve, and we now have new devices currently pending approval with trials complete. There's the LVIS study; there's the Atlas that was just mentioned by our orthopedic friend. The PulseRider has been recently approved. That's sort of the current landscape that we're looking at. There are multiple new technologies that continue to increase the armamentarium that we have to deal with this complex and heterogeneous disease, and I think this will continue to go on forward.

So I think the FDA has carefully approved iterative and transformational technologies with a narrow focus on safety and efficacy. The clinicians are the ones who have refined their toolkits based on pragmatic trials and shared learning. That's really how we have evolved our clinical practice. I think rigorous postmarket data collection can further strengthen this relationship and allow for continued delivery of effective and safe therapies for our patients.

I yield the rest of my time to Dr. Turk.

DR. TURK: Good morning. I appreciate the opportunity to come and address you this morning. I want to start out with just bringing up an interesting article I came across on the FDA website, looking at the strategic priorities going forward, and this is something that, as I read this, I became very, very encouraged and very positive about the direction things are going. And I don't think if you asked any of the physician groups or the industry groups to put into words what is going on and what direction the FDA should go in, I think -- I don't think it could've been done any better.

And I just highlighted a couple of excerpts saying that timely and continued access to safe, effective, and high quality medical devices for our patients and providers is a very key point, and also providing industry with predictable, consistent, transparent, and efficient regulatory pathways. And again, I mean, I think these words are really critical.

Taking it a step further, finding the right balance between premarket and postmarket data collection, I think we've seen, you know, a very strong threat of that going through today, looking for least burdensome evidence necessary to approve a device and really trying to strike the right balance of getting the right data at the right time. I mean, I think all of these things are really crucial, and you know, again, as a practitioner and somebody that likes to do a lot of studies and be involved in next-generation devices, it's really engaging to me.

I'm going to share, you know, some of my experience here of why we came to things like this that many of us participated in, realizing that randomized controlled trials are something that are oftentimes difficult, especially in our patient population where we have a heterogeneous disease and we are about a tenth the size of cardiology where it's easy to run these big studies.

Pipeline is a device that I think we've heard about a bit today. That came out in, you know, the 2012-2013 time frame, and it's indicated for a very -- you know, a very small group of patients with large or giant aneurysms in the internal carotid artery siphon.

The PUFS trial came out and was done, they did 111 patients, and that was really about, you know, the data that we had aside from the European data that we had.

So a group of us put together the LARGE trial, a randomized trial where we figured, hey, we're going to randomize patients between, you know, some way of coiling, whether it be deconstructive, reconstructive, coil alone, balloons, whatever the doctor thought should be done, versus flow diverters because, in reality, as we looked into it, we didn't have great

data on either one of these things when it comes to quality data, and we thought it would be a trial that everybody would want to participate in.

It was a non-inferiority, very, very physician-driven and physician-run study, and this is the result. The orange line is the line that we thought we would have for enrollment, and the blue line was our actual line of enrollment. So we figured it would take us almost 50 years to get this patient done -- this study done at the way it was enrolling.

On the other hand, the PUFS study that got approved as a single-arm, pragmatic design for these patients alone, they were able to enroll 111 subjects at six sites in just over 6 months' time.

So we went and looked at what options -- what issues that we faced, and we found that, you know, we have a very limited population with on-label aneurysms. We had two competing industry studies going on at that same time, the Surpass study and the FRED study, and there were also prospective and retrospective Pipeline registries going on at that same time, so there was a lot of competition for that very small, limited patient subgroup.

Additionally, the technology was transformative. It was something that allowed physicians that had moderate skill sets to be able to go out and treat these very difficult aneurysms that otherwise could only be treated at very select hospitals that did high volumes. It made a much technically easier surgery; it was a faster surgery, a cheaper surgery, and it really created challenges for a lot of doctors trying to consent patients to getting that consent from them and maintaining that equipoise. And the real result that turned out by the time we got a good way into the trial was that there was now more quality data on flow diversion than there was on stent and coiling.

Looking further at the strategic priorities, again, I mean, I think the ability to find a pragmatic and balanced and appropriate level of certainty is very crucial, and I'm really encouraged by the NEST, the National Evaluation System for health Technology, where

you're going to be able to bring in a lot of these real-world data and registry data and to be able to maintain large databases on these devices. Again, I applaud you guys, I think it's fantastic, and I just wanted everybody to hear this because I don't think a lot of people have seen this.

And you're going to gauge your success by having half of the devices of novel technology coming out of the U.S. in parallel with other industries, and that's been a big issue. I think you've heard from everybody, and again, I applaud you for using that for your success.

Just a real quick final example of that: The Penumbra catheter system was approved in Europe initially, then came to the U.S. As the devices were iterated and grew larger, our techniques improved, and we learned new ways to use these devices.

And then subsequently, the devices that came out after that, the ACE 64 and 68, those came out in the U.S. first and allowed us to really be the ones driving a lot of this understanding, and that allowed us to then do prospective studies which we've gone on to publish and then gone on to do a prospective randomized trial after it's all developed.

So with that, I'll end in just saying that, you know, I applaud everything you've done. I think your vision and your direction is fantastic, and I'm super encouraged, and I think we just have to strike the right balance of premarket safety focus and, I think, postmarket efficacy. Thank you.

(Applause.)

DR. JENSEN: Thank you, Drs. Siddiqui and Turk.

Next, we will hear from Christine Buckley and Krissy Svagelis, who will be speaking on behalf of the Brain Aneurysm Foundation. Ms. Buckley and Ms. Svagelis, you have 10 minutes.

MS. BUCKLEY: Hi, I'm Christine Buckley, Executive Director of the Brain Aneurysm

Foundation, and I just want to say thank you to everyone here at the FDA for having this meeting and allowing me to be a part of it.

The Brain Aneurysm Foundation is a globally recognized leader in brain aneurysm awareness, education, support, advocacy, and research funding. Our mission is to promote the early detection of brain aneurysms by providing knowledge and raising awareness of the signs, the symptoms, and the risk factors. We work with the medical communities to provide support networks for patients and families, as well as to further research that will improve patient outcomes and save lives. And it's my honor to be here today as a representative of patients and their caregivers across the United States.

And the BAF encourages the FDA to be less burdensome in delaying aneurysm devices coming into the United States. And you've already heard a couple of great stories as to why it is so important. And I just have a couple points to make before handing things over to another patient.

I think it's important that the FDA understand that although many aneurysms do not rupture, that when it does occur, aneurysm rupture is both sudden and often devastating. And in many other disease states, patients have more warning and more predictability for treatment and discussions with their physicians. The best treatment of a given aneurysm is heavily influenced by many different factors, including patient's age, their overall medical condition, the aneurysm location, size, and shape. And cerebral aneurysms cannot be treated well at all by a one-size-fits-all approach.

Ideally, we have well-informed patients who make decisions with the advice of well-educated physicians, among a variety of possible treatment options. And I don't think it's in the best interest of the patients for them to give up their decisions to regulatory bodies, payers, or anyone else.

So, again, I just want to say thank you for having us here, and I do believe it is just

critical for the Panel to really have trust in the physicians that are treating these patients in the aneurysm space; they're looking out for the best interests of the patients and their families. And I'm going to pass it on now to Krissy Svagelis.

MS. SVAGELIS: Thank you for having me here today. I'm actually a brain aneurysm survivor. My aneurysms were diagnosed by incidental finding; I had a vision loss in one eye and went to a local emergency room where they did a simple eye exam and sent me home. I later then had a very good primary care physician who then proceeded to do a CAT scan and found -- they told me, at that time, I had one brain aneurysm.

Subsequently, I went to Dr. Ogilvy at Mass General Hospital where I am also a nurse in the recovery room, and he then told me that I had two brain aneurysms, an 8 mm in my right anterior communicating artery and a 10 mm in my right internal carotid artery. At that time, we talked about options for me and that it would probably be life threatening if I didn't treat them and they did rupture. I had three small children at home at the time. So we proceeded to do a craniotomy, and we did clip both aneurysms successfully, which I'm very grateful for.

I had no risk factors, I didn't meet any of the listed requirements to potentially have an aneurysm, and at that time we didn't know there was any family history. Unfortunately, 3 years later, my mother was found to have a pulmonary nodule for which she then needed a PET scan to see if there was any more cancer, and they then found a very large aneurysm in the tip of her basilar artery, so now there we have the genetic link that we didn't know about. So further testing of my children and my siblings' children, thankfully, none of them have aneurysms.

But I'm here today because I just want to implore you to safely expedite studies and research to offer patients more safe options, instrumentation, and techniques. I take care of patients every day that have diagnostic angiograms; I recover them and I send them

home, and some of them are petrified that they're going to go home and rupture their aneurysm while they figure out what is the next step for them.

I personally am grateful that I didn't have to wait a long time. I was diagnosed in May, May 30th, and my craniotomy was on June 13th. I did, unfortunately, stay out of work for 5 months. I was unable to return, but now here I am speaking to you and hopefully helping other people like myself to go back to work and be successful and help patients and raise awareness, which then leads me to say that I'm here today and I get to come back on the 19th and lobby on Capitol Hill for research dollars because currently there's only 83 cents spent per affected person for research for brain aneurysms, and I think that really needs to change. So I would like to believe that that will change, and I will keep coming back every year, and hopefully, it does change.

Thank you for your time.

(Applause.)

DR. JENSEN: Thank you, Ms. Buckley and Ms. Svagelis, for sharing your story.

Next, we have Todd Crawford, who will be speaking on behalf of the Lisa Colagrossi Foundation. Mr. Crawford, you have 10 minutes.

MR. CRAWFORD: Good afternoon. It's a good-looking group. I'd like to thank the survivors who are here today who shared their stories. I found them very moving and very touching. We'd also like to acknowledge the work of the Brain Aneurysm Foundation.

Good afternoon, my name is Todd Crawford, and I'm the Founder and Executive Director of the Lisa Foundation, a nonprofit created to lead the fight against brain aneurysms. My financial disclosure is that we receive funding from medical device companies and a few others who are here today.

In 2015 I started the Lisa Foundation in honor of my wife, Lisa Colagrossi, a beautiful, loving wife and mother of our two young boys and a very well-known television journalist

for ABC News who died from a ruptured brain aneurysm while on assignment in New York City. She had symptoms for weeks that we missed, and it cost her her life. Lisa's passing made news headlines around the world, and later this month we'll mark the third anniversary of her death. I'd like to share with you a brief video that captures the essence of what led me to being here today.

VIDEO: "Just one day.

"You're listening to the Glenn Beck Program.

"I want to introduce you to somebody, and I just, I just want to explain just one day, just one day in your life. How many times have you heard your wife or your husband say, 'Ah, I got the worst headache in my life'? And you just take that in stride as the worse headache in my life, I know. I've had that worst headache in my life, too. And after she says it a few times, you say, you know what, let's get -- we should get that checked. But it's not a priority because it's just the stress of life, all the things are going on, you're not sleeping well, everything else. You just -- I'll get to that tomorrow.

"Lisa Colagrossi, she was, she was a reporter for WABC in New York, TV. And we've seen her a million times. If you lived in the New York area, you'd recognize her face in a, in a heartbeat. She goes to, she goes to work one morning, and she covers a fire. And she's on her way home, and her son texts her from his school. And she texts him back in little hearts and smiley faces. He doesn't know that that's one of the last things she does because she has a brain aneurysm. Her husband gets a call. He knows she's not going to make it. The kids never speak to their mom again. They have her on life support until everybody can be there, say their last goodbyes, and turn the machine off.

"This is a horror story, but I want to introduce you to Todd Crawford. His sons, Davis and Evan, are here. We had them on TV last night, and they told this story, and they're here for a reason, because this is more prevalent and more likely to happen than you think.

"How are you, Todd?"

MR. CRAWFORD: It's not only a horror story, it's one that's far too common for those who experience a brain aneurysm rupture. In our final minutes together before I gave the instructions to have her removed from life support, I kissed her goodbye and said Lisa, I love you. Please, go be with God. I promise I'll raise the boys the way that you want me to, and I promise to do what I can to prevent every -- everything I can to prevent this from happening to others. It is with that promise that we set out to create an organization that would lead the fight to help other individuals and families avoid suffering a similar fate like Lisa did.

And that's exactly what we have done. In just 2½ years, we've emerged as the nation's leader in raising national awareness and educating the public, have achieved several milestones along the way, and most importantly, we have been credited with saving lives in the U.S. and abroad. It is in support of this mission that I'm here with you today.

Because of our efforts at the Lisa Foundation, for the first time ever, the battle against brain aneurysms is being taken directly to the people and waged in their living rooms and around the kitchen tables, as well as in the places where they shop and entertain themselves. We are providing the public with the critical tools and information that will not only provide increased knowledge and better understanding, but also empowers them to advocate for themselves and, along with their physicians, make informed treatment decisions that will lead to improved outcomes and save lives.

While there are many who are more qualified in this room than me to talk about the science, we are very well positioned to become the national voice for millions who seek answers, and our initial efforts have centered around reinforcing the prevalence, warning signs, risk factors, and segments of the public who are most at risk. In general, people need to be more aware and encouraged to speak with a medical professional. To that end, the

Lisa Foundation has taken a series of steps to create a national conversation and dialogue around brain aneurysms, much like breast cancer, autism, and others have done.

The first thing we did was to field the industry's very first national omnibus survey to assess how much Americans knew about brain aneurysms. Perhaps not so surprising, the results were staggering as they revealed that over 94% of Americans have either a very limited or no understanding whatsoever about brain aneurysms. To address this disturbing gap in knowledge, last May the Lisa Foundation launched the industry's very first public service announcement directly in homes around the country via national television. The PSA has aired in over 170 out of 210 U.S. television markets, coast to coast, and has been credited with saving lives. I'd like to take a look at it now.

VIDEO: "A brain aneurysm doesn't care if you're busy. It doesn't care that you have important meetings. It doesn't care that you have to drop your daughter off at ballet and your son off at soccer practice. And if you ignore the warning signs of a brain aneurysm, you'll realize too late that the meeting wasn't that important. No meeting is. But you'll never see another soccer game and that your daughter won't see you in the audience at the big recital. So if you suddenly experience the worst headache of your life, sharp pain behind your eye, and blurry vision, don't ignore it. Seek immediate emergency care, because your family is counting on you to take care of you.

"The Lisa Colagrossi Foundation, shedding light on brain aneurysms. Learn more at LisaFoundation.org."

MR. CRAWFORD: The Lisa Foundation leans on the expertise of a distinguished scientific and medical advisory board composed of leading neurosurgeons, neuroradiologists, neurologists, and other healthcare professionals from across the United States who specialize in brain aneurysms and guide us in planning and implementing our body of work. Together, from small towns to big cities across the U.S., we're shedding light

on brain aneurysms and driving more impact than ever before.

Just 3 months after our launch, we received a note with the headline: "You saved my sister's life." In her email, Angela writes, "Thank you for raising awareness about aneurysms. I heard you tell your story on national television, and the next day, while on the phone with my sister, she told me she had the worst headache ever. Normally, I would have just said I'm sorry. But because of your awareness, I made her promise that she would tell the doctor. The next day, she called to let me know she had been diagnosed with a 5 mm and 3 mm aneurysm and both have since been successfully treated."

Another survivor, just a couple of weeks ago, writes, "My sister is recovering in ICU after having a 3 mm aneurysm this weekend that burst due to high blood pressure. She caught it just in time due to a headache so severe she knew something was wrong. She had seen your commercial on television. Thank you, and God bless this foundation."

While I'm not an expert on the science or technology available to physicians and clinicians, I thank and applaud the medical device companies for the cure they have provided that makes endovascular treatment possible, and the others in this room for the work they do to advance new diagnostic and treatment options for patients and survivors.

To conclude my remarks, this is a very serious condition that affects up to 15 million people in the U.S., and ruptures, although rare, are highly fatal and very debilitating. Our job at the Lisa Foundation is to reach people before ruptures occur and drive them to the front door of the comprehensive stroke centers and other facilities throughout the country where they will be properly diagnosed by the trained medical professionals and successfully treated. The testimonials we read from our survivors and others we hear from regularly only underscore the need for further innovation, development, and availability of treatment options for all with aneurysms, regardless of size, so fewer families mark the anniversary of a death each year like we do. The work that all of you do and the work of the medical

device companies is vital to fulfilling our mission at the Lisa Foundation.

Thank you for the opportunity to speak today.

(Applause.)

DR. JENSEN: Thank you very much, Mr. Crawford, for your story.

The last speaker is Babu Welch. You have 5 minutes, Mr. Welch, before we break for lunch.

DR. WELCH: Okay, thanks for the 5 minutes. It won't take that much longer. I'm Babu Welch. I'm a Professor of Neurosurgery and Radiology at UT Southwestern Medical Center and the Vice Chair for the AANS/CNS CV Section, but I'm making this comment as a public comment. And I do have consulting relationships with both Stryker and Medtronic.

I appreciate the comments from both industry and my specialty colleagues. If it was not already clear, both groups have appropriately emphasized that we cannot underestimate the challenges that rapidly evolving technologies and the potential for high morbidity can pose to the decision processes of this Panel and the physicians and patients that you serve.

As a cerebrovascular neurosurgeon who provides both endovascular and surgical therapy, I can attest to the difficulty that is encountered when in the consideration -- and I'm using that word with the hair raising on the back of my neck right now, we use "consideration" so much -- of therapeutic options for the patient who has just acquired a lifetime disease, whether we observe or not.

I found it interesting, in the earlier presentations by the FDA panel, that suggested that outside U.S. studies were considered for their population and the population of the therapy was applied to prior to accepting the data here in the U.S. It is interesting that we don't do this with our own data. This panel, in itself, represents a population that would be much different than any Finnish or Japanese panel and, by proxy, patient group. Yet, we

have quoted the Japanese and Finnish data multiple times today and apply it to our patient population here in the U.S.

In the initial ISUIA study, nearly 90% of the patients were classified as white race. My own institutional data suggests that our unruptured population at UT Southwestern is 21% non-white and the ruptured population is actually 40%. As the Panel considers application of technology to aneurysm care, I would encourage consideration that patient populations are analyzed as well.

I think it's reasonable to consider that post-approval registries will represent a more diverse patient population and really give us the real-world considerations and correlations that Dr. Dion was looking for previously. Such registries would not only provide a better understanding of the U.S. population with respect to adverse events and other scientific endpoints, but we would also gain a better understanding of what happens when we make novel technologies available to the socioeconomically diverse population that is the United States of America.

Endpoints for regulatory studies must be pragmatic, clinically relevant, and appropriate for the type of device being evaluated. The appropriateness of treatment must be determined by the evaluation of a diverse patient population with guidance and input by their physicians.

That's the statement I wanted to make. Thank you.

(Applause.)

DR. JENSEN: Thank you very much, Dr. Welch.

Does anyone in attendance wish to address the Panel? If so, you would be granted 5 minutes. Anybody else?

(No response.)

DR. JENSEN: Does anyone on the Panel have questions for the open public speakers?

Yes, Dr. Dorsey.

DR. DORSEY: I'd love to see that graph of the drop in mortality associated with subarachnoid hemorrhages that one of the speakers highlighted.

DR. JENSEN: Who had that graph?

(Off microphone comment.)

DR. FIORELLA: Yeah, this is quite a provocative slide. So is there a particular question that you have about it?

DR. DORSEY: What struck me was that you said that the drop in mortality clearly coincided with the publication of ISAT.

DR. FIORELLA: With the change in practice in the UK. So in the UK, prior to the publication of ISAT, there was a fairly good split. Endovascular saw a good penetration into the market there, so about a 60/40 breakup for clipping and coiling. And so once the publication of that study came out, clipping really rapidly fell off, and these are the clipping rates.

And NHS is a good system because we can capture the data there, both on mortality for subarachnoid hemorrhage, they have excellent follow-up for that, morbidity for subarachnoid hemorrhage, and for the rates and clipping and coiling. And so you can see it as the rates of clipping drop off precipitously, and now in the UK, again, they have access to many more devices than we do, but endovascular therapies have really, really taken over there. And so when they look at the marketplace there, about 90% of aneurysms are treated with endovascular therapy, and that temporal change in subarachnoid hemorrhage mortality that's demonstrated here, you can see it does have a decline, and so this is a multifactorial problem, and that decline was in place prior to this change in practice with ISAT. But you can see temporally corresponding to this transition that occurred in practice between primarily or half-and-half surgical treatment to primarily now almost exclusively

endovascular therapy, that there has been temporally correlated a tremendous decline in the mortality for subarachnoid hemorrhage.

And so I think this isn't completely like cause-and-effect relationship, but we have to take the data that we have access to. And so I think this very clearly implicates a change in practice for a benefit in outcomes, and I think it demonstrates well how understanding of new technologies and the introduction of new minimally invasive and safer technologies has the potential to really impact patient care over a huge population of people.

DR. DORSEY: For those that don't know, can you tell us a little bit about the design of the ISAT study?

DR. FIORELLA: What in particular do you do you want to know about?

DR. DORSEY: Well, the design of the study.

DR. FIORELLA: This was over a 2,000-patient study where patients were randomized, who had subarachnoid hemorrhage, between clipping and coiling based on the feeling of the physicians that both treatments had equipoise.

DR. DORSEY: So I find this really powerful because ISUIA was a randomized controlled trial, and this provides tremendous evidence of why we do randomized controlled trials, because they change practice. In this case, this randomized controlled trial has probably saved the lives of thousands, tens of thousands, maybe hundreds of thousands of people. So the people who we just heard a lot of moving testimony, this really highlights the powerful randomized controlled trials, and when we don't have randomized controlled trials, we had things like bone marrow transplant being used to treat breast cancer, and not only did that cause the deaths of many women with breast cancer, but also prevented new therapies from coming to market. I think this is actually the most moving testimony that I have seen.

DR. FIORELLA: So one thing, I'd like to respond to that. And I think you're exactly

right on, and one of the things that we wanted to make clear from a standpoint of societies is we firmly back randomized controlled trials, and those of us who presented, I think, participate avidly in them when they are available. But the time frame required for the completion of these studies really makes them not suitable for regulatory purposes in many cases. And so our feeling is that these randomized controlled trials should definitely be done, but we can't necessarily, for every iterative device particularly, and even for some of the more innovative devices, the newer devices, go through a large randomized controlled trial for approval and availability of these devices.

DR. JENSEN: I would just point out that they started enrolling in 1994. It wasn't published until 2002. So it's a very long time period in which to collect the data, but it's excellent data for the FDA to now be able to use, going forward, as we make some deliberations.

DR. DORSEY: And it saves lives.

DR. OVBIAGELE: I just wanted to speak to that. I think we should be very cautious about making this kind of leap. I mean, this particular pattern corresponds very much to the decline in mortality from stroke in virtually all western countries and so -- and that has really been driven by better risk factor control. So I would be very cautious about making this kind of leap.

DR. FIORELLA: But it's a little bit coincidental that the actual abrupt change in the curve -- so the beginning of the curve, I think, very well could represent risk factor management, but there is a fall off a cliff that occurs with morbidity and mortality there.

DR. OVBIAGELE: Yeah, I would be very cautious about making that kind of leap.

DR. FIORELLA: I think you can be cautious, but I think you still have to acknowledge that there is a significant healthcare benefit to this. And if you go back and actually just look at the data for the trial, I mean, there's a substantial absolute risk reduction and

relative risk reduction for endovascular therapies. Whatever you want to make of this, you can make of this, but I do think it's important that we try to move towards more minimally invasive therapies, and it does underscore the main point that the more devices you can give us in our toolbox, the more of an armamentarium we have to treat these in safe, technically straightforward, and minimally invasive ways. I think you have the potential to really change the morbidity and mortality for this disease process for patients.

DR. JENSEN: Thank you. We can have more discussion about this later on in the afternoon. Any other questions?

(No response.)

DR. JENSEN: So we will now break for lunch. Committee members, please do not discuss the meeting topic during lunch amongst yourselves or with any members of the audience.

(Whereupon, at 12:36 p.m. a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:38 p.m.)

DR. JENSEN: Okay, if everybody could take their seats, please. We're going to get started. Okay, so we're all back from lunch now, and what we normally do next is we open the floor to the experts around the table to begin deliberating on any issues that you may have with any of the data that you heard today, either in the panel presentations, the discussions with the FDA, or the material that you have read in your panel packs.

Although this portion is open to public observers, public attendees may not participate except at the specific request from the Panel Chair. Additionally, we request that all persons who are asked to speak identify themselves each time; this helps with the transcriptionist identifying the speakers.

But before we start this, there were two issues that came up from the last part of the session. One was one of the Panelists wanted to know if industry would share the performance goals with the Panel, and Stacey Pugh is going to address that. So, Stacey, if you could come forward, please.

MS. PUGH: In discussion with industry, the actual performance goals themselves are under review with the FDA and are indeed proprietary. So there was not a consistent methodology due to variation in patient populations, and therefore, I cannot provide a comprehensive list of those specific performance goals today. If we want to discuss how the methodology was brought about or any further detail on how those were developed, I'm happy to discuss that, but I'll do it at the Committee's request, or we wanted to make sure that was indeed what you wanted to know or not.

DR. JENSEN: That's fine, thank you.

MS. PUGH: Okay, thank you.

DR. JENSEN: Okay, so one other issue was the representatives from the societies

were under the impression that they had some more time to go over their responses to the FDA questions, so we are going to allow them to speak for 10 minutes.

DR. ARTHUR: Thank you. So the questions at the end of the Executive Summary, we took a stab at trying to answer. Dr. Mocco handled the first two or three in his talk. But just to quickly go through our other questions, the Raymond scale is really only validated for coiling, and essentially, it's a fallacy to believe that when you stop seeing filling in the aneurysm there is no blood flow in the aneurysm; we know that with coiling. It can be modified, but it's not appropriate in and of itself for flow diversion where really it's whether the aneurysm is completely occluded or not, and I don't think there's a difference between a Raymond II or III in flow diversion.

And then for these intrasaccular devices, we know it's not appropriate. You can see a lot more in the aneurysm, and there's been actually more work done on some of those validations than on the initial Raymond score.

I think if the technology continues, we have to be sensitive to physical considerations that may change the appropriateness of the Raymond score. Complete occlusion is a good standard for flow diversion, as I said. Adequate occlusion for other endovascular technology is probably a better standard, Raymond I or II.

And then OPCs, I'll remind you that we did talk about trying to be more robust with OPCs as more data is accumulated, and I am personally a fan of the peer review and open OPC rather than closed OPC so that we can have as many people give input into the literature as possible. There's a lot of literature that needs vetting.

As far as Question 6, angiographic scales must be appropriate for the aneurysms treated and devices treated in the heterogeneous disease state. It would be a mistake to use a one-size-fits-all approach. And for the purpose of follow-up, we believe that stable adequate occlusion at 1 year is sufficient. As I mentioned in my talk, retreatment is not

mandated alone by a worsening Raymond scale. We have to have the ability for physicians to clinically make recommendations for a patient based on the angiographic appearance and more than just the angiographic appearance.

MRA versus CTA is interesting. I would say, and I think my colleagues from the other societies would agree, that if it's a "me too" device in a worked-out segment like flow diversion, then MRA with contrast may be adequate. But for new devices, something that really works in a way unlike what we've seen before, I believe we have to have DSA.

This is a paper that was published last month that indicates that for intrasaccular devices, there may be a Faraday cage-like phenomenon where it would hide, on an MRI, flow. Honestly, as somebody who has studied intrasaccular technology, I didn't know that and thought MRA was okay. We have to be able to change when we see new data.

Only two more questions left. Question 10 was "Should a post-approval study be warranted?" The societies are a big fan of more post-approval data. For "me too" devices, I think maybe a 2- to 3-year post-approval study would be adequate. We've just seen the publication of the PUFS 5-year cohort. I think, for a new technology, it's very appropriate to ask for data out to 5 years. We need to know what's happening to these patients. As other speakers have mentioned, we're trying to protect them for the course of their lives so that they eventually die of cancer or heart disease, but neither the aneurysm nor attempts to fix the aneurysm.

And then the last question was about labeling and what patient characteristics should be specified in the indications for use. I think, again, if we're going to try and improve survival rates by using a diverse, different armamentarium of technologies that may be appropriate in different kinds of aneurysms, we need to look at the study and the research and apply that to the indications for use. I don't believe indications for use should be restricted by age or a prior history; I think it's probably more appropriate to look at

whether a given technology is useful in a sidewall aneurysm or a bifurcation aneurysm and where its safest use is. Thank you.

DR. JENSEN: Thank you very much.

Okay, so now we're going to open this to our Panel, and we've heard from most members of the Panel but not everybody. So to open this up, is there anything that anyone wants to start with that's a burning question that you feel we need to discuss openly?

So we have Dr. Ashley, yes.

DR. ASHLEY: Yeah, I just had a quick question. When we're talking about the Raymond scale and then we were talking about the type of angiographic follow-up, are we specifying how we're defining the Raymond scale? Are we using DSA, or are we using MRA, or how are we dealing with that issue?

DR. JENSEN: So that's an excellent question for the Panel, and one of the things I'd like to point out is in the different drawings that we saw of the Raymond scale throughout all of these different presentations, I saw three separate Raymond III pictures. Yes, so even just among your own presentations that we just saw, we can't seem to agree exactly what Raymond III is.

So, for example, one of the things I saw was a central fill in a coiled aneurysm, and my opinion, and I'd like to have the opinion of other people who do this on the Panel, is that that's a helmet of metal around that aneurysm, and I don't think there's a risk of rupture there. And I also know that from DSA. And there are plenty of MRA studies that have shown that at high field strength magnets with contrast, you can actually see central fills better on MRA than you can on angiography. So, you know, when we're talking about DSA versus MRA, we have to keep those things in mind.

So everybody is welcome to speak, but for those who actually do endovascular treatment, let's start with you. So, Dr. Ashley, what do you think?

DR. ASHLEY: You know, I think DSA is still the best, but mainly because we have the most data to compare, you know, each aneurysm and the subsequent potential for rupture. You know, it's still not clear whether aneurysm that doesn't fill on DSA but does show filling on MR, how do we understand what the risk of rupture is? We have a lot of data that shows the ones that don't fill on DSA are probably well treated, Class I, so I still think that, at least, as an initial test, the DSA is good. And if we have concurrent data with the DSA and then a noninvasive imaging modality, I think that helps with follow-up down the road.

DR. JENSEN: Okay, thank you.

Dr. Thompson.

DR. THOMPSON: I agree with the last comment. I think that DSA is still a very important study and comparatively advantageous to MR in many cases. In addition to what you said, I think the other part of it is, and there's been information from some of the scientists in this group, that have shown that confirmation is very important and that we get that information from DSA better than we do with MR.

DR. JENSEN: Dr. Do.

DR. DO: I think DSA is the gold standard, at least definitely for the initial follow-up, if feasible, either at 6 months or a year, and depending on what that showed, it may -- you may continue to follow with DSA, or if you feel comfortable enough, you can follow it noninvasively in our -- I would recommend MRA and particularly now with contrast, I think that may obviate some of the physical artifact that we see now with non-contrast MRA.

DR. JENSEN: And Dr. Tsimpas.

DR. TSIMPAS: So from my perspective, I agree with pretty much what everybody else has said. In my practice, I use a DSA follow-up at 6 months, and then I do routine MRAs with contrast after intervention for another 4 years and then a final DSA at 5 years. I agree with Dr. Ashley, in terms of if you see something on MRA inside the aneurysm but you don't

really see it on an angiogram, how you're supposed to interpret this, it is something which is real, is it -- I mean, which is not real. That's something that we need to take with a grain of salt.

DR. JENSEN: Does any other Panel member want to weigh in on DSA versus MRA in discussion? Oh, I'm sorry, Dr. Erkmen --

DR. ERKMEN: That's all right.

DR. JENSEN: -- I forgot to -- I apologize.

DR. ERKMEN: No. I agree with a lot of the comments made so far, that DSA is our gold standard. MRA has obviously been validated in a lot of these. I think the confusion comes when you switch from DSA to MRA. At some point, how do you account for differences? Is it apples and oranges, and would it be worth having an MRA concurrent with an angiogram or the DSA to then, in the future, be able to follow an MRA simply, because if you find new filling on an MRA that you didn't see on a DSA a year ago, is that new or was that there prior? You're just sort of comparing two different modalities. So doing a concurrent study, if you want to convert to MRA as a future following mechanism, might be ideal.

DR. JENSEN: So I think that's an excellent comment, and that's sort of what we do. Our first follow-up is a DSA, but then we get a concomitant MRA so that we can actually compare apples to apples. I realize it's an added cost, but, you know, what does everybody think about the potential cost of complications associated with multiple DSAs? And I think that's a very real patient safety issue if you're talking at looking at patients at 6 months, you know, 12 months, 18 months if we can do this safely with MRA.

Yes, Dr. Grotta.

DR. GROTTA: Yeah. Well, I'm not an interventionist, but I do follow these patients, and you know, we also do DSA immediately or the first post-study to be sure of what has

happened with the procedure and then follow with MRA. But I guess I'd be careful because the field is obviously evolving in imaging, and what we're hearing is that MRA is sensitive, in fact, shows us things sometimes we don't see on DSA. So if we get locked into doing -- by making a statement that DSA is required when down the road we find that we validated that MRA actually may be a better way to follow patients, and so I think it sounds to me like MRA needs to be validated against DSA in following these patients and may eventually enable us to get rid of the follow-up DSA.

DR. JENSEN: Thank you.

Dr. Tsimpas.

DR. TSIMPAS: So my question is how much do you actually trust the MRA with the same variability between different machines? So one says send the patient out for an MRA if you have -- for example, at our hospital where I know the quality and I know what to expect, I tend to trust it more compared to going to an outpatient, you know, MRI that is maybe less Tesla, less sensitive, so how much do you accept in interpreting this data? So I tend to use the MRI predominately as a surveillance, and if I see something I don't like, then I jump back to DSA.

DR. JENSEN: So, again, that's another strategy is that once it's surveilled, if you see a discrepancy, then you go to DSA as opposed to just doing DSA all of the time. And again, I think one of the things that we could discuss is what would be the correct protocol for MRA; in other words, is it a 1.5 T, 3 T with and without gad? I don't know how you all do it, but we do both time of flight, which actually allows you to see the coil ball pretty well, and then we do gad, which sort of masks out the coil ball, but then you can really see the remnant better. So, you know, perhaps what we need to suggest is there's more of a protocol driven, so that if you're going to follow patients with MRA, they must be done at certain places.

Dr. Erkmen and then Dr. Selim.

DR. ERKMEN: And I would reiterate the point that was just made that with novel technologies, MRA has to be validated first, and that DSA should be the absolute standard with newer devices, such as the example that was provided with the intrasaccular braided device; MRA may not be ideal for that. And so with novel devices, absolutely, I think DSA should be the follow-up of choice, and once validated, then other modalities might be appropriate.

DR. JENSEN: And Dr. Selim.

DR. SELIM: Thank you. I think I wanted to reiterate the same point. It seems like an important part to define how we follow this, is actually to validate it, and that's important for the field to do, but I think one way to do it is a hybrid of what you mentioned. So maybe early on we do DSA, and then once you are sure of stability, then maybe follow-up can be with an MRA after that.

DR. JENSEN: And then we also have to decide is there a difference between ruptured aneurysms being followed and unruptured aneurysms --

DR. SELIM: Correct.

DR. JENSEN: -- right? Because the unruptured aneurysm data may have remnants, but as we discussed at our 2015 Panel, it's very difficult to find any literature that said how often a coiled unruptured aneurysm ruptured, right? So the risk of rupture, at least, based upon lack of evidence in the literature that I know of, is that they don't really rupture after they've been coiled, whereas we know ruptured aneurysms do. So is there a role here for us separating the two ideas of how we follow them up between just talking about coiled aneurysms ruptured versus unruptured and then we can talk about flow diversion?

DR. SELIM: Yeah. I mean, I thought even just without following them, even for the safety concerns, we'll have to separate them, but we'll come to this discussion later, I think.

DR. JENSEN: Yes, Greg.

DR. THOMPSON: To answer that question and also to address something and make sure it's clarified, based on -- it may not have been based on Dr. Grotta's comment. I do think, as Dr. Erkmen said, DSA is the standard. But just to be clear, for instance, we image it typically after coiling at 6, 12, and 24 months, but our goal would be to have one DSA possible, and we use MR in the interim, and the way we do it depends on how the patient presented.

As you mentioned, unruptured aneurysms tend to be less problematic; ruptured aneurysms, more problematic. And if there's any residual, they get their DSA study immediately at 6 months and may get another one thereafter if there's some subtle change; but generally, if they're not, then we would go get MRA. If we have an unruptured aneurysm and they have, say, a very small remnant, we typically would do it with the DSA at the delayed imaging juncture rather than immediately. In other words, it depends on our clinical suspicion, but we try and do just one DSA study rather than three.

DR. JENSEN: Dr. Do.

DR. DO: Just a comment. It's a very interesting question, but I wonder if we have a diagnostic neuroradiology consultant to the FDA? That way we can ask, seek advice and input on this.

DR. JENSEN: That's a very good point, to use all of our colleagues.

Dr. Tsimpas.

DR. TSIMPAS: One more quick question. I just want to get everybody's opinion on how people deal with dissecting aneurysms in terms of follow-up after treatment intravascularly, and also blister aneurysms because they tend to behave in different ways than the routine saccular aneurysms that we see.

DR. JENSEN: So that's a nice segue into how do we follow patients that are treated

with flow diversion, whether it be a true flow diversion device like the Pipeline or if it's, say, multiple overlapping stents, right? So I have a question for my colleagues about CTA, because quite frankly, CTA, I have found, will often show contrast outside of the device if it is not completely healed. So I'd like to hear from anybody who has experience with that because we sort of dismissed CTA as having a role here, and for ruptured, I mean, for coiled aneurysms, I think that's true because of the amount of coil ball artifact, but perhaps not so for a flow diverter.

So what do people think about that? I'll start with Dr. Ashley. Well, I'll start with Dr. Erkmen since -- and we'll come that way.

DR. ERKMEN: I like to use CTA with flow diverters before I do my first angiogram just because if you see that there's an aneurysm still filling, it doesn't help to get a DSA at that point, and so I often will use a CTA in following flow diverter patients, and if you still see filling of the aneurysm, I would delay the first DSA since we really want to show occlusion of the aneurysm at that time. And so oftentimes CTA, I think, is a great screening tool for flow diverters.

DR. JENSEN: Dr. Ashley.

DR. ASHLEY: I'll usually do a diagnostic angiogram at 6 months to look for, you know, the first look, and if it's still filling on DSA, then, you know, I'll get another DSA at about 6 months. If it looks like it's shut down, I usually will get some kind of noninvasive image, usually an MR but sometimes CTA depending on the patient, whether they can tolerate it, and I also will get a regular MRI with contrast to kind of look for the mass around -- particularly with large ones. Sometimes there's some kind of neovascularization or other kind of excess flow that we see in aneurysms, that even though they seem to have shut down, it's something to watch.

DR. JENSEN: Okay. So staying on the CTA topic, Dr. Thompson, do you have any

thoughts about that?

DR. THOMPSON: I'm sorry, staying on?

DR. JENSEN: Using CTA as opposed to DSA for flow diverters now, not for -- this came up because we were talking about dissecting aneurysms or blister aneurysms, and those are sometimes, you know, treated with flow diverters.

DR. THOMPSON: I think that's perfectly useful. We tend to use MRA because we use it a lot. Obviously, when you have more metal in, sometimes you get more artifact, but CTA, I think, is a perfectly reasonable way depending on the specific aneurysm.

DR. JENSEN: Okay. And Dr. Do.

DR. DO: Yes. Sorry, I should have qualified the -- the previous comment was pertaining to coiled aneurysms and aneurysms that we flow divert, I like to do a 6-month angiogram, but then thereafter, I do like to follow these with CTA. I find that they're -- especially with -- and then we have to specify like how many slices, how many detectors, multi-detector, which one do we want, but usually the sub-millimeter slices with multi-planar reconstruction and curved planar reconstruction, in particular on CTA, is very helpful to look for endoleaks and also for any signs of intraluminal stenosis due to intimal hyperplasia and also to look for, obviously, aneurysm occlusion. And then you assume that the patient is endothelialized, that you can then take them off dual antiplatelet, right; that's the thought process. I mean, we're not sure if it's endothelialized, but we're going by the Raymond I classification for flow diversion as re-endothelialization. So yes, CTA is very important for follow-up for flow diversion.

DR. JENSEN: Very good, thank you.

And Dr. Tsimpas.

DR. TSIMPAS: So the same as everybody else, I tend to do a 6 months' angiogram after treatment, and if there's a residual -- actually, with or without residual, I tend to

follow up, for a short period of time, with annual CTAs. Our quality is actually good enough, and it tells me is there's still endoleak or any residual or anything like this, and if I see any of this change, then I go back to DSA.

DR. JENSEN: Okay. And our other Panelists, I'm sorry, who are not treating the patient necessarily but may have comments about any of the imaging?

Yes, Dr. Dorsey.

DR. DORSEY: So I think your point about people who are at lower risk, especially presumably those with unruptured aneurysms and the risks of angiography, the number one environmental risk factor for breast cancer is radiation from us and anything, this 1% complication rate. So I think it would be pretty easy, I would think, it would be pretty easy to compare MRA or whatever imaging modality against DSA, have 100 consecutive patients, have both assessments done, have a blinded independent rater evaluate both and see the level of correlation between the two, and you could have an answer in a relatively short period of time and inexpensively.

DR. JENSEN: That's an excellent point, and I'm embarrassed, as a radiologist, that I didn't mention radiation dose. I think sometimes we get sort of inured to it because we stand in it all day. So yes, I think it's very important that we take radiation dose into consideration.

Oh, yes. Dr. Ovbiagele.

DR. OVBIAGELE: A little bit of an aside, but I'm not sure if we've exhausted this topic yet, but it's related to what Dr. Dorsey mentioned. But I think Dr. Ashley might be still on this topic, so I'll wait.

DR. JENSEN: Okay, thank you.

I did have one other question for Dr. Ashley because he brought up a very good point, and that's at what point in time or do we think that the patient needs after a

treatment an MRI? And the reason I bring this up is, you know, we have seen, with flow diverters in particular, some intraparenchymal hemorrhages that were asymptomatic or at least subclinical; they seem to be subclinical. We certainly know, from carotid stent trials, that you can have lots of little emboli, you know, after a stent on MR, and supposedly it doesn't cause a problem but it turns out that actually it may.

So is there a role in terms of doing parenchymal imaging at some point in time from the time the patient is treated through the follow-up period where MRI should be done? And I'd like to hear from anybody. Dr. Ashley, I think you were --

DR. ASHLEY: So I think the answer is yes for that, and then probably at the time that you think it's occluded, right? I mean, if you're still seeing flow through the stent, then you're planning to look again; then, maybe not. But once I think it's occluded, then that's the time to look for any more subtle signs that there could be a problem, so that's usually when I get it. So if it's 6 months, then I get it then; if I have to look longer, then I'll get it then.

And then, you know, the aside question I had was what is -- kind of separate, what is the size of the remnant that we worry about when we're thinking about remnants that either don't give us a problem or do? I mean, because certainly those can vary. I mean, just the size of the neck can vary. If we're just talking about a neck remnant only, some are big, some are small, some are kind of off to the side, some are in the center, as you mentioned, so I think this is a separate point of discussion.

DR. JENSEN: So that sort of hearkens back to my thought about what is a Raymond III; what's a dangerous Raymond III? To me, it's if there's exposed dome, so if there's like dissection among -- between the coil ball and the dome of the aneurysm, that's what is of concern to me. What does the rest of the Panel feel about that? Those would be the ones that you would --

DR. ASHLEY: I would agree with that. I think it's -- when active aneurysm recurrence is directly adjacent to the aneurysm wall, that it would seem to be higher risk.

DR. JENSEN: Any other comments about doing parenchymal imaging at some point in time during the evaluation of the device?

Yes, Dr. Tsimpas.

DR. TSIMPAS: So I'm not sure how valuable it is, to be honest, because sometimes just for plain catheterization, you may see small little hits in the brain and then you can -- I do it because of the actual catheterization or from the aneurysmal treatment so the patient -- how do you interpret this; does it make any clinical difference to actively look for this or not? So I personally don't tend to give them MRIs unless there's a clinical indication.

DR. JENSEN: So that would be primarily immediately after the procedure as opposed to at your 6-month point, to see whether or not there is evidence of, say, intraparenchymal, unsuspected intraparenchymal hemorrhage?

DR. TSIMPAS: Correct. And another reason that I would personally give them MRAs is if I deal with a larger calcified partially thrombosed aneurysm, I would like to see how the mass effect looks on the brain itself. Then I would entertain the idea of getting an MRI.

DR. JENSEN: Okay, thank you.

Dr. Grotta.

DR. GROTTA: Yeah, I think it's important to distinguish between whether you're talking about routine practice or you're talking about clinical trials. I think if you're doing a clinical trial, that you're evaluating a new device that you're putting in someone's artery, that a follow-up MRI is perfectly reasonable and, in fact, probably should be done as part of that trial. You're looking for distal embolic events. You're going to see them on an MRI that you're not going to see clinically and you may not see angiographically, and it's an objective way to determine if they're occurring. So it seems to me that you would want to have an

MRI as part of a trial evaluating a new device.

DR. JENSEN: And what timing would you think that that should be done? Just one in conjunction with the MRAs, if people are doing MRAs? Just one standalone? What's your thought?

DR. GROTTA: No, post-procedure.

DR. JENSEN: So immediately post-procedure?

DR. GROTTA: Yeah. Maybe not immediately, but during the same hospitalization.

DR. JENSEN: Okay.

DR. GROTTA: Or during the same time frame. That's a separate question in whether you got adequate obliteration of the aneurysm or not. That's a blood vessel wall. With blood vessel imaging, you're talking about the end organ and you want to look at -- you do an MRI, any neurologic event.

DR. JENSEN: Okay. Other thoughts about that?

Dr. Dorsey.

DR. DORSEY: I would agree. I think it would be great to have objective safety data on these new procedures.

DR. JENSEN: So you would look at that as perhaps one of the secondary or primary safety endpoints? Don't you think a primary safety endpoint? So let's talk about endpoints.

DR. GROTTA: Well, in the adverse event list --

DR. JENSEN: Um-hum.

DR. GROTTA: -- one of the prominent ones is distal embolization, so to me it's how do you define whether there's, you know, distal embolic phenomenon? That's one of the ways, probably the most sensitive way, to determine it. And you're probably going to see it in a majority or a large number of patients, but at least you have an objective way. It doesn't mean it's necessarily a serious adverse event if it's not clinically relevant, but if you

don't look for it, you're not going to see it.

DR. DORSEY: It would be just like doing it for tPA.

DR. GROTTA: Right.

DR. SELIM: Can I add to that?

DR. JENSEN: Okay, so Dr. Selim.

DR. SELIM: So I mean, it's always good to know, I guess, if there are silent infarcts or embolization going on, but I think the timing would be important. So if you do it right after the procedure, how are we going to tell if it's from the device or from the procedure? So if you want to be perfect, you want to do it after the procedure, you want to do it probably after a few months to make sure that there's no ongoing embolization. But maybe in the bigger picture, what you want to know is the effect of the silent infarcts, which may be more something related to the patient, maybe cognitive functions or something like that.

DR. JENSEN: Okay, thank you.

Other comments about the timing, if we feel that parenchymal imaging needs to be done, you know, at what point in time? Because I do agree that we do know, just with catheter angiography, you can have some silent hits, so is that just because of the catheter angiography or is it actually from the device? I can see how that can be confounding. Also shows you how good an angiographer you are, too. Any other questions about -- yes, Greg.

DR. THOMPSON: Dr. Jensen, I have just one additional comment about Question 1, which is the (a) question is, is the list complete and what should be added? I think not listed here are visual deficits, and although some may have presumed that it was under stroke, I think it's different because actually it's oftentimes not vascular, it's a compressive deficit. For instance, one of the reasons we started using endovascular widely over clipping was the advantage of the endovascular technique over surgery with respect to visual deficit. By the same token, if you compare intrasaccular versus flow diverters for -- well, with

respect to the visual deficits on the optic apparatus, I think we well may find a difference. I've seen that in my own practice, so I think we ought to add that.

DR. JENSEN: So would the visual changes fall potentially under a minor ipsilateral stroke or are you --

DR. THOMPSON: I think I might list them separately as one of the adverse events, just any visual changes, and it may need to be carefully evaluated for studies.

DR. JENSEN: Okay. And --

DR. GROTTA: One -- sorry.

DR. JENSEN: I'm sorry.

DR. GROTTA: One of the recommendations that was made was cranial neuropathy as an added adverse event. You can include, you know, visual deficits along with facial numbness and, you know -- muscle, the deficits with cavernous sinus aneurysms as a broad category, cranial neuropathy, and include visual symptoms in there.

DR. JENSEN: Any other thoughts about -- since we've seemed to move on to the topic of adverse events --

DR. GROTTA: Right.

DR. JENSEN: -- we sort of got there by talking about MR, so let's go ahead and talk about adverse events.

DR. GROTTA: Okay.

DR. JENSEN: Yes, Dr. Selim.

DR. SELIM: So since we were talking about the imaging and MRA, I think you made a good point at the beginning about the timing of when you're going to do the angiogram or the MRA.

DR. JENSEN: Um-hum.

DR. SELIM: So it seems like from what I heard from everyone is that's your practice,

you're doing it at 6 months, and you seemed to indicate early on maybe 3 months would be a better timing for that.

DR. JENSEN: So --

DR. SELIM: In the ruptured aneurysms.

DR. JENSEN: In the ruptured aneurysm group, right. So we're trying to look at, sort of, three different animals. We've got our unruptureds, our saccular aneurysms that we're coiling or stent coiling, modeling coiling for the most part, small neck, larger dome, and we've got our ruptured aneurysms and it's a different animal --

DR. SELIM: Yeah.

DR. JENSEN: -- right? And then we have our either large, wide-necked or fusiform aneurysms that we're talking about flow diversion. So what I'm hearing sort of from the Panel is that we're all thinking that the Raymond scale I, II, III is appropriate for the coiled aneurysms, be they ruptured or unruptured, recognizing that coiled aneurysms recur more frequently and earlier, so maybe what we need to think about is when does that first study get done? But we're saying that with flow diversion cases, it's a one or nothing. I mean, anything past a one is failure. Am I stating, I think, what I'm hearing the Panel say correctly? Is that true?

DR. GROTTA: Anything more than one what?

DR. JENSEN: Pardon?

DR. GROTTA: Anything more than one Raymond. Oh, yeah.

DR. JENSEN: Anything more than one is a failure. In other words, you've got to have complete occlusion of a flow diverter, and you can't have a partial occlusion of a flow diverter and say that you've got a satisfactory treatment there, but the idea being that with flow diversion, until you have to have endothelialization of the entire device to exclude the -- you know, the aneurysm. Otherwise, you're at risk of having thromboembolic

complications because there's no real true healing there.

DR. GROTTA: Right, at 6 months. But not right after the procedure.

DR. JENSEN: No, no. As a matter of fact --

DR. GROTTA: Right.

DR. JENSEN: -- if they shut down entirely, immediately, that's always actually worse; the entire vessel is going to shut down. But I just want to make sure that we're all on the same page with what we're talking about in terms of at least the radiographic outcome.

Okay. So yes, Dr. Pilitsis.

DR. PILITSIS: I just had one more questions about the radiographic follow-up. You know, listening to the discussion, it sounded like DSA is the gold standard for novel technology, and so probably when you're looking at a novel technology in a study setting, you're going to use that for at least the early follow-up. What do you do after that 1-year follow-up in the postmarket aspect? Is there a time to integrate MRA or CTA? I know it's probably dependent on the device, but just do we have any thoughts on that?

DR. JENSEN: Yeah, I think that the imaging for novel devices is going to be yet to be determined and probably may remain with DSA for now. I think the reason why we can actually discuss MRA with coiled aneurysm is there's actually a fair amount of diagnostic neuroradiology literature looking at the comparison of DSA to MRA in the follow-up of aneurysm. So I think that there will be studies there that actually have good data that we can utilize, but we don't with some of these novel devices, yeah.

Dr. Grotta, your light is on.

DR. GROTTA: Well, I'm just confused. So we're finished -- we're still on Question 4, or are we going back to Question 1?

DR. JENSEN: So this part, what we're supposed to do is, you know, anybody that's got like a burning question --

DR. GROTTA: Oh, understood. Okay.

DR. JENSEN: -- you know, and wants to have more robust discussion about it, which, of course, is obviously going to be around the questions, but we're not necessarily going -- yet. We will do that; we will do that towards the end, that's fine. But we did get on to the topic of adverse events, so we're back to adverse events.

DR. GROTTA: Okay, so back to adverse events?

DR. JENSEN: Uh-huh. And then we had talked about some --

(Off microphone discussion.)

DR. JENSEN: So once we actually get to the questions, and Dr. Loftus will come to the table and we will go through each of the questions at that time, so this is really more for discussion for the Panel, and out of this discussion, we got on the topic of adverse events, and we talked about that yes, maybe there are some ones on here that should be added. And when it actually comes time to do the questions, then we'll basically vote, you know, on who wants to say yes or no about these various adverse events.

DR. GROTTA: So when we go over them, when we go over them, we'll have a chance to add others that we think --

DR. JENSEN: Yes, you can. But since we're just discussing it now, you can say, hey, I think maybe --

DR. GROTTA: All right.

DR. JENSEN: -- this or that, it gives people an opportunity to think about it, and when it comes time to vote, they'll have thought about it.

DR. GROTTA: So, you know, when I go to a neurovascular conference and my interventionists do -- plan a procedure and then they suddenly in the middle of the procedure have to do something that was unplanned, to use an additional device or an additional type of stent, that's usually considered, in their minds at least, an adverse event.

So I don't see anything like that on this list. So if you have to do some unplanned additional thing during the procedure, it seems to me that -- you know, let's say there's protrusion of the device; obviously, that's more with coils, but if there's some where it doesn't seat properly and you have to do additional things, I wonder if that would be considered an adverse event.

DR. JENSEN: So, for example, if a coil pops out and you need to place a stent and it wasn't part of your plan --

DR. GROTTA: Right.

DR. JENSEN: -- do you think that's an adverse event? What does the rest of the Panel think about that? To me, that's sort of an extension of the initial procedure, just stuff happens and you take care of it, but it's not --

DR. GROTTA: Well, let's say you start doing -- you're coiling it and you wind up having to put a stent in, right? That wasn't your original plan, so no longer is it a coil procedure; it's a stent-assisted coiling. I'm just --

DR. JENSEN: Um-hum.

DR. GROTTA: You know, I'm not an interventionist, but I just hear this happen all the time, or not all the time but occasionally, and it's not -- obviously, our interventionists are skilled and adaptable and do things and you can end up with a good result, but is that a failure of the initial device that you're trying to put in when you can't -- you need to do something else than use the initial device you planned to put in? Is that a failure of that initial device?

DR. SELIM: But would this be safety or more efficacy, that the device didn't do --

DR. JENSEN: Well, I think what you're --

DR. GROTTA: Well, because you're doing a procedure, the question is, is it an adverse event for that? As you're evaluating a device and you put this device, you intend to

put this device in and you cannot solve the problem with that device, you got to use some other device that's maybe already -- that's already on the market or already approved in order to make it work. It seems to me that's a failure of the device that you're intending to put in.

DR. JENSEN: So, Dr. Do, what are your thoughts on that?

DR. DO: I think it's stated here. I think number 1, 2, 3, 4, 5 down on the adverse event list is a device failure. I don't necessarily think of other -- if the device -- it's a little bit hard of a question without being more specific, but you know, when we plan these procedures out, we do plan not just one plan. There's alternatives; there's A, B, C, D. That's how I was taught, and that's how I teach my fellows, is that you -- there are -- basically, as Dr. Jensen said, it's an extension of the procedure, and I don't consider them adverse events unless the device itself fails or there's a clinical event.

DR. JENSEN: And I happen to agree with you, maybe because I trained you.

(Laughter.)

DR. JENSEN: But yes, exactly. I'd like to hear from the other Panelists how you feel about that, too.

Dr. Ashley.

DR. ASHLEY: I agree. I think it has to do with how we're thinking about using a different device. I think, for study purposes, if we think that there's a device to be used that may be a standalone device for a wide-necked aneurysm and then we're forced to cross over to something else, that may be interesting to look at, you know, the number of times where we start out trying to use this standalone device and then we had to switch to old-fashioned stent-assisted coil, for example. But certainly, if you're starting with an aneurysm and you're starting out with a plan to coil and then you decide you're going to add a stent because it doesn't look like the neck will hold or there's some other thing, that

kind of dynamic change within the case, I don't think, counts as a failure. I think that's just part of the process of getting the thing treated.

DR. JENSEN: Dr. Erkmen.

DR. ERKMEN: I don't understand this. I mean, it seems obvious to me that these would be adverse events. If you're doing a procedure and you have to do an additional unplanned maneuver to make your procedure work, I think that's an adverse event that should be recorded, absolutely. You know, whether or not you're prepared for it -- you should be prepared for it as a good practitioner. That's -- and have thought about it ahead of time, what would I do in this scenario, that's absolutely appropriate. But if the planned procedure is not going as you think and you have to do an unplanned additional maneuver, I think that absolutely should be considered an adverse event.

DR. JENSEN: Okay, so Dr. Tsimpas.

DR. TSIMPAS: I really think it depends on the situation. Certainly, it needs to be recorded as an adverse event. For example, if I'm coiling an aneurysm and I'm not planning to use a stent and having prepped the patient ahead of time, especially for an unruptured case, and something -- a coil comes out, well, it's certainly an adverse event because then it increases the risk for the patient, putting a fresh stent and having to do acute blood thinning. But the question is, when you look at it from a critical perspective, is it actually a failure of the actual coil because that would happen in technique -- coil has been out there for years and years.

DR. ERKMEN: The question isn't is it a failure of the device; the question is did you have an adverse event with --

DR. TSIMPAS: Yes.

DR. ERKMEN: -- the procedure, absolutely.

DR. TSIMPAS: Absolutely. Yes, it's an adverse event. You increase the risk for the

patient.

DR. ERKMEN: It doesn't mean that it's a device failure, but --

DR. TSIMPAS: Exactly.

DR. ERKMEN: -- you know, just like if you treat an aneurysm and you have, you know, a distal -- you know, if you're putting in flow diverting of a distal hemorrhage doesn't mean the device failed, but that's still an adverse event.

DR. TSIMPAS: Right.

DR. JENSEN: But you're talking about something that actually has a clinical consequence, and I think that's -- to me, that's a big dividing point. If a coil pops out and I have to drop a stent and the patient has no harm from it, why is that an adverse event? Why is that not just, you know, treating a coil that popped out?

DR. ERKMEN: Well, would a clinically silent hemorrhage be an adverse event?

DR. JENSEN: So now we're back talking about a silent hemorrhage that's found on MR?

DR. ERKMEN: Yeah. I mean, I think anything that's unplanned, any outcome of your procedure that was not planned should be considered an adverse event. I mean, you know -- yeah.

DR. ASHLEY: Sorry to interrupt, but I think that the issue that now we're talking about planned or unplanned, certainly you can start out with someone who has an aneurysm where the neck is kind of wide and you think you may be able to coil it without a stent, but you start them on aspirin and Plavix with a plan to do coil embolization with possible stent assist or you start out with coil embolization with possible balloon assist. And so I don't know that deciding to change that initial plan to, you know, an adjunct in those cases -- but I think if there is a problem that we didn't kind of talk about it and I don't see it on the list, something like vessel injury, so you start out with a case and you end up

with a dissection that now needs a stent, that is a different -- that's a different animal, I think, and that kind of vessel injury may need to be part of this list. And then as an aside, something else on the list would be the radiation exposure, which I don't see on it.

DR. JENSEN: Dr. Connor, and then we'll go back over here.

DR. CONNOR: Right, so I agree with Dr. Erkmen, and I think this is a key point of what is a clinical trial versus the practice of medicine, and then, right, it may not be clinically significant in any way to the patient, but if half of the patients in a trial for a device require some other device, that's a review issue. It needs to be understood that, you know, this is an expectation of using this device or even, you know, 10 or 15%, just to inform the subsequent practice of medicine, then. So it's not necessarily going to be negative for the trial, but it's the reason we run the trials, to collect information on how a device is used, and it sounds like that would be pertinent information.

DR. JENSEN: That's a good point.

Dr. Do.

DR. DO: Again, I think we're confused by Dr. Grotta's initial question because I think what you described is described here under mechanical device failure, you know, so I'm not sure. So that's why I need -- you need to clarify is it intra-aneurysmal, is it a coil, the protrusion? Well, it may be the fault of the interventionalist not planning right, not measuring or picking the wrong coil. So I'm a little bit unclear as to adding on more adverse events unnecessarily when we're not -- you know, I don't think we're all clear on that we're talking the same -- about the same thing here.

DR. JENSEN: So can we agree, as a board, that such situations as Dr. Connor just verbalized, where basically you're excusing the device that's being looked at in the appropriate manner and you find that even though it's used in an appropriate manner you have now had to go forward and do something else to salvage the situation, that that would

be considered a device failure as opposed to it being just basically the art of medicine of, you know, putting more than one thing together in order to make it whole?

DR. GROTTA: Well, I mean, I don't really care whether you call it a mechanical device failure or not; it just needs to be recorded, it seems to me. If you're doing -- and again, I want to emphasize we're talking about a clinical trial where you're evaluating a new device that's not been tested before. It seems to me that that's just something that needs to be recorded as an adverse event. Now, whether you want to call it a mechanical device failure or call it a separate, you know, category --

DR. JENSEN: We just want to make sure we capture everything.

DR. GROTTA: Right.

DR. JENSEN: So when we talk -- when we give the FDA our recommendations, they know what we're --

DR. GROTTA: Right.

DR. JENSEN: -- looking at, too.

Anybody else have any -- yes, Dr. Pilitsis.

DR. PILITSIS: I think it's important to capture, and I think, as we all know who use devices, that some devices are easier to use and some aren't, and sometimes there's more unexpected surgical difficulty or expected surgical difficulty depending on the device. So I'm not sure that I would call it a device failure, but maybe an increased surgical difficulty or complexity. I think it is something that needs to be documented so that -- especially in a trial situation.

DR. JENSEN: Okay, all right. Dr. Thompson.

DR. THOMPSON: I just agree really with Dr. Grotta. What Julie -- Dr. Pilitsis just said, and I think an easy way to state it, your thought, I think, it would be to say adjunctive treatment required.

DR. JENSEN: Okay. Yes, Ms. Edwards.

MS. EDWARDS: Okay, from a consumer perspective, I have a question. So on these devices, the materials that are used, are there ever adverse events as far as allergic reaction to these metals, these mesh devices, and how are they -- how is this data collected?

DR. JENSEN: So, Dr. Peña, is it appropriate for me to ask you to talk about biomaterials testing?

DR. PEÑA: Sam, do you want to come and talk a little bit about biomaterials testing, and then I'll talk a little bit about how we might monitor that in a study.

DR. JENSEN: Thank you.

DR. PEÑA: Because these are focused on IDE studies.

DR. RABEN: Sure. So all these tests, all these devices are tested preclinically either on the bench or in animal models. The most common material that may have an allergic reaction would be nickel, and there's -- with most of these devices, especially with the nitinol devices, all go under leachable and extractable testing looking for nickel ion release to make sure that that is captured and, as well, will typically be included in the labeling that patients that have a sensitivity to nickel are advised of that prior to implantation. So that's included in the labeling for the device, as well as the preclinical testing that is done before the device comes to market.

DR. PEÑA: With regard to the topics that are being discussed, we're sort of interested in your perspectives within a clinical study rather than just sort of patient care. So if that could be sort of the context; you know, things happen, those could be unanticipated adverse events, if there's a negative effect upon the patient that would be captured. That would be not -- that would be sort of outside -- falling outside how the protocol has been drafted and put together. So if that helps keep the context focused on adverse events within a clinical study, that might be helpful to the discussion, especially if I

think we're moving towards Question Number 1, so it might be helpful to go there.

DR. RABEN: Did I answer your questions?

MS. EDWARDS: Yeah.

DR. JENSEN: Dr. Grotta.

DR. GROTTA: Okay, not to pile on the adverse events, but there's another one that I thought of that Dr. Arthur also mentioned. What about if there's local thrombus formation in the parent vessel when you're putting in one of these devices, even if it doesn't lead to a stroke? Is that something that would be -- I don't see that as captured in the current list.

DR. JENSEN: So you're looking at it just as thrombus on the device but not necessarily with distal emboli?

DR. GROTTA: Correct.

DR. JENSEN: What do the other Panel members think about that?

DR. THOMPSON: I just would suggest one other thing that might go along with that is -- or a correlation is that oftentimes, even asymptomatically, we will see vessel stenosis where an intravascular event or an intravascular device was placed, and it might be good, in order to find out what the natural history of that is, to include that as well.

DR. JENSEN: Dr. Do, your microphone is on.

DR. DO: I agree.

DR. JENSEN: Dr. Erkmen.

DR. ERKMEN: I would agree with that, absolutely.

DR. JENSEN: Dr. Ashley.

DR. ASHLEY: I agree with that.

DR. JENSEN: The rest of our Panel members? Everybody is -- it makes sense. So this would be thrombus formation without obvious embolization could be a potential adverse event, especially if I think you do something like give ReoPro or Integrilin or something,

obviously.

DR. THOMPSON: I'm not sure if I made it clear, but sometimes we'll see -- I don't mean in the acute phase, but chronically, you come back at 6 months and there's stenosis in the vessel, sometimes quite dramatically, and the patient is asymptomatic, and my question is what does that mean? I think we often don't know, and as Dr. Grotta, I think, is suggesting, maybe this would be a way to find out.

DR. ASHLEY: A question.

DR. JENSEN: Um-hum.

DR. ASHLEY: I think part of the issue may be, at least for me, is understanding the language of adverse, meaning we think it actually causes some harm to the patient versus an event that's important to understand for the purposes of the study. So if we see this thrombus formation and it's -- and it is clinically silent, should it be something for study that we are, in an organized way, recording but yet are not calling adverse? The same way we may think about these silent strokes on an MR, or this stenosis, you may see it, it's silent. So until we can define, over time, that that stenosis is actually adverse, we may find that after 25 years of follow-up, it's meaningless and it's not adverse.

So I think even with this discussion about adding an adjunctive device, the language calling it adverse may suggest something that isn't actually true, you know, the same thing that we assumed that retreatment, for example, may have been a problem, but when we think about it in terms of the risks and benefits of retreatment, we certainly see that there's not much bad that comes from retreatment. So should we use the word "adverse" for all these things that are important to understand but we don't know necessarily that they're bad for the patient yet?

DR. JENSEN: Dr. Grotta.

DR. GROTTA: I can't imagine a clot in a blood vessel as not being a bad thing, and so,

to me, you know, when you're acutely -- you're doing a procedure and there's thrombus formed in the blood vessel, I don't think any -- most people wouldn't leave it alone, or I mean, I don't think you could consider it not an adverse event, I think. I mean, I'd defer to the interventionists, but it seems to me that I'd be anxious about it.

DR. JENSEN: So there's acute thrombus formation, which obviously can result in embolization or thrombosis of the vessel, and then there's actually stenosis of the vessel which occurs, which is sort of a long-term, you know, perhaps a normal response to endothelialization but does not cause an issue. So I would think that the thrombus formation would be an adverse event, but the stenosis that it causes is a clinical issue or flow issue for that matter would be observed, but I'm not really certain I can call it an adverse event.

DR. THOMPSON: I think you're correct, and I'm just unclear how much leeway we have in putting the labels on this adverse versus unexpected event, but I think you're right. I mean, at 6 months the stenosis that we sometimes see, the question is what does that mean, and we don't know yet. It's most often, I think, well tolerated.

DR. ASHLEY: Is there such a classification for notable events? Certainly, we can pick on each one. We think that, you know, thrombus is bad, and we think this one isn't, but I just mean, in general, there are things that we are going to see that we, I think, can decide as a group are important things to take note of for the future and we need a way to classify them without assigning them the negative value of an adverse event, because an adverse event, I think, has to have real meaning, like maybe we stop the study kind of problem versus some other event that we note but don't know what it's going to do.

DR. PILITSIS: I guess, in my experience in clinical trials, there's adverse events and then there's serious adverse events, and so when we're looking at adverse events, you know, that could be the patient goes home and gets a cold and -- or gets strep throat and

we have to call in antibiotics, so it's something that we document but, you know, does that have anything to do with the device? Hardly likely, you know, but I think when we're talking about serious adverse events, then those are the things that, you know, we all think are more device or procedurally related. So, you know, maybe there just needs to be a clarification between an adverse event, which is anything that happens in a certain defined period of time, and then serious adverse events.

DR. JENSEN: Um-hum.

(Off microphone discussion.)

DR. JENSEN: So any other burning questions right now, because we would then move on to the question session.

DR. OVBIAGELE: Sorry, I've been waiting to change the topic for a while, but right. So I have a little bit of an issue, and it's this issue of conflating everything together, so this one-size-fits-all issue. And so I was hoping I could get help from my colleagues so I can better understand the approach to this because I think this pertains especially to Question 3.

So it's really the issue of the small unruptured aneurysms, and of course, we know that the natural history of rupture for these patients is unclear, but again, I agree with many of my colleagues from the professional societies that to hold -- you know, hold this up to the gold standard of RCTs might be difficult, but that means it's especially important for us to better define what we mean by natural history.

So a lot of time was spent in many of the presentations on ISUIA and the selection bias; I completely agree with that. I think there are several flaws there, but not enough time, I think, in my estimation, was spent on the trials that were actually cited to support this notion that most aneurysmal subarachnoid hemorrhage is small aneurysms. And so two studies were cited, the Bender, which I asked about before, and ISAT which, of course,

is a clinical trial. And so I took a look at the Bender during the break, and it's a single center, and so it's a single-center experience over 25 periods spanning from 1991 to 2016. So, of course, doesn't take into consideration saccular trends and everything. And so when you have these convenient samples, like Dr. Posner mentioned, it's a little bit misleading to now generalize it and say, I mean, you really don't know what the denominator is there, so I'm a little concerned about that. In the study, about 1 out of 5 data were missing as well, and then interestingly, the average size of an aneurysm went from 10 in the first 5 years to 6 more recently, so aneurysms have generally gotten smaller over time, and you might ask why.

So I guess the issue here is if we're talking about safety, we're talking about natural history. If we're not going to go to the gold standard of RCTs, how do we approach these particular patients? It's clear that there's no -- not zero risk, that's clear, but what is the risk, because that's the issue here. For all the questions that were raised about radiation, about materials and all those things, to be able to understand what the natural history truly is, I think, is important. So I'm struggling with that, with the issue of these smaller aneurysms, and we seem to conflate everything together, while I think the discussion should be somewhat separate, especially if we're speaking about safety, but I hope to learn from my colleagues about how they view this.

DR. LYDEN: Could I add to that?

DR. JENSEN: Yes, sir.

DR. LYDEN: So I've been thinking along the same lines, and I heard the argument against the RCT, Bruce, this morning, and some of the arguments sounded familiar to me, like lack of surgeon equipoise, for example, or the fact that patients won't tolerate walking around with a ticking time bomb that could go off at any time, or the fact that these are actually heterogeneous lesions and they're heterogeneous treatments. There's, you know,

this treatment and that treatment. And I'm reminded of previous situations that we've been in that involved situations where there was no surgical equipoise, where patients were told they had a ticking time bomb that could go off at any time and cause a massive stroke or death, and where there was a variety of approaches and a variety of lesions.

And in three particular cases that I can remember, but there's more, studies were organized, and despite these misgivings, patients were randomized, and in some situations recruitment was slow because the disorders were uncommon, but in other situations, sort of, the surgical community got on board and finished the trials rapidly. One of the reasons for slow recruitment is when patients are treated outside of the trial, and that will definitely slow down, slow down the trial.

So in the case, for example, the EC-IC bypass study, it took an inordinate amount of leadership on the part of surgical leaders and nonsurgical leaders, and at no time was any individual suffering from equipoise. So the surgeons knew the procedure worked and the non-surgeons knew it didn't work, so any individual investigator had no equipoise, but the community, the community had equipoise. And so the trial went forward, and it turned out that the patients with the ticking time bomb who got operated did less well than the patients who didn't get operated; in contrast to the carotid endarterectomy trials where the opposite happened, where, you know, the group that got the surgery did better than the group that didn't get surgery.

And the most illustrative, I think, is our most recent experience with thrombectomies where the initial work in thrombectomy was actually negative and recruitment was slow and everybody knew the answer without doing the studies, but the studies turned out to be negative. And then there was a partial regulatory push to do quality trials to use the devices, and of course, there were five trials reported with tremendous results as a result of that.

So I'm with Bruce. I'm a little curious. You know, we heard a presentation this morning that there are 15 million people with these lesions, and so if we just think about the unruptured and if we just think about aneurysms, not AVMs, not giant this, you know, just think about the largest group, is it really going to be impossible to conduct a quality trial?

DR. THOMPSON: I would respectfully disagree with Dr. Lyden on this. I think many of the points were good ones, but because we have a mixed group here, I would not characterize the appreciation of the clinical question like he did, and I'm at a different center and it may be different, but I know that surgeons were very much involved, as were interventionalists and non-surgical specialists, in the question without being convinced of the answer before the trial was done.

DR. DORSEY: So maybe some disagreement. I agree completely with Dr. Lyden. I think, especially for asymptomatic intracranial aneurysms, especially the ones that are small, the ones that everyone is talking about that's causing 50% of the unruptured aneurysms, that reasonable assurance of safety and efficacy is even greater in doubt than it would be for people who have aneurysms that either had ruptured, so therefore, the cost-benefit analysis is much different, or people who are at much higher risk for doing it.

We've learned from carotid artery that 90%, 90% of surgeries and stents that are put in for carotid artery disease are done for asymptomatic people, and according to the *New England Journal* editorial, up to 90% of those people are not getting benefit. So 90% of the time carotid artery surgeries or stents are done, are done for asymptomatic disease, and 90% of them getting it inappropriately. We can repeat the exact same mistakes by following the same path here, and to say that we can do that without rigorous studies for people who have an asymptomatic disease or pathology would be, I think, foolhardy.

DR. JENSEN: Dr. Grotta.

DR. GROTTA: Yeah. Well, since we're going on the record, I want to weigh in and agree. I think that for the unruptured small aneurysms, there's clinical equipoise as to what to do with these, so I think there's room and there's -- that is, as we've heard, the majority of these unruptured aneurysms. And I think whether we're at the point where we have the right devices to do such a randomized trial, I'm not sure because there are, as we've heard, a variety of anatomy with these lesions, and it may require a trial that allows different -- it may be a trial of best intervention plus best medical therapy against best therapy on whatever best medical therapy is, stopping smoking and all the rest of the stuff, similar to -- but I do think, in principle, there's definitely room for a randomized trial for that population.

DR. JENSEN: Dr. Erkmen.

DR. ERKMEN: I think that that raises a lot of really serious concerns. I mean, we went through this experience with the ARUBA trial where you're looking at a disease that has a lifetime risk and comparing it to a treatment that has an upfront risk, and I think those types of studies are very, very harmful to the understanding of what we're doing here. So to propose a randomized trial for unruptured intracranial aneurysms, I think, is wrought with all the same problems we had with ARUBA, and I would vote that that would be a very dangerous problem.

(Off microphone comment.)

DR. ERKMEN: Sorry. Because you're comparing a treatment that has an upfront risk, an immediate risk, to something that has a lifelong danger to the patient, and so it's impossible to study that. You would follow these patients for 30 years in your randomized trial?

DR. DORSEY: So what would you do, instead?

DR. ERKMEN: Well, I mean, that's why I think we've heard some really nice

arguments as to why observational studies are great for looking at outcomes in these patients, but to look at a disease that has lifelong risk for patients -- not to mention that, you know, we've heard beautiful stories from some patients who, you know, discovered aneurysms before they ruptured or patients who, unfortunately, didn't discover them. There's a lot of emotion and personal angst that goes into this. I think to even talk about a randomized trial for unruptured aneurysm is very, very scary.

DR. JENSEN: Dr. Ashley.

DR. ASHLEY: Yeah, I would agree. I think there are several differences between aneurysms and the expression of the mortality and morbidity from them. You know, certainly when we think about carotids, many carotids, you know, they can present with stuttering symptoms, with slower onset symptoms. When we're thinking about aneurysm rupture, it's very sudden, and so the time between when you actually find out that you have the aneurysm and the result is many times different. So I think that that's one big issue that creates a reason for us to think about treatment, but also one of the reasons why patients have so much anxiety regarding it.

And, you know, the study that we would propose, although I do think there is some validity to thinking that, you know, understanding it in a randomized way is good, the group of patients that we're thinking about, now we're talking about just small aneurysms that are not clearly dangerous to the person evaluating the aneurysm. So that gives us a very tiny group, and we still don't have a great way to figure out which patients will bleed and won't bleed; that phenotype is still unknown to us. So, you know, again, I think we're going to end up with a lot of patients that have a relatively rare but high morbidity and mortality event that, in looking back on it, you could prevent, and I think you could prevent it using a potentially low-risk treatment modality. If the treatment modality was a high-risk treatment modality, I think, you know, the bar would change. So I think it's important for

us to define what we think is the amount of risk that's acceptable for the treatment, and we may very well have to define that based on aneurysm size. But, you know, defining a trial of this magnitude, I think, would lead us down a road that we could never get to the end to, end of.

DR. JENSEN: Dr. Connor, Dr. Selim, and Dr. Pilitsis.

DR. CONNOR: Right. So I think along this line we've heard a lot about this 50% this morning, and 50% of ruptured aneurysms are small and we didn't know about, but I think we never heard what fraction of aneurysms are that type. I mean, if it's 90%, then, in fact, you know, the risk is much lower than we hear, and it's like people get conditional probability wrong all the time, right? Like 100% of NBA basketball players are men, but your odds of being a man who makes the NBA is about 1 in 10 million. So, you know, it's the difference in sensitivity and positive predictive value. So saying 50% of these are small means absolutely nothing without understanding what fraction of aneurysms are small.

And people, in general, are terrible about understanding their own risk and weighing their own risk. I mean, I know women who won't have a sip of champagne at their sister's wedding, but as soon as a baby is born will drive with her cell phone all the time. That's a much bigger risk than having, you know, a little bit of champagne at your sister's wedding. And people, including statisticians, are terrible at understanding risk.

So I think to put this risk in context, particularly for small ones, I mean, I designed the PUFS trial, and we saw the PUFS trial enroll incredibly fast because these were aneurysms that there was nothing else out there to treat. So these were men and women waiting for a treatment, and as soon as a treatment became available in a trial, the trial filled up really fast. But we have many small aneurysms, potentially, where we're having this debate: is it appropriate to randomize or not? It's hard to randomize, we acknowledge that. But I think understanding more about objective performance criteria would be

beneficial, and I think, along that line, that would take a commitment from industry maybe, to put their data both from the trial in a registry so we can get these objective performance criteria but also then industry committing in the postmarket to keep making this information available so we can continue to have, you know, good data because I think we need patient-level data. We've heard about how heterogeneous this is. As soon as you say heterogeneous, a performance goal is really, really hard because who knows what a Type I error is; who knows what we're comparing to in a heterogeneous patient population? But I think if we have patient-level data, now your OPC is very specific to the population you enroll. So if you enroll harder-to-treat/easier-to-treat patients, that all gets aligned as long as you, you know, have maybe an independent group, as was discussed, come up with this OPC that's really at a patient level.

DR. JENSEN: Dr. Selim.

DR. SELIM: So I think we're all kind of hovering around the same point. I want to get beyond the design for how best to study this question, but I think it's really important, we all agreed that these are different animals. Not all these aneurysms are the same. And all these trials so far, they're lumping everything together and making it really very difficult, so even your assessment of outcome, your assessment of safety has to vary depending on these kind of aneurysms, and this is something that we haven't discussed or we haven't heard so far, so I think it's important, going forward, that that's actually what we look at.

DR. JENSEN: Okay.

DR. PILITSIS: So in terms of randomized clinical trials, I think, you know, there's some very appealing things about them in terms of the type of data that you obtain. Having said that, I think there is some difficulty in terms of long enrollment periods. The other thing is the group of patients that you're able to recruit into an RCT, you know, and thinking about people that I can recruit for certain trials, it is not always the same socioeconomic

folks that sign up for an RCT. I think there's a lack of diversity of patients oftentimes, and so I think that may also be one of the difficulties in who -- the data that's seen in an RCT and then what we see in more observational, real-world types of studies. So, you know, I think there is value for observational studies for a number of different reasons.

DR. JENSEN: Huy.

DR. DO: So I think we need to make a distinction here, unruptured aneurysm, symptomatic versus asymptomatic, and I think the symptomatic ones, I don't think there's a question there. I think we would want to treat the asymptomatic one. I think that it's possible. I think randomized controlled trials may be entertained. But what I would like to know is the -- besides myself, what do the Panel members think about what's been coming around a lot lately? Certainly, in the radiology literature is the propensity score analysis and now the OPC. How do you think that would weigh up against RCT? Obviously, you're going to say it's not good enough, but how -- is there a quantitative way you can assess that and enlighten us?

DR. LYDEN: So the propensity matching approach, and I'll yield some time to Bruce who's actually more of an expert, but the requirement is, as I understand it, that the natural history is pretty well defined and that you know precisely what to expect or -- and/or there's a group that is relatively like the treated group that doesn't get treated whether they're randomized or not. So it's an un-randomized experiment, given, but there still has to be a group that doesn't get treated that you can match against, and you have to know very well how to do the matching.

So I think at this point, if I understand what you all have -- how you all have characterized the natural history of this disease, you're not there yet, and I want to emphasize that the barriers to doing this sort of work are exactly as you all have eloquently described; these are the barriers, and they have been overcome previously in situations of

true lack of knowledge. So, again, equipoise needs to exist at the community level, and it's expected that there would be advocates who can't imagine a world where you don't treat these patients; that's expected. Then it would be expected that on the other side there are others who say but we don't really know the natural history here, so we don't know if, over a lifetime of unoperated risk, if the victims of the surgical morbidity, if it ever makes up for that, if you ever get to a point over a lifetime that the risk of the surgery is outweighed by the risk of waiting.

So I'm, you know -- I'm just saying, as an adviser, that it seems to me there is community equipoise here, although maybe not here in this room, but it seems that there's community equipoise as to whether or not this really -- the risk outweighs the lifetime benefit.

DR. PEÑA: Dr. Jensen, just a point of -- you know, to help the Panel move forward, I think it may be helpful to sort of move to the questions now that we have data questions, and that might be a good next step as we try to -- you know, we've had a discussion about trial design and now we actually have data questions for you, that might be the next best step if we can lay out these questions.

DR. JENSEN: Thank you very much. Let me just let anybody else who has anything else to say. I guess one thing I want to say is a practical matter here, and having been involved in the TEAM trial, which was taking patients who would be randomized either to treatment or to observation and having that discussion with them, the knowledge, as we can all imagine, of knowing that you have an aneurysm, even if I explain it as the risk is very small from what we know, many patients simply cannot wrap their mind around having something that might bleed and kill them 50% of the time. And I recognize that there are other disease processes that are probably similar, but what ended up happening with the TEAM trial was that patients just said, where can I go to get treated? If you're going to -- if

it's your site that's randomizing, where can I go to get treated? So just from a practical standpoint, I'm not -- I am not hopeful that doing a randomization --

DR. LYDEN: The same issue with carotid stenosis, middle cerebral artery stenosis, coronary artery stenosis, and on and on. I mean, it's a fact and it is overcome-able.

DR. THOMPSON: I would just add again, that I think in all specialties there are people who agree with your concerns. For instance, Dr. Grotta, you expressed it pretty well about the risk of -- let's just use the extreme -- very small, say, 2 mm unruptured asymptomatic aneurysms, and I think we have data that would lead us to where some studies would be useful, but I think we ought to be very careful about how we refer to the disagreement, not about cutting across specialty lines, number one; but number two, how we propose those studies be done, because we do have data about the difference in the natural history risk for unruptured asymptomatic aneurysms as dependent on size.

DR. JENSEN: One last comment, and then we should move to the questions.

Dr. Erkmen.

DR. ERKMEN: I think the idea of randomized controlled trials, they're great if they're doable and done well, but you know, the original thrombectomy trials were randomized trials and ISUIA was a randomized trial, so there's inherent deficiencies in the way those trials are run sometimes. I mean, you know, the original thrombectomy trials were negative and were randomized trials that looked at, you know, heterogeneous treatment, which is what we're proposing or would be proposing in aneurysm treatment, you know, and so just the fact that it's a randomized controlled trial does not make it the answer to the situation, which you actually, you know, made an argument against it by using the thrombectomy as an example. And I think we've talked about how ISUIA was -- that's exactly what would be proposed is looking at aneurysm treatment by size, and we found that the selection criteria bias is so strong in that, that it gave us data that, if anything, confuses the situation, not

answers it.

DR. JENSEN: One last comment, and then we're going to move on.

DR. GROTTA: So I would argue that the thrombectomy trials that were "not positive" were not negative. They told us that in an unfocused group of patients with an outdated -- with a device that didn't -- that wasn't good, that the treatment didn't work, and it made us go back and select the patient population properly and get better devices.

So, to me, when the intervention community thinks they have the right devices, I don't -- maybe this isn't the time to do it; maybe we need to wait until we have devices that we know are safe and have low morbidity. In these -- in this low-risk population, that is the ones with -- we are, of course, only talking about asymptomatic, unruptured, very small aneurysms. But I know there's equipoise because if I send -- I know which interventionist to send my 2 mm aneurysm to if I don't want them to get operated, fixed, and which ones not because there's equipoise even among the interventionist system. You know, what is the point where we need to intervene? And I just think that there's room and will probably always be room, at some point, for a randomized trial in that edge of our population.

DR. ERKMEN: But you just said you don't have equipoise because you pick who you send them to because you don't want them to get treated.

DR. GROTTA: No.

DR. ERKMEN: So you're saying that you don't have equipoise.

DR. GROTTA: No, but my point is, is I don't know. I honestly don't know, and I'm hunker-buggered as to who I should send the patient to, right?

DR. JENSEN: Okay, so we're going to move on to the questions now after that lively discussion. Okay, everybody ready?

So Dr. Loftus.

(Off microphone response.)

DR. JENSEN: Are you ready?

DR. LOFTUS: My name is Christopher Loftus. I'm Professor of Neurosurgery at Temple Medical School, and I'm the Chief Medical Officer in the Division of Neurological and Physical Medicine Devices. I served 10 years, maybe more, as an SGE panel member like yourselves, so I know what it's like to be there, and then as a consequence of that, hopefully, a happy consequence that I should come to work for the FDA, which is why I'm at this podium today.

This Panel, as you know, is about these particular questions, and the reason that it's been convened and the reason that we have written these questions as a little group among ourselves, and all the principals who have written these questions are here in this room today, is because we would like them answered by this group of experts who have been assembled for just this purpose, truly to seek information and guidance as we do daily look at these devices and make decisions about studies and events and surveillance and various things that we deal with every day.

So I think, perhaps, you may have seen one or two of these questions already, but just for the purpose of this discussion, I'm going to go through them, and we seek a clean record, so even though there's been a lot of deliberation and debate about some of these questions, we would like to get a clean record and a consensus. I will pose the question, I'll pretty much read it and not embellish upon it, and then we will ask the Chairperson to lead the discussion among the experts and present us with a consensus, which our Division Director, Dr. Peña, will adjudicate and decide whether the question has been answered to his satisfaction. So with that little set of baseline information, let me move on.

So Question Number 1 -- and if you will hearken to the heading, as I will do, of each of these, it will lead us to what we're kind of driving for in each question, and they are safety and efficacy, as you've heard all day, and then a number of other smaller things at

the end. So Question Number 1 regarding Safety: Adverse Events and Endpoints. I'm well aware that this has been discussed for the last hour, but nonetheless, we want a clean answer.

So, typically, aneurysm device trial primary safety endpoints have focused on death and major ipsilateral stroke (defined as an increase in the NIH Stroke Score by 4 points at the time of stroke event within the first year after treatment). Additional safety events, adverse events -- and perhaps we should call them serious adverse events -- or AEs that are considered in our safety assessment of new devices -- and this list we compiled:

- Access Site Issues (i.e. dissections or hematomas);
- Aneurysm Leak, Rupture, Contrast Extravasation;
- Distal Embolic Phenomena;
- Adverse Events Related to the Institution of DAPT, Dual Antiplatelet Therapy;
- Mechanical Device Failures and/or Acute or Delayed Device Migration or Embolization;
- Minor Strokes (i.e. those with a change in the NIH Stroke Score of less than 4); and/or
- Transient Ischemic Attacks

So we would ask the Panel to please address the questions: Is the AE list above complete? If not, what -- and I'm well aware that this morning we did have some epi phenomena like facial swelling and things like that, but this is not what we're talking about now. If not, what serious adverse events should be added? We've heard some, but once again, we need to get them on the record.

And Question (b): Are there any specific rates of these adverse events, either individually or in the aggregate, that would raise concerns, serious concerns, about the safety of any specific device if one device was being studied?

And to hearken back to what we heard before, this is about -- from Dr. Peña, this is mostly about clinical trials because that's really what is the question that we're asking.

DR. LYDEN: So a quick problem. The --

DR. LOFTUS: And I turn it to Dr. Jensen, please, to lead the discussion.

DR. JENSEN: Yes. Doctor.

DR. LYDEN: So the definition of minor stroke, NIH less than 4, isn't quite right. You can lose your entire PCA territory and only have 2 points on the stroke scale. You can be aphasic and only have 2 points on the stroke scale, so usually the terminology is disabling stroke rather than minor stroke or non-disabling stroke such as stroke scale less than 4, but it allows for, you know --

DR. LOFTUS: So you would suggest to replace that with non-disabling stroke?

DR. LYDEN: Something like that, yeah.

DR. JENSEN: Dr. Posner.

DR. POSNER: Yeah, I hate to say this, but the question itself, I would expand that to say during the implementation of the device and when you're following the procedure, in case you find a device that's so difficult to use that there are adverse events before it's even implanted.

DR. LOFTUS: I hear you. I defer to Dr. Jensen to lead the discussion, please.

DR. JENSEN: So Dr. Grotta.

DR. GROTTA: Okay, just to be -- so this is on the record, I'll just go through the things that I mentioned before. So I would add visual loss, which isn't really technically considered a stroke, but you can get loss of vision from occlusion of the ophthalmic artery during a procedure. I would call local thrombus formation at the site of the -- in the artery, and also an unplanned intervention, as we discussed. Add those three things to the list.

DR. JENSEN: So did anybody else have anything -- I'm sorry, Dr. Posner, I had trouble

hearing what you were saying. Could you please just repeat what you said?

DR. POSNER: Yes, I was just saying the question is 1 year after the treatment, and I was suggesting that it actually start with the beginning of the treatment in case there's an adverse event because the device is so difficult to use that you have an adverse effect during the implementation.

DR. JENSEN: So that would be considered an adverse event, the actual placement --

DR. POSNER: Exactly.

DR. JENSEN: -- of the device? Exactly.

DR. POSNER: Yes.

DR. JENSEN: So to --

DR. LOFTUS: I think, if I may just clarify. Many of the adverse events can certainly be logged and recorded at any time frame. We only mean to say that at least as currently, in our current evaluation, you know, it kind of stops at 1 year, but not to say that we have to wait that long to log the event.

DR. THOMPSON: Dr. Jensen, just to be complete again, like Dr. Grotta, we spoke about this, but I think it would be worthwhile to include current vessel stenosis where there is an intravascular device used, even if it's asymptomatic.

DR. JENSEN: So, Dr. Loftus, the Panel recommends that we add certain serious adverse events to your list. Excuse me. Do you need to --

DR. ASHLEY: I did want to add one thing to the list, which is radiation exposure. We haven't -- I mean, you know, they can be bald, they can be burned, but they also can have just too much radiation, and that wasn't on the list. And also, vessel injury is also not on the list. You can have a dissection of the intracranial vessel, you can have a whole host of things. It may be good to add it on the line with aneurysm leak, rupture, extrav, or other vessel injury, but I didn't see a specific notation of something like that.

DR. JENSEN: Anybody else have anything they want to add?

(No response.)

DR. JENSEN: Okay, so to our serious adverse events, we would like to add significant visual change. Cranial nerve palsy was also mentioned. Direct vessel injury that requires some sort of treatment or results in an injury to the vessel, such as a stenosis. Excessive radiation dose. And as to whether or not that is simply the increased dose or actual injury, it is unclear to me whether or not you're just talking about an actual number or if you're actually talking about injury such as hair loss or scalp injury. That's where I think the radiation dose should go. And increased difficulty or complexity of the use of the device that requires some sort of adjunctive procedure. And thrombus formation. So these are the things that have been added. Does that satisfy the FDA?

DR. PEÑA: Thank you. That satisfies. And just, you know, to be absolutely crystal clear, death and stroke are part of that list, although they're not on the table.

(Off microphone comment.)

DR. PEÑA: Just to be absolutely crystal clear, death and stroke, which is in the content of the question, is also included in that table as a serious adverse event.

DR. JENSEN: So death and stroke are our primary safety endpoints; we do agree that those are our primary safety endpoints.

For the Panel, are there specific rates of these adverse events that would raise serious concerns about the safety of any specific device?

DR. GROTTA: Dr. Jensen, could I just -- I'm sorry, just on this last issue, not to belabor it, but Dr. Lyden mentioned disabling -- non-disabling as a minor stroke. I think that the flip side of that is I don't think a stroke has to be an NIH Stroke Scale score of 4 to be considered a serious adverse event. I think if it's a disabling stroke, regardless of the NIH Stroke Scale score, so someone could have loss of function of their hand, for instance, as a

result of a stroke or something that would cause an NIH of 3 but still be disabling to them.

DR. JENSEN: So is your suggestion that we change the wording so that the primary safety endpoint is death and just major disabling stroke --

DR. GROTTA: Yeah.

DR. JENSEN: -- as opposed to giving it an NIH Stroke Scale score?

DR. GROTTA: That would be my suggestion.

DR. JENSEN: Whereas with the --

DR. GROTTA: Well, I would say that if it's more than 4 points, that would be -- that would be, but I think it could be a disabling stroke with less than 4 points as well, would still be considered. So I would word it as an NIH Stroke Scale score by 4 points or disabling, something to that effect.

DR. JENSEN: Simply add "or disabling stroke."

DR. GROTTA: Right.

DR. JENSEN: Is the Panel in agreement with that?

(Off microphone response.)

DR. JENSEN: Okay. And that we would change the minor ipsilateral stroke to actually non-disabling stroke, is that --

DR. PEÑA: Thank you.

DR. JENSEN: Um-hum. So part (b) of this question: Are there specific rates of adverse events that would raise serious concerns about the safety of any specific device?

Dr. Thompson.

DR. THOMPSON: I would suggest that the suggestion made by our professional group, Dr. Mocco, I thought, for unruptured aneurysm is very reasonable, which is unruptured aneurysm, I think it was greater than 10% stroke rate a year later; after that seems reasonable. I'd like to hear what others think.

(Off microphone comment.)

DR. DO: I think that was mRS 3 to 6; is that right, Dr. Mocco?

DR. JENSEN: Is Dr. Mocco still in the audience?

DR. LOFTUS: What we're asking here is a percentage, you know, the consensus of the Panel about what particular rate of these adverse events and the ones that were added onto the list, either singly or in the aggregate, would raise enough concern that the safety of a specific device in a trial would be brought into question.

DR. GROTTA: So we're talking about total aggregate incidents, not of any one of these?

DR. LOFTUS: Well, either way. Either way. I mean, this is about patient safety, Dr. Grotta, as you know.

DR. JENSEN: So Dr. Erkmen.

DR. ERKMEN: I think it would be really hard to set a hard line for -- because of the disease, you know, we're talking about varied disease processes, ruptured, unruptured, but all these studies would presumably have a data safety monitoring board, and I would defer to them to look at safety issues within the trial as far as when a trial should be stopped and not set a defined hard mark.

DR. GROTTA: Right, but --

DR. JENSEN: Dr. Ashley.

DR. ASHLEY: So I think they're all very important, but I think it may be difficult for this Panel to define each one with any reasonable numbers. I think each one of those things needs to be defined based on a systematic review of the literature that has to do with that particular thing, so then you can come up with how many access site problems are too many and then you can say that number; how many, you know, vessel -- so I think each one probably does have a number that we could potentially agree upon, but I think we

would need some data to be able to do that in a reasonable way.

DR. JENSEN: Dr. Pilitsis, do you have anything to add? Anything to add? Sorry.

DR. PILITSIS: Sorry. You know, I think in terms of -- I agree with Dr. Ashley. It's hard to come up with those numbers, and it's hard, especially in ruptured aneurysm cases. In the unruptured aneurysm cases, I do think that greater than 10% for death or major stroke would be of some concern.

DR. JENSEN: Dr. Connor.

DR. CONNOR: No comment.

DR. JENSEN: Dr. Selim.

DR. SELIM: Oh, well, I go back to the unruptured cases, and I think 10% would be too high for unruptured cases. So, yeah, it's hard to come up with a definite number, but I think we'll have to split them between ruptured and unruptured cases, and maybe I would go even with 3% for unruptured cases.

DR. JENSEN: Dr. Thompson.

DR. THOMPSON: I went back to look at that, and you are correct; the data was that in the ISUIA, 1-year modified Rankin Scale 3 to 6 was 6.6 and then 7.1 for clipping in a baseline population of 0 to 2, and so he suggested that greater than 10% would be reasonable, and I think that sounds entirely reasonable.

UNIDENTIFIED SPEAKER: Can I clarify? That's a misinterpretation of the society --

DR. JENSEN: So I would like to finish actually talking to the Panel.

Dr. Dorsey.

DR. DORSEY: I would agree with the earlier comments by Dr. Erkmen, and I can't see your name there, but I think it varies greatly on the risk of aneurysm, especially asymptomatic ones.

DR. JENSEN: Dr. Ovbiagele.

DR. OVBIAGELE: Nothing to add. I agree with what's been said.

DR. JENSEN: Ten percent is what you said?

DR. OVBIAGELE: I think it's hard to determine a particular, but I also agree with Dr. Selim that you definitely have to distinguish between small unruptured and the rest, yeah.

DR. JENSEN: Dr. Do.

DR. DO: I think it's very difficult to give specific rates, for me to give -- it's impossible for me to give the specific rates.

DR. JENSEN: Dr. Grotta.

DR. GROTTA: Well, I do think you can get specific rates. If we're talking about the absence of the need for a randomized trial, then clearly we must know something about the natural history. So, I mean, we have data on unruptured -- I agree, we have to distinguish between unruptured and ruptured aneurysms, but for the unruptured aneurysms, we have a general idea of what the yearly rate of serious events, stroke and death, is for unruptured and ruptured aneurysms of various sizes.

It seems to me that you can project what that rate is and figure what the chances are; if the periprocedural risk is above a certain amount, that the intervention could never, ever be superior to the natural history. So, I mean, we do this all the time when we do stroke prevention trials, and we figure out what is the acceptable complication rate of the treatment. So I do think that an assessment could be made. I can't tell you right off what it would be because I'd have to look at the actuarial curves, but it would seem to me that we have the data to determine that.

DR. DO: To clarify myself, what we're trying to answer right now is are there specific rates, and I'm just saying that -- I'm not necessarily disagreeing with you, but you also agree with me that you can't give the specific rates right now.

(Off microphone response.)

DR. DO: But I think the recommendation is to go back to the literature and tease those out.

DR. JENSEN: Exactly. So Dr. Tsimpas.

DR. TSIMPAS: So, again, I agree with pretty much everything that was said. I think we should distinguish between ruptured and unruptured cases, and actually, I do agree with Dr. Grotta, that we should look back into the literature, but I think 3 to 5% for unruptured cases and 10% for ruptured cases seem very reasonable to me.

DR. JENSEN: So, Dr. Loftus, the Panel believes that it is difficult to give you individual rates of adverse events that would raise concern such that it would alter the trial; however, the group does believe that there is clearly a difference between the rate for ruptured aneurysms versus unruptured aneurysms. Most of the Panel is unable to give you an actual number, although greater than 10% for ruptured aneurysms and 3 to 5% for unruptured aneurysms has been offered by some of the Panel members, and that the Panel feels that to find specific rates, we should look more closely to the literature to see what the rates have been in other major trials. Does that help satisfy?

DR. LOFTUS: Dr. Peña.

DR. PEÑA: So just to clarify, the 3 to 10% numbers, is that referring to a specific SAE, or is that for the sort of overall --

DR. JENSEN: That was for the primary safety endpoints, I believe.

DR. PEÑA: Okay.

DR. THOMPSON: Actually, it was for unruptured intracranial aneurysms, the 10%.

DR. JENSEN: Well, there was 10% for --

DR. THOMPSON: For unruptured intracranial aneurysms, was the number that was from Dr. --

DR. ERKMEN: I believe the question is, is it for any individual adverse event, or is it for everything compiled together; is that correct?

Is it an aggregate risk or for any individual or just for the primary outcomes?

DR. LYDEN: Exactly. It's for the primary outcome, correct?

DR. JENSEN: So my understanding, from the Panel, was that we were talking -- that we could not agree upon set numbers for each individual adverse event; is that correct? Yes.

DR. ERKMEN: Yes.

DR. JENSEN: And the Panel agrees that there is a difference between the trigger number for ruptured aneurysms versus unruptured aneurysms in terms of a threshold, correct? Okay. And some of the Panel members here felt that for unruptured aneurysms, 3 to 5% was an appropriate number, correct?

DR. ERKMEN: For the aggregate or for just the primary outcomes?

DR. JENSEN: For the primary safety endpoints.

DR. ERKMEN: For the primary.

DR. JENSEN: Is this correct?

DR. LOFTUS: As I understand it, may I just -- that's for the aggregation of the two defined primary safety endpoints and this other list of SAEs as embellished by the deliberations of the Panel; is that a correct understanding as you see it?

DR. JENSEN: No, my understanding is that we are willing to give you -- some of us give you a number for the two primary safety endpoints, but we are unable to give you an actual number for each of the individual adverse events.

DR. PEÑA: That is acceptable to --

DR. JENSEN: That's acceptable?

DR. LOFTUS: That's fair.

DR. JENSEN: Is that fair?

DR. LOFTUS: Thank you very much. The question was answered.

DR. POSNER: I have a question. You've differentiated ruptured versus non-ruptured. You haven't differentiated by size, and I would think that you would tolerate more adverse events if they occurred in trying to repair a large aneurysm than a small aneurysm, just because of the statistics of which ones are more likely to burst. Just a question from a patient.

DR. JENSEN: So Dr. Ashley.

DR. ASHLEY: Two things. I think size is an issue to consider. I didn't say what you thought I would say. But it's going to be very difficult to define several different things, again, in this forum. And then the issue about this 10%, I just want to clarify for myself, one issue was 10% with respect to a change in the mRS score, so is that what we're saying, or are we saying 10% of the total number done, right? Because I think there's some confusion that some people are saying 3 to 5% for unruptured and then 10% for ruptured, or 10% for unruptured based on if you do 100 cases, whereas I think that 10% that Dr. Thompson was talking about had to do with mRS score change, change in it.

DR. THOMPSON: Correct.

DR. JENSEN: Yes, that --

DR. THOMPSON: And I can read it specifically.

DR. JENSEN: But that is not -- we were not discussing mRS score, right? We were discussing --

DR. THOMPSON: Actually, I misspoke initially, but mRS is the correct modified Rankin Score of 3 to 6 in an original 0 to 2 modified Rankin Score population; a change aggregate of more than 10% would raise a serious concern. That's how it was defined.

DR. ERKMEN: I believe modified Rankin is a separate question --

DR. LOFTUS: When we get there.

DR. ERKMEN: -- that we will get to. But I mean, I think this is why it's really hard to set a hard threshold number because we're talking about lots of different things, and that's why, you know, the DSMB should be assigning these percentages for the particular study. If you're studying small ruptured intracranial aneurysms, it may be a very different number than if you're studying giant ruptured aneurysms, and that's why I think giving a number right now is difficult and probably ill advised.

DR. JENSEN: But I believe the mRS question is the second question here, is it not?

DR. LOFTUS: We're going to get there.

DR. JENSEN: Okay.

DR. LOFTUS: Honest. Are you satisfied, Dr. Peña?

DR. PEÑA: So why don't you summarize that, Dr. Jensen, just for clarity; 1a is you've given a list, there was consensus; 1b, there was not specific consensus around specific adverse event rates, but a subset of the Panel believes there could be a rate of 3 to 5% for the primary endpoint that's in the content of the question of one -- of the first question. Is that --

DR. JENSEN: So --

DR. PEÑA: -- accurate?

DR. JENSEN: -- I guess the question that we hadn't answered there was we discussed unruptured aneurysms as saying 3 to 5%, looking at the primary safety endpoints, and what was the discussion around ruptured aneurysms in terms of a percentage, because I think we got off on the 10% that you were talking about, which was actually separate.

So, Panel members, does someone want to throw out a number that they think is appropriate based upon experience in trials?

DR. ERKMEN: I would vote no numbers.

DR. ASHLEY: I think we can find it out. I think we can agree that we should find it out, but to say it now may be -- you know, maybe give us a number we're not going to use in the future.

DR. PILITSIS: I agree, no number on the ruptured.

(Off microphone comment.)

DR. JENSEN: Um-hum. So we're not going to give you a number on the ruptured.

DR. PEÑA: That's okay, too.

DR. JENSEN: Okay.

DR. LOFTUS: All done?

DR. JENSEN: All done with that one.

DR. LOFTUS: Question Number 2, Safety again. Safety question, Adverse Events and Endpoints.

So the modified Rankin Scale has often been incorporated as a secondary safety endpoint, the first being the death and the NIH Stroke Score change. Can the modified Rankin Scale at 1 year also be a potential primary safety outcome measure for all endovascular aneurysm device trials? If yes, what magnitude of decline in the mRS and for what percentage of treated subjects with a decline in the mRS at 1 year follow-up would raise serious concerns about the safety of the device? If no, what alternative primary safety outcomes are possible, and again, for what duration of time?

DR. JENSEN: So let's start with the other, other end of the room and take the first portion of that question as whether or not the mRS should be considered as a potential primary safety outcome measure for all device trials. So this is a yes or no.

Dr. Tsimpas.

DR. TSIMPAS: I think it's a good start.

DR. JENSEN: Dr. Grotta.

DR. GROTTA: I do for unruptured aneurysms. I don't for ruptured aneurysms. And for unruptured aneurysms, since -- I think getting a baseline Rankin score is notoriously difficult, but I think it can be done in patients with unruptured aneurysms, and if so, then I think a change of 1 point or more in the Rankin Scale would be an adverse outcome in a patient with an unruptured aneurysm.

DR. JENSEN: Dr. Do.

DR. DO: I would agree that you have to make a distinction between ruptured and unruptured. You can't do it with ruptured aneurysm, I agree. For unruptured, I think an mRS of greater than 2, I think, would be -- 2 or greater because then you're dependent in your activities of daily living.

DR. JENSEN: So you're considering 2 a dependent disability or -- because 3 to 6 is -- isn't 3 to 6 usually considered dependent disability?

DR. DO: So for unruptured --

DR. JENSEN: Yeah, we're talking about unruptured aneurysms.

DR. DO: Unruptured, if the patient is 0 to 1, and if they go to a 2, I think that's --

DR. JENSEN: So a change in 1 point?

DR. DO: Yeah.

DR. JENSEN: Dr. Ovbiagele.

DR. OVBIAGELE: So I agree. I agree it has to be dichotomized, I think. I know we're now making a distinction between unruptured and ruptured. I would love to focus a little bit more on small unruptured, but fair enough, between a ruptured and unruptured, I think the focus should be on unruptured for mRS at 1 year. Now, I know that, of course, the representatives of industry raised this concern about how far out a 1-year measure might be from the index event itself, which is a valid concern. So the issue I raised earlier also stands as to whether we could consider an earlier time point before 1 year, but I definitely

think for unruptured, we should do an mRS 3 to 6 cutoff. The issue really would be whether it should only be at 1 year or we could consider an earlier time point.

DR. JENSEN: Okay. Dr. Dorsey.

DR. DORSEY: I agree with the comments just made.

DR. JENSEN: Dr. Lyden.

DR. LYDEN: Yeah, 0 or 1, or 0-1 or 2 makes sense for the asymptomatic unruptured aneurysm patient. With respect to the concern that at 1 year the patient population accumulates non-stroke disability, that's true, and in ischemic stroke studies and hemorrhagic stroke studies, the patients are typically older than this population, that's even more of a concern, and yet treatments do have an effect that outweighs the accumulation of non-stroke-related disability. So I think 1 year is feasible since this population is quite a bit younger than the ischemic stroke population.

DR. JENSEN: Dr. Thompson.

DR. THOMPSON: So yes for unruptured intracranial aneurysms, no for subarachnoid hemorrhage.

DR. SELIM: I think it should be done at 6 months and at 12 months, and I think, for the unruptured one, the change from 0 to 1, I think that's a problem. Therefore, the unruptured one, it's a little bit more challenging, I think. I probably would go to 3 to 6. I would suggest, for the unruptured ones, having also another measure with something to look at quality of life or cognitive function that we're not looking at.

DR. JENSEN: Dr. Connor.

DR. CONNOR: I would agree with no for ruptured. I think I'm less likely to agree on yes for unruptured. It seems that death and ipsilateral stroke are already primary safety outcomes, so this would only give us information for changes in mRS unrelated to stroke. I think I agree with Ms. Pugh from earlier that says this is sensitive but not specific in those

cases. And given the size of these trials, I think I would be more likely to keep these as secondary but have information on any change in mRS of maybe more than a point or anything that drops to below a 2 so we could try to understand the cause for this, because I do think it's -- many of the reasons for these may not be specific and may not be related to the procedure. So I think understanding the nuance of these changes would be more important than just making a simple primary outcome.

DR. PILITSIS: Agree on ruptured. On unruptured, I think Dr. Connor just raised some points because I was struggling with the last question, which was if you say no, what is your alternative, and I think you just kind of answered that, that all the information would be gathered in the stroke and death data, or a lot of it would. My concern with the mRS is first, the 1 year aspect, I do think that's too long, especially for the older patient population. I think 3 months is likely too short. And I worry that if there is -- if you consider 6 months or a year and then you do a post hoc analysis later on, older patients are going to be at a disadvantage, potentially, later on in receiving the therapy because they're more likely to have that mRS change that takes it out of context.

DR. JENSEN: Dr. Ashley.

DR. ASHLEY: I think it should probably still be a secondary endpoint. I agree with recording it and following it serially for both groups really. I also agree that it's probably more meaningful for the unruptured group, but I think, you know, a 6- and 12-month time point, but it probably should not be a primary endpoint.

DR. JENSEN: Dr. Erkmen.

DR. ERKMEN: I would ditto everything Dr. Connor said. I think the stroke and death really captures most of what we want, and I wouldn't include mRS as a primary outcome measure, definitely not in subarachnoid hemorrhage. Whether it's a secondary outcome measure in unruptured is -- you know, I'm okay.

DR. JENSEN: Okay. So to the FDA, the Panel has -- is rather split on whether or not the mRS should be in use as a primary endpoint and instead seems to feel that it should remain as a secondary endpoint; that it does not apply to patients with ruptured aneurysms but can apply to patients with unruptured aneurysms; that the 1-year endpoint is perhaps too far out and that data should be collected at 6 months and 1 year. And I think that answers most of those points.

Of the people who said yes, that it should be used as a primary safety outcome, the magnitude of decline in the mRS, people thought, and correct me if I'm wrong, that a 1- to 2-point change was considered significant, and half of the group felt that the primary endpoints of death and major stroke were the better endpoints and that the mRS should remain as a secondary endpoint.

Does that satisfy the FDA?

DR. PEÑA: Yes, thank you.

DR. JENSEN: And did I misspeak for anybody?

DR. POSNER: If I might add, when you do the analysis of this, I would compare that to what change in these scores occurs just with plain old general anesthesia at the age of the patient. So rather than giving you a number, I think when the data come in and they have a lot of adverse events, they may not be any more than the effect you would get just doing general anesthesia in someone of that age without having to put in a device. So I think that's part of your analysis for the FDA to look at, not to just take a number and say it's magic and say it's a bad thing.

DR. JENSEN: Thank you.

DR. LOFTUS: Thank you. Move on?

DR. JENSEN: So we have answered Question 1 to your satisfaction?

DR. LOFTUS: And 2.

DR. JENSEN: And 2.

DR. LOFTUS: Questions 1 and 2, yes.

DR. JENSEN: Okay, good. So I've just been told this is probably a good time to take a break, so we will have a 15-minute break; is that correct?

(Off microphone response.)

DR. JENSEN: What, pardon?

MS. ASEFA: Fifteen.

DR. JENSEN: Yeah, a 15-minute break, and then we will reconvene.

(Off the record at 3:39 p.m.)

(On the record at 3:52 p.m.)

DR. JENSEN: Okay, so let's go ahead and move on with the Panel questions. I think we've got most of the people here that we need.

So moving on to Question Number 3: Considering the AE list above and any additional AEs specified in response to question #1.a., what patient characteristics (e.g., malignancy, advanced age, aneurysm size) justify foregoing treatment for an aneurysm that would otherwise be considered for treatment?

So let's start over with Dr. Tsimpas.

DR. TSIMPAS: I'm sorry. So, in my opinion, life expectancy of a year should be entertained. Advanced age should also be entertained, and we can -- that is a little arbitrary because the general population is actually getting older, but I think, in my opinion, a good guesstimate would be 85 years because as we get older, even if we live longer, our vessels, they're not as robust anymore; there's a little vascular tortuosity, plaque formation that can increase the risk. And malignancy, I would say yes, as well, in conjunction with life expectancy of a year.

DR. LOFTUS: Dr. Jensen, can I just embellish on this? What we meant to say in this

question was as you read it, but also aneurysm size meaning small, right? Meaning how small --

DR. JENSEN: How small.

DR. LOFTUS: -- would seem unjustifiable.

DR. JENSEN: Correct. So just to --

DR. LOFTUS: So age, large -- size small, malignancy as you wish. And anything else.

DR. JENSEN: So I guess one question is how do we define small, because we've seen several definitions of small.

DR. LOFTUS: Well, that was the question.

DR. JENSEN: We've seen 10 and less, 7 and less, 5 and less. And we don't have data from ISUIA on 1 to 2 mm, is my understanding, so that's ultra-small. So do we have any -- do you have any opinions about size of aneurysms?

DR. TSIMPAS: I would say you, again -- the patient overall, but if the life expectancy is marginal and the age is older, I would say 5 mm.

DR. GROTTA: So off the top of my head, if it's less than 7 mm, I'd say the patient has to have a 5 for unruptured, they'd have to have a 5-year expectancy. And I would add excess bleeding in patients who need stent retrievers and other things that require antiplatelet therapy; I think you should have to assess the patient's bleeding risk. If it's somebody who can't take an antithrombotic agent, then that would be something that has to factor into your decision making.

DR. JENSEN: Dr. Do.

DR. DO: I don't have anything other to add, then, to what Drs. Tsimpas and Grotta added, but regarding aneurysm size, I would think 3 mm or less.

DR. OVBIAGELE: Yeah, I heard the latter part of Dr. Grotta's discussion, which I fully agree with. I also think size should be a consideration, and while 3 mm is, in some ways

arbitrary, I concur with that as well.

DR. JENSEN: Yeah, sorry. Three is --

DR. OVBIAGELE: Millimeters.

DR. JENSEN: -- your cutoff?

DR. OVBIAGELE: Yes, I concur with that, even though it is, in many ways, somewhat arbitrary.

DR. THOMPSON: A question. The question about these three risk factors, are they for the purpose of a study or, say, some type of approval specifically, either HDE or PMA?

DR. LOFTUS: You know, it's an excellent question, Dr. Thompson, and I'm sorry it wasn't spelled out more carefully. I think, along the lines of what Dr. Peña said in the preamble, you should assume that everything here today is for the purpose of allowing us to better deal with clinical trials, and then we're not really here to deal with the practice of clinical medicine. That's not the purview; am I correct? So I would assume that you should say, well, we're looking basically for exclusion criteria, exclusion and/or inclusion criteria for clinical trial design; do you agree?

DR. THOMPSON: Okay.

DR. PEÑA: Correct. And I think we're looking for the Panel's advice to the Agency on that, and if it wants to share other information, too, we'll accept that, but we're looking at trials.

DR. THOMPSON: Or for the process of labeling and the PMA approval. The reason I just think that it's so important to be careful about what we say, because I think generalizations apply to the vast majority of those, you know, two-thirds in the middle of the bell curve, and I kind of pointed that out this morning, I think, to Dr. Dion. There are exceptions for very small aneurysms. If you ask neurosurgeons about 2 mm dorsal wall aneurysms, they'll say those are potentially fatal and very dangerous. Now, how often do

they occur? Very rarely. But are they something that we should think about when we're making generalizations? Absolutely. We have to be aware of the exceptions. So that being said, I think for the purpose of either a trial or for labeling for these devices when they're under examination for 2 to 5 years after, say, postmarket approval, I think, if you ask me that, then I'd say I would limit it to greater than, say, 3. So 4 mm or above on one size.

DR. LOFTUS: And if I may embellish that -- and a saccular aneurysm, then.

DR. THOMPSON: For saccular aneurysm, yes.

DR. LOFTUS: Saccular aneurysm. I think that's fair.

DR. THOMPSON: And then as far as malignancy goes, obviously we all know that depends greatly on the malignancy. I mean, if you have a basal cell carcinoma, I think that has absolutely nothing to do with your -- whether you should be treated or not. And then I think Dr. Tsimpas made a very good point about age, though. Age is not just about your life expectancy; it's about the fragility of your vessels when you reach age 85. Even if you have, you know, 10 or 12 years, whatever that was, on the actuarial tables, you still aren't -- the operative risk is still not the same as it was, say, at age 65.

DR. JENSEN: Dr. Selim.

DR. SELIM: Okay, I agree. Malignancy by itself, probably we should not use it. So I would go with the expected survival, probably at least 3 or 5 years after the procedure.

DR. JENSEN: Um-hum.

DR. SELIM: For age, it's difficult to come up with a cutoff. I really don't know, but it doesn't make sense, for example, someone 85 or 90 and it's unruptured; again, we get into the unruptured and ruptured story. For size, I think 3 I would feel more comfortable with.

DR. SELIM: Dr. Connor.

DR. CONNOR: I'm kind of glad Dr. Thompson asked that because I was really confused by the question, too. I think I'm still a little confused. I mean, if it goes to who

would write exclusion criteria for a trial, I feel like I would leave it up to sponsors in negotiation with FDA, only because, you know, a sponsor's not going to want to include anyone with a relatively short life expectancy anyway. And given the described heterogeneity of these patients, it seems like it would be more relevant left to, you know, an individual trial basis. But to me, that again goes back to maybe the need for, you know, an OPC or something pre-specified to identify even what the efficacy performance goals would be, given the heterogeneity of these patients.

DR. PILITSIS: You know, I think, in terms of -- again, this is thinking about inclusion and exclusion criteria, so I feel comfortable saying, you know, if life expectancy is less than 1 year, probably those patients should be excluded. I'd defer on commenting on the other factors.

DR. ASHLEY: I think one part of this question that's assumed is that we are talking about unruptured aneurysms, because some of these things, such as size, may not be an important question with a ruptured aneurysm because you're going to fix it. I think a year is a good time point for life expectancy because it kind of correlates with some of the data that we're going to obtain. We want it at a year.

And malignancy, I agree, you need to know what kind of cancer, and I think you get back to life expectancy if you have a malignancy but it's not going to kill you in less than a year. I think that may be okay.

And then the issue of age, I think, is really a proxy for the angiographic appearance of the vessels, and there have been some studies that actually look at calcification and tortuosity and other factors to help us decide whether or not we think the vessels are safe or not safe. And so you may have an 80-year-old with young looking vessels, and you may have a 60-year-old with awful looking ones. So if we're just going to pick a number, 80 may be a good age, but I think, in fact, more detailed specification of what we're looking for on

the angiogram in terms of calcification or tortuosity may be a better way to define that aspect.

DR. JENSEN: Thank you.

Dr. Erkmen.

DR. ERKMEN: I think life expectancy of greater than a year is appropriate, and malignancy doesn't matter because it's covered by life expectancy. I would caution us giving a hard age because I think age is a physiological issue, not a chronological issue, and I think we've all seen 80-year-olds who are healthier than some of our 50-year-olds in the clinic, and you know, a 50-year-old with renal disease, coronary disease, and you know, two amputations is probably a higher risk patient than the 80-year-old who exercises every day, so I wouldn't put a hard number on age. And the same with aneurysm size, you know, there's so many factors that go into looking at an aneurysm. You know, if you wanted to use 2 mm with the caveat of the carve-out with the blister aneurysms, you know, then 2 mm would be, you know, if we have to have an absolute cutoff.

DR. SELIM: Dr. Posner.

DR. POSNER: Yeah, along that same line, I would go for physiological age and anything that's connective tissue vascular disease, like Marfan's or diabetes, hypercholesterolemia, what have you. And so I would take a look at what the vessels look like, and you've already addressed that.

DR. JENSEN: So to the FDA, the Panel has opinions based upon the three different topics that you have expressed here. First, in terms of malignancy, it is felt that 1 year would be an appropriate cutoff point of life expectancy. In terms of advanced age, the Panel cannot give you a definite age because they feel that a lot of that has to do with actual vascular age plus chronological age, although 80 to 90 has been mentioned, but there's been no specifics. In terms of aneurysm size, it appears that the Panel is discussing

this primarily with unruptured aneurysms, and there has been a range given everywhere from 7 mm down to 2 mm, with the majority feeling that 3 mm or smaller would be the size where you could justify foregoing treatment for an unruptured aneurysm of that size in a trial situation.

Does that answer the FDA's question?

DR. PEÑA: Yes. And just a point of clarification, because this came from the morning. Are there clinical guidelines for aneurysm treatments that FDA would like -- the Panel would like to make sure to share with the FDA? Just to, you know --

DR. THOMPSON: Yes, there are.

DR. JENSEN: Yeah.

DR. LOFTUS: May I point out that Dr. Thompson authored those guidelines?

(Laughter.)

DR. ERKMEN: Can I also clarify that all -- I think all of those primaries are in the unruptured state. Is that correct, for the Panel? I mean --

DR. JENSEN: Yes, I think --

DR. ERKMEN: There aren't very many ruptured aneurysms that we'd decide not to treat?

DR. JENSEN: Correct.

DR. THOMPSON: Yeah. Just to be clear, there are guidelines for unruptured and ruptured aneurysms. And also, I thank you, Dr. Loftus for that note, but actually, the group of individuals were 15, including neurosurgeons and neurologists, radiologists, and epidemiologists, that put those guidelines together. Thank you.

DR. JENSEN: So let's move on to Question 4 under Effectiveness Measures.

DR. LOFTUS: Yes, thank you. So we switch now from safety to effectiveness, okay, and once again, you've heard some of this, but let's go through it once again for a clean

record.

Typically, intracranial aneurysm device trial primary effectiveness endpoints have focused on the percentage of subjects who achieve a Raymond Classification I (complete 100% occlusion) -- just to be redundant -- without significant parent artery stenosis (i.e. > 50%) or retreatment, need for retreatment at 1 year post-procedure. Please address the following for us:

a. Do you consider the Raymond classification scale to be the standard to address effectiveness for ALL endovascular intracranial aneurysm treatment devices? If you do not consider the Raymond classification scale to be standard, please identify an alternative well accepted assessment(s) to adequately assess effectiveness for ALL intracranial devices, meaning -- you know the classes I'm talking about: flow diversion, endosaccular, or the -- I don't quite know the term for them, but somebody said intrasaccular flow diversion this morning, the latest class.
b. Many studies have used the Raymond -- as we said, many have used the Raymond scale. If the Raymond scale is used, is Raymond II (or higher) classification a satisfactory outcome for aneurysm patients with unruptured aneurysms? And is Raymond II (or higher) a satisfactory outcome for aneurysm patients with ruptured aneurysms?

DR. JENSEN: Okay, so let's start over on this side. Dr. Posner, for Question (a), do you consider the Raymond classification scale to be the standard to assess effectiveness for all endovascular intracranial aneurysm treatments?

DR. POSNER: Yes, I'm not an expert. I would refer to the horrible slides that were presented to us with all of the Raymond data this morning and all the discussion that the experts have done on that, and I think you guys got it right this morning. So I will defer to

the experts on the Panel.

DR. JENSEN: Dr. Erkmen.

DR. ERKMEN: I think the Raymond classification is very good for coiled aneurysms and should continue to be used for that, and Classification I or II is a satisfactory outcome in unruptured or ruptured aneurysms. I think for flow diversion, I think we've talked a lot today about having a binary classification system for that, that's separate from Raymond, which I think is appropriate. And I think the newer devices, I would say, we'll have to go, you know, as they're developed, but with the intrasaccular braided devices, there may be appropriate alternative classifications like the one classification for those types of devices.

DR. JENSEN: Dr. Ashley.

DR. ASHLEY: I agree.

DR. PILITSIS: I agree. I'm just hoping that some of the Panel can comment on the idea of near complete occlusion and whether that would be considered a Raymond I or whether we needed to talk further about that.

DR. CONNOR: Yeah, I agree with Dr. Erkmen. I mean, I think the thing to keep in mind, as you just said, that really all these are really just proxies or biomarkers for risk thereafter, and it sounds like, you know, what may be a risk after -- for instance, Pipeline is different than the way the vessel looks after a coil in terms of, you know, a little bit of remaining aneurysm, that sort of thing. So I think that the key is probably to quantify the risk afterwards, if we're going to use any of these as biomarkers in terms of efficacy outcomes.

DR. SELIM: I'm not really aware of an alternative, so I agree that we should be using it. And I think I or II probably is good.

DR. JENSEN: Okay. Dr. Thompson.

DR. THOMPSON: So I would agree with what Dr. Erkmen and Dr. Connor said, that I

think the first question is that the Raymond scale is not appropriate for all devices. It probably is for intrasaccular devices, but for flow diverters it's probably, as Dr. Connor just pointed out, a proxy that doesn't really represent the subsequent risk.

DR. JENSEN: But do you agree that you can use the Raymond classification for flow diverters in a binary fashion, either --

DR. THOMPSON: Yes.

DR. JENSEN: -- it's completely gone or it's not?

DR. THOMPSON: Yes.

DR. JENSEN: Okay, thank you.

DR. LYDEN: I agree with that, and I want to emphasize the need for data after these devices are placed, and only time and observation will tell which of these definitions are the best.

DR. DORSEY: I defer to my colleagues.

DR. OVBIAGELE: I also have nothing to add. I can't provide any other sophisticated input here.

DR. DO: So I agree with all the points that have been said about intrasaccular devices using the Raymond I and II, and for flow diverters, a binary system; either it's there or it isn't there. But my problem is with the intrasaccular flow diversion. I think we saw a slide by one of the -- I think Dr. Fiorella showed where the morphology mirrors that of the device itself, and I don't know what to make about that. So I don't know if that's up for further discussion, but for intrasaccular flow diversion, I don't have an answer.

DR. JENSEN: That's a perfectly appropriate response.

DR. GROTTA: I agree with everything that's been said. I just want to point out we're talking about the follow-up arteriogram and not the time of the procedure.

DR. JENSEN: Correct.

DR. TSIMPAS: I agree with everything that's been said.

DR. JENSEN: So for the FDA, we have -- we agree that the Raymond classification should be the standard to assess effectiveness for all the current devices, i.e., intrasaccular, coiling, stent coiling, and endovascular and flow diversion. We are uncertain whether or not this scale would be appropriate for some of the newer endosaccular flow diverters, but we also agree that there's no other scale currently at this time that we would prefer to use besides the Raymond. So that, I think, answers Number 1. Or number (a), letter (a).

In terms of (b), for saccular aneurysms, it is felt that Raymond classification of I and II is a satisfactory outcome for aneurysm patients with unruptured aneurysms, that Raymond I or II is also satisfactory for ruptured aneurysms. But I guess one thing that we discussed earlier on was that this is for the initial findings, and further treatment of the aneurysm or needed treatment will actually depend upon what the trend is for the follow-up studies. So as a starting point, yes, I or II is appropriate for both ruptured and unruptured aneurysms. For flow diversion it is -- must be a one. Does that --

DR. PEÑA: Thank you.

DR. JENSEN: Okay.

DR. ERKMEN: Can I just add? Would we add that for Raymond II that we would want demonstrated stability at II?

DR. JENSEN: So that's -- I mean, in terms of the question, we really didn't get into the follow-up, but yes, that is the point, is that the expectation is that we are looking for Raymond II stability.

DR. LOFTUS: Thank you very much. Question 5, another Aneurysm Occlusion and Effectiveness question. This hearkens back to the day, really, before the Raymond scale, and so judge this -- take that for what you will, when we went with percentages.

For device effectiveness, what percent of morphological occlusion is acceptable, and

in what percent of patients should this result be achieved?

DR. JENSEN: Okay.

DR. LOFTUS: Or, frankly, I might ask is it no longer applicable.

DR. JENSEN: I'm sorry, say that again?

DR. LOFTUS: You know, I don't want to embellish the question officially, but is it even applicable in the current Raymond scale era?

(Off microphone comment.)

DR. JENSEN: So I think we are in agreement that the Raymond scale doesn't really look at a percentage of occlusion. We feel that I is 100% occluded and is therefore applicable for flow diversion, needs to be 100% occluded, but for neck remnants and trying to determine what the percentage of that is depends upon what the size of the aneurysm is in relationship to the neck to get a percentage, or we've also discussed how what we're really more concerned with Raymond III's, is the amount of exposure of the wall as opposed to the -- to inflow as opposed to the actual percentage.

So I will go around the table, but does anybody here feel that we should be giving an actual percentage for morphological occlusion that is acceptable? Are we willing to continue to simply use the Raymond scale based upon completely occluded neck remnant and residual lumen against an unprotected wall? Does that --

DR. TSIMPAS: So --

DR. JENSEN: Yes.

DR. TSIMPAS: -- as we discussed before, the -- as we discussed before, it's going to be extremely difficult to allocate a number. I think we should just go by the -- certainly the dome and decide -- of the aneurysm. If they're well covered, I think it should be sufficient.

DR. JENSEN: Any other discussion?

DR. ERKMEN: So, yeah, I'm confused. I think it's an irrelevant question now with the

Question 4 answer, but when you're talking about percentage, we're not sure, is it angiographic or is it by volumetric? And by volumetric, you'll never get to 100% really, right?

DR. ASHLEY: I agree. I mean, does this mean packing density?

DR. ERKMEN: Yes, yes. Packing density, exactly, that's what I'm talking about.

DR. ASHLEY: I think you could come up with a number. There are studies that look at what that number is that correlates with potential, you know, occlusion down the road, but if we mean just what it looks like, does it look like it's filled or not filled, then I think Raymond is good. I think the other part about this is when do we mean? Do we mean right after we finish treating it, immediately, or do we mean at follow-up? So I think that would be important regardless of the underlying question if we're talking about just looking at it.

And then Dr. Tsimpas mentioned something about the dome, and I think we may have neglected to kind of include that, which is if you have a Raymond II where the rupture point -- particularly for ruptured -- where the rupture point is very close to the neck, how do we feel about that, or the proposed rupture point; is that the same as one where we think the rupture point is at the dome and it's well packed? And so some of the features of the coiling, you know, are maybe more subtle, the same as, you know, these Raymond Class III's, which can be Type a or Type b.

DR. JENSEN: So for trial purposes, though, are we checking the box, Raymond I, II, III, or are we saying no, we want to give an actual volumetric amount based upon packing density?

DR. ASHLEY: I think for trial purposes, we should use the Raymond. Stick with Raymond.

DR. JENSEN: So, to the FDA, the Panel agrees that using the Raymond classification as opposed to a percentage of occlusion is acceptable.

DR. PEÑA: Thank you.

DR. LOFTUS: Question Number 6, Aneurysm Occlusion (Effectiveness) question: Do your aneurysm occlusion assessment recommendations using Raymond -- and the next, but then it becomes redundant -- differ for endosaccular devices (e.g., neurovascular embolization coils, BAC, SAC, or the saccular obturation devices)? And intraluminal flow diversion devices? If so, how?

I realize there may be a little redundancy, but we need to go through them in order.

DR. JENSEN: So I believe that the Panel has already given your opinion on this. For intraluminal flow diversion, it's Raymond I; there must be complete occlusion. For the saccular obturation devices, we're going with the Raymond classification simply because we don't have a better one right now to go to. And the Raymond classification would be used for endosaccular devices, both just coiling or coiling with stent or balloon assistance.

Does that answer your question?

DR. LOFTUS: Or intraluminal flow diversion, so it's being intrasaccular flow diversion?

DR. JENSEN: Right.

DR. LOFTUS: The more novel devices.

DR. JENSEN: It's the one that we're not certain that there's a better measurement for, so we want to use Raymond for that now.

DR. LOFTUS: Dr. Peña?

DR. PEÑA: Thank you. I think that helps us.

DR. LOFTUS: Question 7, regarding Follow Up. We've addressed this, also, somewhat in the course of the day.

What length of follow-up is recommended to assess effectiveness for endovascular aneurysm treatment devices? Please discuss how your recommendation is impacted if the

aneurysm status of the patient at 1 year is a Raymond II or III.

DR. JENSEN: So let's start with Dr. Thompson and go this direction.

DR. THOMPSON: I think this is a question much like the earlier one that depends on if it's being done for a study. If it's being done for study, I would prefer a 2-year follow-up.

(Off microphone comment.)

DR. JENSEN: Dr. Dorsey. I'm sorry, Dr. -- sorry.

DR. LYDEN: So I think that if you're doing a study and you're going to seek a clearance for a device, something like 6 months or a year makes a lot of sense, but with the proviso that after approval or licensure, there's an extended period of follow-up because the natural history of these lesions, one thing we do know is there's a long ramp. So maybe for initial approval, a little bit shorter, 6 to 12 months, but then extended follow-up after that.

DR. THOMPSON: If I could just add that, I didn't make that clear, that's a very good point. There's pre- and post-follow-up approval, and I think to answer your question directly, 2 years ought to be the minimum in post-follow-up, but I think his point is a good one about the initial approval.

DR. JENSEN: But do you feel that if we are doing -- recommending data points at, say, 6 months and 12 months and one of our considerations is actually a change to determine stability, is 1 year enough to actually say stability? And let's look at that from unruptured aneurysms and from ruptured aneurysm standpoint. So, I guess, how many -- since the first true picture you're going to get at 6 -- is going to be at 6 months, since we all agree that at, you know, ground zero there's always going to be some filling and you're not looking at this again until 6 months, that's sort of your first look at the aneurysm. Do you think that just a second look at 12 months is enough for you to feel that this has, you know, been effective, or do you feel that there needs to be stability?

DR. THOMPSON: I think we ought to probably stick with the definition of 1-year stability.

DR. JENSEN: Okay.

DR. DORSEY: So would that be 18 months or --

DR. THOMPSON: One year of stability if it hasn't changed at all. You may not have any at all at the time of coiling, and if it's the same thing at 12 months, I think that's a reasonable outcome.

DR. DORSEY: That's fine by me.

DR. OVBIAGELE: Yeah, I agree with Dr. Lyden's approach. One question I have, though: For those techniques that require dual antiplatelet therapy, how long is required for the patients to be on dual antiplatelet therapy, because I don't know. And the reason why I ask is because as you're all well aware, I mean, the risk of systemic hemorrhage rises especially after 1 year, so I just wondered, if they're going to be on it beyond 1 year, depending on how long they're on it, I mean, one wants to follow that a little bit longer, so I don't know what the answer to that is.

DR. JENSEN: So I'll let the other members who do this, you know, speak for themselves, but for us, when we use a stent assistant, they may be on dual antiplatelet therapy for 3 months and then you stop the Plavix and usually leave them on an aspirin. For flow diversion, we usually look at them at 3 months and 6 months, and once they're occluded, we stop the Plavix and we leave them on an aspirin. I don't know how the other operators around the table manage it. For the most part, I think that antiplatelet therapy, dual antiplatelet therapy is usually done at 6 months for at least stent assistance.

DR. OVBIAGELE: Okay, sounds good. Thank you.

DR. JENSEN: Everybody agree with that? Okay, so do you agree with --

DR. OVBIAGELE: I agree with 1 year and then a longer term follow-up, or for

pre-approval, 1 year.

DR. JENSEN: Okay. And is that true for both ruptured and unruptured?

DR. OVBIAGELE: Sure, yeah.

DR. JENSEN: Huy.

DR. DO: Is this clinical and imaging or just -- or one or the other?

DR. JENSEN: I'm sorry --

DR. DO: Is this clinical follow-up and imaging follow-up or both, the question?

DR. JENSEN: This would be --

DR. DO: Effectiveness would be imaging?

DR. JENSEN: I think it would be imaging follow-up.

DR. LOFTUS: Imaging follow-up.

DR. DO: Imaging follow-up.

DR. JENSEN: Right, um-hum.

DR. LOFTUS: Sure, imaging follow-up.

DR. DO: So right now, what is the requirement for a clinical trial to follow up? I thought it was longer than 3 years; 3 years or longer, is it not?

DR. JENSEN: I think that's what we get to recommend.

DR. PEÑA: We're asking you to weigh in on the follow-up for these types of products, and I mean, if we want to go into more detail, that brings in a host of other issues about the aneurysm characteristics, patient demographics, device technology. So we're looking for some overall follow-up needed for effectiveness when we look at these studies and the results.

DR. DO: Okay, because I think we've heard from industry that the number 5 years have been thrown about, so I think I would agree, 1 year and at least 3 years of follow-up, if not longer.

DR. DORSEY: I would do clinical and radiological. I mean, if you're going to do an imaging thing, you're going to get clinical data.

DR. JENSEN: Oh, yes. You're going to be seeing the patient at the same time, but I think what we're trying to determine here is how are we going to follow them radiologically to determine stability?

DR. GROTTA: So I would say 1 year after it's been established that it's stable, so for I's to II's, you know, for a year after that, and if a III goes to a II or a II goes to a III, then it needs to be continued for a year after stability, but I don't think it needs to be followed radiographically necessarily longer than that. But, you know, I'm not in the habit of following these myself, so I have to defer to my interventionists, but how often do they change radiographically once they've been stable for a year?

DR. DO: So we do surveillance follow-up long term at 5 and 10 years where I practice, and even longer, not only to look at the aneurysm that's been treated but for -- to look for appearance of new aneurysms.

DR. GROTTA: Right, for that, but what about --

DR. TSIMPAS: I agree, 1 year for stability and for initial approval and then at least 5 years of data.

DR. JENSEN: Dr. Selim.

DR. SELIM: I agree with 1 year if it's stable, and then long-term follow-up may be up to 5 years.

DR. JENSEN: Okay. Dr. Connor.

DR. CONNOR: Yeah, I agree with that, and I would add the caveat for the Raymond II. Stability needs to be established, which may take more than 12 months, or even if the hard cutoff is 12, at least following those patients who came to a trial early so the label could appropriately reflect, you know, what percent maybe don't stay stable would be

important.

DR. PILITSIS: One year with 5-year follow-up for the long term.

DR. ASHLEY: One year and then 5 years, I agree.

DR. ERKMEN: I would echo what Dr. Connor said. One year with the caveat to follow the patients who are changing -- unstable II's and III's -- for longer, and then the post-approval follow-up could be even longer; 3 to 5 years, I think, is appropriate.

DR. ASHLEY: I agree with the experts.

DR. JENSEN: All right, so the Panel agrees that a 1-year assessment for the treatment is appropriate provided that the aneurysm is stable. If the aneurysm is not stable, i.e., the I has gone to a II, II has gone to a III, then further follow-up is required until stability is established, and once stability is -- or retreatment. And once stability is established, then a 5-year follow-up is appropriate.

Does that answer the question?

DR. PEÑA: Thank you.

DR. LOFTUS: Question 8 concerns Retreatment.

Some initial interventions result in a clinically unacceptable outcome, and retreatment is considered. Does a worsening in the Raymond scale at follow-up imaging warrant retreatment, and should FDA consider a worsening of the Raymond scale during the 1-year follow-up to represent a failure of treatment?

DR. JENSEN: So let's start with Dr. Erkmen.

DR. ERKMEN: I would say that a worsening Raymond scale, by itself, does not necessarily warrant retreatment or device failure or else, you know, a lot of our coils are failing. So I would not say that it would automatically prompt retreatment and/or device failure. But it would prompt further close follow-up.

DR. JENSEN: Dr. Ashley.

DR. ASHLEY: Yeah, I think that worsening does not necessarily suggest retreatment or failure and, you know, we can define how much worsening that is. If it goes from, you know, a I to a III, that suggests something completely different than I to II.

DR. PILITSIS: I defer to my colleagues.

DR. CONNOR: So I tend to agree, but I at least would think that anything that would warrant retreatment, if somehow that were not considered failure, would need to be clearly captured and clearly labeled what percentage of patients required retreatment.

DR. SELIM: Yeah, I completely agree with that statement. It would not be a failure of treatment, but we need to know these cases, of course.

DR. JENSEN: Okay. Dr. Thompson.

DR. THOMPSON: I agree with Dr. Connor's statement.

DR. LYDEN: So the critical information gap here is the connection between these worsenings and rerupture or rupture is unknown. Do I have that right? So to that extent, it seems like these, if you don't call them treatment failures, they are at least a watchable event that requires, you know, further study and further observation to get to a point where we know if this is a risk for rupture or not.

DR. JENSEN: Dr. Dorsey.

DR. DORSEY: I agree.

DR. OVBIAGELE: Agree as well.

DR. DO: I would say it would be a yes or no, yes and no answer. I think that worsening does not necessarily warrant retreatment because the re-bleed rate is extremely low from the ISAT data, and also, should the FDA consider worsening of Raymond scale during 1-year follow-up to represent a treatment failure? Yes, if it requires retreatment by the treating physician, but if it doesn't require retreatment, I don't think it's a failure of treatment.

DR. GROTTA: Yeah. Well, I think worsening of a I or a II to a III that is -- should be considered a bad outcome and because, I think, wouldn't you re-treat? If you treated an unruptured aneurysm and it turned about to be a IIIb where you still have incomplete occlusion, you're going to re-treat that patient, or I would imagine. So I think that that's a treatment failure.

DR. JENSEN: So one thing we didn't talk about is the difference between, again, a ruptured and an unruptured aneurysm, right? So a clear -- I mean, from my standpoint, if you have a worsening from a II to a III in a ruptured aneurysm, I'm going to re-treat it, and if I have to re-treat it, I'm going to consider that a failure of the device. An unruptured aneurysm, though, from a II to a III, I'm -- it has certainly gotten worse, but am I compelled to re-treat it?

DR. GROTTA: Right.

DR. JENSEN: Not necessarily. So do we call that a failure of the device and we're simply just not re-treating it?

DR. GROTTA: Yeah, I would consider it a failure of the device, I would. I mean, you're not occluding the aneurysm, and that's what you're intending to do with the device.

DR. TSIMPAS: I agree with most of the comments. It really depends on the device. Coils, for example, you may have some coil compaction. If it doesn't -- if it's not significant recanalization, then it shouldn't be considered a failure of treatment.

DR. LOFTUS: You know, before you go on for the summary, I find, personally, this to be a little ambiguous. By definition, if it goes from I to II or II to III or, God help us, I to III, this is an unstable -- this has not achieved clinical stability, right? So what I'm hearing is that even though it's clinically unstable, that's not necessarily considered a treatment failure, so how would you define a treatment failure?

DR. GROTTA: I think it is a treatment.

DR. JENSEN: So I think we -- perhaps the Panel got sort of into the idea that if we called it a failure, that we then had to re-treat it; is that one of the issues here? In other words, are we using instability as a failure, or instability plus must re-treat as the failure? Because I personally feel that if it's unstable, then that is a failure whether or not I actually end up re-treating it.

DR. POSNER: Can I ask a question? Is it the device was the failure or was the aneurysm the failure? In other words, was it an unstable vascular situation, and did it change its category not because the device didn't work but because the physical structure of the aneurysm changed over that period of time?

DR. JENSEN: Well, that may be unknowable because the device may actually be causing the aneurysm to change, so we're going to assume that it's the device that's the failure since we're putting it in to treat the aneurysm and the aneurysm's not being treated; it's getting worse.

DR. ASHLEY: So a couple things I thought were ambiguous, but if you just answer it based on the wording, it says worsening at 1 year, right? So, certainly, when you include flow diversion here, if you start with a flow-diverted aneurysm at time zero, it's going to fail, and if you look at 1 year, it's not clear whether that's a failure or whether it needs more time. I mean, if you have a 3- or 7-year aneurysm, for example, it may take longer. So you can't call it a failure. You cannot, if you -- so the answer would be no. And then for aneurysms that go from I to II, if we're accepting II's, that change is not a failure, if we say that a II is good enough treatment.

So the question doesn't really get into exactly the timing of the follow-up and the move from one level to the next, so I think it may be better to suggest stable versus unstable, right, so that allows us to capture I to -- the move from I to III, which, you know, both of us said, you know, may be bad. It may capture the aneurysm that -- and we need

more follow-up for the flow diverters because I've never experienced a flow diverter that's occluded and then when you look back again it's not occluded, but certainly that would suggest a problem. And that would be after a year probably.

DR. JENSEN: Yes, Dr. Erkmen.

DR. ERKMEN: And to clarify my answer, what I was saying is that a change in the Raymond scale by itself would not represent treatment failure. If the change was significant enough that I deemed it necessary to re-treat, then absolutely, that's a treatment failure.

(Off microphone comment.)

DR. ERKMEN: I would use retreatment as the decision point as to whether it's a treatment failure or not, a worsening of the Raymond scale, because we see a lot of I's become II's at 1 year. Those are not all treatment failures.

DR. JENSEN: But --

DR. LOFTUS: Obviously, there is a potential conundrum in the context of a clinical trial if it's negatively reinforced to re-treat a patient because that puts them into the failure category. You know, we wouldn't want to create a situation like that where an investigator was perhaps -- is disincentivized from --

DR. JENSEN: Right.

DR. LOFTUS: -- doing what they thought was the right thing just to keep out of that basket.

DR. ERKMEN: Well, then at a minimum, it would have to be a I to a III change, not any change in the Raymond scale, because a I to a II is really common, I'm sure, you know. All the practitioners in the room would say that that's a pretty common phenomenon that we would not necessarily consider a treatment failure, but it's when we have to go back to retreatment that I think we worry about did the original treatment fail.

DR. JENSEN: So I think if we go back to a lot of the conversation we had around stability versus instability, that if you have an aneurysm that is changing from a I to a II to a III, that's an unstable aneurysm, is a failure of treatment because the device is not doing what it's supposed to do. Do we have agreement upon that?

DR. DO: I'm sorry, going from a I to a II is unstable?

DR. JENSEN: Well, from like a I to a III.

DR. DO: Oh, I to a III.

DR. JENSEN: So you would have --

DR. DO: Yeah, a III is unstable. I don't think any one of us would leave a III alone, right? We would re-treat, so it's by the same criteria, either retreatment or Raymond III.

DR. JENSEN: So I think part of the issue is that we -- you know, we're really only going to -- well, we will have three data points, but the first one is kind of a pseudo data point because it's immediately after the treatment. I personally feel like the data point at 6 is really what you've got, and then if you're looking for instability, you need at least two more to see whether or not it's actually unstable, but we've chosen that 1-year point. So are we saying that if a patient goes from a I or II to a III at the end of 1 year -- that is for saccular aneurysms -- if that is considered unstable and therefore it's a failure to treat? And we are in agreement on that, okay.

(Off microphone comment.)

DR. JENSEN: Yeah, but I mean, unfortunately -- I think then, that's -- that puts the subjectivity into it that -- you know, I mean, I could say, well, that was kind of a II before and it's still a II. I think if we have defined numbers and we can say you're I-II and you go to a III at 1 year, you're unstable because it's not staying the same, it's not getting better. It's actually now, at least according to our definition, starting to involve an unsecured wall. And we are all, at least, going to start thinking that we're going to re-treat it, correct? At that

point, that that would be a failure. That would be my take on it, but please.

DR. GROTTA: I agree. I think the analogy is put a carotid stent in and at a year the patient's got a hemodynamically significant restenosis; whether or not you decide to treat that, you know, that's a failure of the stent. So it's the same thing. You put this device in to obliterate the aneurysm, and it goes to an unacceptable degree of filling, which is a Raymond III, that's failure of the device, of your intended device.

DR. JENSEN: Dr. Thompson, did you have something to add?

DR. THOMPSON: I agree with that. I think we're saying the same thing by summary, that an unstable II, when you've gone from I to an unstable II, not just I to II, but an unstable II, that's -- that would be a failure, but not a I to II. So an instability at II or treatment -- retreatment rather, both of those should be considered a failure, I think.

DR. JENSEN: So we are looking more at instability when there is, over the three time points, increasing in the size of the aneurysm such that at the third time point the aneurysm is larger than it was at its initial one, it's considered instability, and that would be a failure. Is that an appropriate --

DR. DO: What if it goes from a II to a III on one -- at one time point in follow-up? That would be a treatment failure, in my opinion.

DR. JENSEN: So it would probably be at the II-III-III unless it went II-III-II, which is unlikely but --

DR. DO: Or a II to a III. You don't need a third time point.

DR. LOFTUS: So what you're saying is you've got -- you know, to define treatment, you've got to have three points of observation.

DR. JENSEN: That's what my opinion is. I don't know if everybody else feels the same way, but I think you need three points.

DR. ASHLEY: Well, but I think the thing that we've said all together is that if it gets to

a III or an unstable II, right, which is we're assuming it's going to go to a III, that constitutes a treatment failure, right? So if you start out at a I and you look back at a year or 6 months and it's a II, you may have been happy with a II anyway. You're not going to re-treat it because we've already said earlier that we accept a I or a II. But if that II is obviously unstable or at the next time point it's now a III, that constitutes a failure. If you have to -- if you choose to re-treat it for something else, that automatically makes it a failure, too. So let's say it's a II but you feel funny about it, you know, whatever it is. You re-treat it; that automatically makes it a failure. But this idea that the question asks worsening, that's not good enough. We have to define what worsening is, and it sounds like it's the transition from II to III, whatever the time point is.

DR. LOFTUS: I need to make sure this is very lucid for our purposes. So in this particular situation, you have a I and it goes to a II, okay. And then at another, at the third observation, it remains the same II. Is that an unstable II?

DR. ASHLEY: No.

DR. LOFTUS: No. So it has to be a II that worsens by the third observation to fit into that category; is that correct?

DR. JENSEN: Correct.

DR. LOFTUS: So just going from I to II isn't enough to call it unstable.

DR. JENSEN: Correct.

DR. LOFTUS: Okay, thank you.

DR. JENSEN: The Panel agrees with that.

DR. PEÑA: Right. And just to reassure, I mean, a lot of the discussion that we hear now, the stability, the timing of the change, the magnitude of change, the retreatment options, these are the types of factors that we will also be carefully thinking about rather than just sort of an *n*, some number. That is also helpful to us in our deliberations.

DR. JENSEN: Can I just go back to the flow diversion, though? How many people believe that if the aneurysm is still filling at 1 year, that is a treatment failure for flow diversion?

DR. THOMPSON: Still filling?

DR. JENSEN: Is still filling. So do you believe that's unstable if it's still --

DR. THOMPSON: For a flow diverter, I think it's a failure if it's still filling in a year.

DR. JENSEN: And our other colleagues, do we believe that that's a failure?

DR. DO: I disagree. It depends on the aneurysm. I think there's a large aneurysm, then there's giant aneurysms, then there's giant-giant aneurysms. Some of them I've been following for longer and no clinical events, but the -- it still fills and then, you know, I --

DR. JENSEN: But is that a failure? I mean, the device is supposed to occlude the aneurysm.

DR. DO: No, no. It progressively fills less and less but, you know, it's protected from subarachnoid hemorrhage, I believe, where there's only a tiny little remnant that's filled, so I have a hard time reconciling that's a treatment failure when 95-98% of the aneurysm is thrombosed.

DR. JENSEN: Okay, Dr. Ashley or Dr. Erkmen.

DR. ASHLEY: Yeah. I think you have to define the size of the aneurysm, that's one, because at a year, you may -- if you have a huge aneurysm, it may still fill. And then the other question that becomes important is are they still on dual antiplatelet agents? So if at a year it's still filling and you stop the aspirin or you stop the Plavix and then it shuts down, do you consider that change in treatment part of it or not?

So I think you may have to define a time point for the study purposes. You could call it a failure just so that we have a time point that we kind of arbitrarily pick. But I think that, in terms of follow-up, you may very well see an aneurysm occlude by 18 months that was

still filling in a year without doing any additional treatment. So I think you have to disconnect the retreatment and calling it a failure. So I would say a year to call it a failure, but not necessarily for the retreatment part.

DR. JENSEN: Dr. Connor.

DR. CONNOR: So I think, to me, how we went off the rails here is like 4, 5, and 6 seemed very clear, we gave a pretty clear answer to, and they were set by flow diverters versus coils, etc., and so that seems to take precedent. This question seems to be more nuanced, when there's a need for retreatment, whether retreatment occurs or not. So it seems like the definition for success on Questions 4, 5, and 6 take precedent, and this is these more nuanced cases, and suddenly, we're letting the nuanced cases define what is an overall success. So if we reframe it that way, can we answer this just pertaining to the more nuanced cases, not the overall definition of success, because I feel like that's how we got off the rails here.

DR. JENSEN: So are we talking about both sides, the flow diverters and the saccular ones that we're talking about? You're talking about flow diverters?

DR. CONNOR: I mean, I think that this is the nuanced question. For instance, you know, I think in general any flow within the aneurysm at -- for a flow diverter, it sounded like we had agreed, in Questions 4, 5, and 6, was a treatment failure.

DR. JENSEN: Right.

DR. CONNOR: You know, here if -- right, if there's a II that needs retreatment, it sounds like people think, well, that was an original treatment failure because there was a need to reintervene again, and so it seems like now these nuanced discussions are trying to supersede Number 4, which is, you know, the official original definition of success.

DR. JENSEN: So I agree. We really have come down hard on binary for flow diversion, right? You know, it's either occluded or it's not. And we're looking at time point,

which is 1 year, which we've already, you know, been around the block about, whether or not the 1 year is -- if you really need another data point at 18 months to consider stability, but we've agreed to 1 year. So my particular vote is if it's still filling, because you've had plenty of opportunity over 12 months to back off on your antiplatelet agents, etc., etc., if it's still filling at 1 year, to me, that's a failure.

DR. DO: So it depends on how you do your flow diversion. Are you doing a one device treatment? Are you doing a multiple device treatment? And if you do a one device treatment and at a year, year and a half, you decide to put another device in, is that a treatment failure versus somebody who's put --

DR. JENSEN: Well, yes, because you put another one in.

DR. DO: But there's such a heterogeneity across different centers how one treats using a flow diversion.

DR. JENSEN: But we're talking about trials.

DR. DO: Some of us choose --

DR. JENSEN: We're talking about --

DR. DO: -- to continue to follow patients longer than a year with no adverse event and there is progressive thrombosis. So I'm a little bit uncertain here.

DR. JENSEN: Dr. Grotta.

DR. GROTTA: Yeah. I mean, you're evaluating a device; you're not evaluating the center, and you're not looking at clinical outcomes. You simply are asking -- you've got an experimental device; you're being asked a question you have difficult -- obviously, if using a flow diversion, that's not an easy aneurysm, right? It's a complicated issue. So you want to know is your device fixing this complicated issue, and it just seems logical to me that if the aneurysm is still filling, it's not -- it doesn't mean that the patient is going to have another hemorrhage necessarily or that you failed as an interventionist. It just means that device

has not done what you really want it to do, and are you going to look for another device or try to find something better than that device so that you can get total obliteration of the aneurysm? So it just seems to me -- and it doesn't mean you're going to give up on that device, but it just seems to me that's not the end result that you're trying to achieve.

DR. JENSEN: Well, I think instability works both ways. You can have instability with an increasing carve-out of whatever, and you also can have instability where it's getting smaller but it's not getting smaller in the manner in which the device is designed to do, which is to be occluded at a year.

DR. THOMPSON: So the devil is in the details in these, and it has to do -- if we were prospectively making a decision whether the device was successful or not, it has to do with, I think, what Dr. Posner said earlier about the size of the lesion. Dr. Do made a good point. If it's a 25 mm ophthalmic giant, ophthalmic artery aneurysm, and you had 1 or 2 mm filling in a year, even though it was still filling and the patient is asymptomatic, you'd consider that a success. But if it's an 8 mm or 7 mm ophthalmic aneurysm, same location, and there's filling of 2 mm in a year, it would not be so much. So really, I think -- again, the devil is in the details. We have to keep track of both, but I think your point was a good one. It can be a success with some small filling.

DR. JENSEN: Dr. Erkmen.

DR. ERKMEN: And, you know, I guess the point that I disagree with is this 1-year time point, because we know that with flow diversion, that's not the endpoint, and if you say at 1 year it's a failure but then at 18 months the aneurysm is now fully occluded, then did the failure now become a success all of a sudden? You know, if it's progressively thrombosing, in the natural history, we know, with flow diversion, that a year we only have 75% of the aneurysms are going to be totally occluded; at 2 years, it's going to be 98%. And so I think using the 1 year as a mark for flow diversion, of any flow means a treatment

failure, I think, is dangerous.

DR. ASHLEY: But I agree, about a year. But I think that the spirit of the question is, is there a time point at which we can define failure for the study? And I think you have to pick it. Maybe it's not a year; it could be 18 months or maybe we'll say it's 2 years, but at some point, in order to be able to say that we think this thing works or not, we just have to pick a time. And it can be arbitrary, and I agree that a year isn't enough for big aneurysms. But whatever time we decide on, we can --

DR. DORSEY: Could you do a year for non-giant and 2 years for giant?

DR. ASHLEY: Maybe. I mean, I think something like that is the way to go. I mean, there has to be a consensus, but doing something like that may be the way.

DR. JENSEN: So, Dr. Loftus, can we do that? Can we recommend, based upon size for this particular question, a difference, or since we've chosen 1-year follow-up, do we stick to that?

DR. LOFTUS: We asked you for your expertise. I think we should listen to what you have to say. I'm just sitting here thinking, as we go through this whole morphological conundrum, to me, the issue remains -- the issue always circles back to the clinical issue, right? I mean, the point of treating an aneurysm is to prevent subsequent subarachnoid hemorrhage and leave the patient safely and effectively treated. That's the real point. And so I guess I would ask, in making this decision clinically, what does it take for a treating clinician to achieve that goal in their own heart and to their satisfaction? That's how I would --

DR. ERKMEN: I mean, I thought the question was if you had a giant aneurysm and you treat it with flow diversion, at 1 year if it was still filling, would you re-treat that patient, or would you wait longer before you'd do anything? If you're going to wait longer, then I would say you're still in the natural evolution of the treatment, and I wouldn't

consider it a treatment failure at 1 year. But that would be my practice. I would continue to follow that patient. I would not add a second flow diverter device at 1 year if there was persistent flow because we know that 25% of the aneurysms are still going to have flow in it. We would wait longer.

DR. LOFTUS: But I would say, Dr. Jensen, you know, having now not answered your question, please tell us what you think, and then we'll ask if it's okay.

DR. JENSEN: That's what I was going to do. Okay, so --

DR. GROTTA: Dr. Erkmen, would you tell the device company to go back and make you a better flow diverter in that situation? Or try to do a better job designing or a better -- you know, a better mousetrap?

DR. ERKMEN: I think there's always continued attempts in improving the devices we have, but if we know the natural evolution of the treatment takes up to 2 years, I don't know why we'd say at 1 year it's a failure and how you reconcile the failures that then become successes 3 months, 6 months later.

DR. JENSEN: Okay, so we're going to move forward because we've got three more questions to do and people want to go home, right?

DR. LOFTUS: Yeah.

DR. JENSEN: All right, so this is what the FDA Panel says. For saccular aneurysms, we feel that a worsening of a Raymond I to II to a III showing instability at 1 year is a failure of treatment. We cannot come to consensus on whether or not the 1-year time point is appropriate for residual filling of aneurysms treated with flow diverters. And it has been suggested that for flow diverters, that the time frame should be longer, perhaps either 18 months or 2 years, to determine whether or not it's a failure.

DR. LOFTUS: At what size? At what aneurysm size, if I may?

DR. JENSEN: We really couldn't come to agreement on that either, but it was

considered large or giant aneurysms.

DR. PEÑA: Right. And you provided a number of factors to consider during that --

DR. JENSEN: I'm sorry, say that again.

DR. PEÑA: And you provided a number of factors to consider during that assessment.

DR. JENSEN: Correct.

DR. PEÑA: Yeah. Thank you.

DR. LOFTUS: Thank you very much.

DR. JENSEN: Um-hum.

DR. LOFTUS: Question 9, we've been over this also today.

DR. JENSEN: Yes.

DR. LOFTUS: Alternative Imaging Assessments: We consider DSA to be the gold standard to assess aneurysm occlusion at follow-up. Can magnetic resonance angiography, or MRA, or CTA, computed tomography angiography, serve as a surrogate follow-up exam, and when should this take place?

DR. JENSEN: So can I stomach this because I think we had a long conversation about that? Okay. So the Panel agrees that DSA, at least for the first point of reassessment of the aneurysm, is the gold standard. The Panel also agrees that MRA carries considerable benefits, including diminishing the amount of radiation exposure that patients have and the complications that can occur with DSA on follow-up studies. The Panel believes that MRA could serve as a surrogate if it is done contemporaneously with the DSA so that we have an ability to actually compare the two side by side at the same time point and then can move forward using MRA as a surrogate follow-up exam.

We feel, also, that there needs to be some very strict rules around the type of MRA that needs to be done in terms of the field strength and the actual technique that is used.

And at any point in time, if there is a consideration that the MRA is not adequately showing what is truly going on, that DSA would then be performed. Does the Panel agree with that? Okay.

DR. PEÑA: Thank you.

DR. JENSEN: Um-hum.

DR. LOFTUS: Thank you. Question 10 refers to Post-Approval Studies. In some cases -- and we've nibbled around the edges of this today. In some cases, a post-approval study may be warranted, for example when limited follow-up exists for patients. What is a sufficient long-term follow-up period for a post-approval study when the majority of patients -- and here it bifurcates a bit -- when the majority of patients have the following outcomes for ruptured or for unruptured aneurysms?

- Raymond I
- Raymond II
- Raymond III

DR. JENSEN: Okay, so let's start with unruptured aneurysms. Dr. Thompson, would you like to start?

DR. THOMPSON: So the longitudinal -- what is a sufficient long-term follow-up period for a post-approved study where the majority of patients have ruptured -- you want ruptured or unruptured first?

DR. JENSEN: Yes.

DR. THOMPSON: For ruptured, I'll say a minimum of II, and I'd prefer a 5-year follow-up. Do you want the unruptured as well?

DR. JENSEN: Yes.

DR. THOMPSON: I'd say 2 years would be my answer for unruptured.

DR. JENSEN: And is that for --

DR. THOMPSON: Minimum.

DR. JENSEN: -- all Raymond classifications?

DR. THOMPSON: Well, if the aneurysm still is a stable II at the end of that follow-up, yes. If it's an unstable II or III, I would advise longer follow-up.

DR. JENSEN: And that is for both ruptured and unruptured?

DR. THOMPSON: Yes.

DR. JENSEN: So we're again looking at stability as really the defining factor as to how much --

DR. THOMPSON: Yeah. And the hard part --

DR. JENSEN: -- more follow-up you do.

DR. THOMPSON: -- again, is this -- I mean, I'm thinking about the clinical management, and that's a little different, as noted before, than for a study.

DR. JENSEN: Okay. Dr. Lyden.

DR. LYDEN: So I think if you separate out (a), (b), and (c), then you're assuming you know more than I think we really have data for, so I think one has to have the same amount of follow-up regardless to see what happens because we don't know. And then again, for ruptured or unruptured, I'd defer to the surgeons as to how long they want to go, but you know, years, multiple years, seems rational.

DR. JENSEN: Dr. Dorsey.

DR. DORSEY: I defer.

DR. OVBIAGELE: No special insights here.

DR. JENSEN: Um-hum. Dr. Do.

DR. DO: I agree with Dr. Thompson.

DR. JENSEN: Dr. Grotta.

DR. GROTTA: Yeah, I agree.

DR. ERKMEN: Agree.

DR. ASHLEY: I think 5 years for all of them, just because we're also looking at other factors such as parent vessel changes or other things, so ruptured/unruptured, we don't know, and regardless of class, 5 years.

DR. PILITSIS: I agree with Dr. Thompson.

DR. CONNOR: So I agree with Dr. Thompson with the caveat, maybe, that it seems like if a majority of patients were Raymond III, it wouldn't be an approved device in the first place.

(Laughter.)

DR. SELIM: Yeah, I agree with that, too.

DR. JENSEN: So, Dr. Thompson, stop me if I misspeak for you, but you felt there is a difference in terms of follow-up between the unruptured and the ruptured aneurysm group, that for the unruptured group, you felt that 2 years was the follow-up period?

DR. THOMPSON: Yes.

DR. JENSEN: Um-hum. That as long as, in the follow-up, it remains stable?

DR. THOMPSON: Yeah, I think the way I said it was a minimum of 2 years, and 5 years for the ruptured. And I note that some would say 5 years overall, and again, that's probably what I would do clinically, but for the purpose of a study, you know, it would be nice to have, but there are other issues that go along with that.

DR. JENSEN: And if the unruptured or ruptured aneurysm is not stable at the time of the last data point, what is your recommendation to follow? Continue to follow?

DR. THOMPSON: Continue to follow.

DR. JENSEN: And is that what the Panel would agree to, continue to follow on a yearly basis?

DR. SELIM: Yes, but when I agreed, I agreed to 5 years follow-up.

DR. JENSEN: Yeah, 5 years. Okay, okay. So the Panel believes that there is a difference in the follow-up that's required for unruptured versus ruptured aneurysms, that the unruptured can be followed out to 2 years and that there is stability. No further follow-up is needed in terms of the trial. I'm assuming that people clinically will probably continue to follow them, at least most people I know do. And in terms of the ruptured aneurysms, out to 5 years, and at any point if clinical -- if imaging instability, i.e., continued growth or change in the remnant is seen, then follow-up should continue on a yearly basis until stability or retreatment is reached.

Does that help? Does that answer the question?

DR. PEÑA: Yes.

DR. LOFTUS: Yes, thank you. Our final question concerns Labeling.

What patient characteristics should be specified in the Indications for Use (IFU) (i.e., age, aneurysm morphology, location, size, Type 1 or Type 2 status, ruptured vs. unruptured)? For intraluminal flow diverters? And for the aggregated group of endosaccular devices?

DR. JENSEN: Okay, let's start with Dr. Grotta this time.

DR. GROTTA: Well, I mean, I guess the easy answer is it should reflect the inclusion and exclusion criteria of the trial. You know, I think that one of the -- and this is a general comment, right? I mean, one of the problems with clinical trials is when you adopt the inclusion/exclusion criteria directly from the trial to clinical practice, then it becomes sometimes too restrictive, and so I think you have to allow for postmarketing surveillance of certain areas around the edges. Just think back, even our current thrombectomy trials and the trial of thrombolysis, they just took the inclusion/exclusion criteria and just applied them to practice, and it turned out it took years to get them more liberalized. But I do think that, you know, whatever, your inclusion/exclusion criteria for the study should be a

starting point.

DR. JENSEN: Dr. Do.

DR. DO: I agree with Dr. Grotta. I think, definitely, the aneurysm morphology should be included as well as location. The other criteria, age, size, type status, ruptured/unruptured, I'm ambivalent, and probably I would not recommend putting them in the IFU.

DR. OVBIAGELE: Yeah, I think I would largely agree with that. Yeah.

DR. DORSEY: I agree with Dr. Grotta. I think ruptured versus unruptured is a big issue, and I might think about unruptured as symptomatic versus asymptomatic.

DR. LYDEN: Yeah, I want to emphasize that the label is increasingly used as a reimbursement template, and that's not appropriate. So, on the other hand, you only have data from the study to write the label, so you know, you're caught between a rock and a hard place. But as long the label states these are the circumstances under which we have data that it does work, but outside of those parameters it may or may not work, we just don't know, as opposed to it doesn't work.

DR. THOMPSON: I completely agree with that statement.

DR. SELIM: I think it obviously depends on the device, but I think the three major ones are the morphology, the location, and the size.

DR. CONNOR: I agree with Dr. Grotta, and I think, just from having been on a few of these myself, it seems like location is a big deal; in particular, some of the posterior locations are somewhat rare. So I think labeling using like hierarchical models to share information across locations is important.

DR. PILITSIS: I agree with Dr. Grotta. One caveat in terms of the devices that are used with dual platelet therapy, sometimes I think that may affect decision making, so in terms of ruptured versus unruptured, so when those need to be used with dual platelet

therapy, that should be noted.

DR. ASHLEY: I agree with most, you know, a lot of the comments. I think morphology and location are important, but I think, like Dr. Grotta said, those are the things that we're defining in the initial decision to undergo the study.

DR. ERKMEN: I'll agree with Dr. Lyden's comments, that the indications from the study should drive the original labeling, but with the understanding that they could used outside those, may or may not be safe and efficacious.

DR. JENSEN: So, for the FDA, the Panel feels that the inclusion and exclusion criteria should drive what is actually placed on the label, that in situations where special needs such as use for dual antiplatelet agents for use in that device should specifically be indicated, and that there should also be an understanding that the device is approved for the study trial inclusion and exclusion patients, and that it may or may not be useful or benefit in people who would not meet those criteria.

Does that answer the question?

DR. PEÑA: Yes, thank you.

DR. JENSEN: Dr. Loftus, anything else for us?

DR. LOFTUS: No. No, thank you. Thank you very much for all of your help today.

DR. JENSEN: Let's see. Well, I would like to thank the Panel and the FDA for their contributions to today's panel meeting.

Dr. Peña, do you have any final remarks?

DR. PEÑA: Just to again, thank the Panel and many of the attendees that stayed for the duration of the meeting. We appreciate the time that you've invested.

DR. JENSEN: Well, thank you for all the hard work that you've done on this, too, and thank you to everyone who participated today. I now pronounce the March 1st --

(Off microphone comment.)

DR. JENSEN: I am so sorry. We have to address the Consumer Rep and the Industry Rep, and I really apologize for that.

So, Ms. Edwards, have you anything to say? This is the first time you've been on our Panel, and I'd like to know your thoughts.

MS. EDWARDS: Okay. Well, as far as the clinical trials. So I heard someone, one of the representatives from one of the companies mentioned today that we look at demographics, ethnic demographics. He mentioned something about 40% higher in some ethnic groups so -- and I wondered about that, with that 50% higher number being brought to us today versus the zero, you know, with the smaller aneurysm, so I wonder did that play into that number, and I wondered if there should be greater effort to get that ethnic group in to be a part of these trials, because if that's been the case, if you have that many ruptures, it's probably because they don't maybe go to the doctors as much because there is trust issues in that group. So that was just something that I thought about as far as clinical trials and having everybody represented and actually getting a correct number on the amount of ruptures, because they did -- I did hear that gentleman say that there were 40% more likely higher rupture rates in a specific demographic. Did you all hear that?

DR. JENSEN: Yeah, I think my understanding of what he was saying is that many of the trials lack diversity, and so the numbers that we have represent one particular group over other diverse groups and that there needs to be more inclusion --

MS. EDWARDS: Um-hum.

DR. JENSEN: -- within the trials and therefore, you know, as you pointed out, you know, there may be a lack of trust for certain groups to not want to participate in trials either due to a lack of trust -- and we should make an effort to reach out to those groups, to almost target them, to ensure that they are also able to, you know, partake of these clinical trials and I don't -- this is -- I don't have any idea. Maybe Dr. Peña can explain what the FDA

can do in terms of improving or increasing diverse populations in the trials.

DR. PEÑA: All right, so the Agency is taking a closer look at subpopulations in the various studies that it provides oversight to. Gender/minority is beginning to also take a closer look across the different product areas. This has begun more so in some of the drug studies, but hopefully we'll see these discussions be part of the interactions that we have with agencies across the different product areas.

DR. JENSEN: Thank you very much for bringing that to the attention of the Panel again, because that was an important point that was made.

MR. WREH: Thank you, Madam Chair. My only question to the Panel, I know when the Chair asked on the device labeling, it sounds like the Panel was not in favor of, you know, including the age in a device. I feel medical device manufacturers spend a lot of time on device labeling, and it sounds like this Panel, you know, they're not in favor of including the patient age in the device labeling.

So my question to the Panel is what kind of -- what do you use for adjustment when treating patient with this kind of disease, you know, because FDA classify, you know, patient population for -- you know, we have newborns, we have pediatric, we have adolescent, and adult patient population. So I want to understand, you know, if we don't include the age in the IFU, how are you going to use your judgment on when using, you know, this product, you know, on patient with this kind of disease?

Thank you.

DR. JENSEN: Does anybody want to tackle that question about how do we make sure that pediatric patients are included, should they be included in the -- for the trial standpoint and when -- if they're not included from the trial criteria, what do we put on the labeling that allows the device to potentially be used in a pediatric population, or can we do that? I think that maybe it falls under the category of what we said may or may not be the same

outcomes in populations that are, you know, not included on the labeling.

The problem is that aneurysms in children are really rare, and they're usually associated either with trauma or congenital or infections of some sort, and so they're really not necessarily the same aneurysm as we see in the adult population. So I think it's difficult to really make a special inclusion for them because you're not going to have enough of them, and it's going to be a different type of aneurysm. We're not ignoring them, and in practice, the devices will usually be -- that's necessary to be used would be used. So I don't think they're not going to have access to the device, but I just don't think it can necessarily go on the labeling, and I don't think we're trying to exclude pediatric populations.

Does anybody else have anything to add to that?

DR. DO: Yeah, I agree. I don't think, as Dr. Lyden said, with reimbursement and medical legal stuff, we should be putting age on there. And to be frank, I don't think there's anything that's used in children and pregnant women that has an approved indication, like everything we use is off-label use.

DR. JENSEN: Yeah.

MR. WREH: Just a follow-up, just given my -- you know, FDA classify -- actually from age, I think, 0 to age 21, so just to clarify.

Dr. Peña, is that right?

DR. PEÑA: We have different classifications for children and adolescents, and you know, in general, we encourage pediatric studies, where possible. We have a pediatric extrapolation guidance when it's appropriate to use for different studies, and we also will try to make as generalizable as possible where those studies can be helpful and valuable to pediatric patients.

DR. JENSEN: Thank you.

Any other comments? Yes, sir.

DR. GROTTA: Well, since these patients present with subarachnoid hemorrhage, it's not like your screening population, so why would you not include an adolescent or a pediatric patient in these trials if they met other criteria?

DR. JENSEN: Well, I think that --

DR. GROTTA: Particularly a ruptured, particularly if it was a ruptured aneurysm.

DR. JENSEN: I don't have a good answer to that. I mean, in terms of putting them into the trial --

DR. GROTTA: I mean, these are device phase -- early phase trials. We are trying to assess whether a device works or not, so --

DR. JENSEN: Well, again, I think part of it may be because the reason behind pediatric aneurysms may be different from an adult aneurysm. Most of the ones I've seen have been traumatic. I don't know if I'd want to include a traumatic, which is potentially a II aneurysm in a trial but -- Dr. Ashley.

DR. ASHLEY: No. I mean, I just think that the basic answer would be that when you set the inclusion and exclusion criteria for the study, you may pick the age group based on that. So you may actually do a study looking at a device particularly for pediatric aneurysms, and then you -- but you wouldn't include a one-off or two-off pediatric patient necessarily, because I think that the results of that may be very different, you know, even thinking about the size of the vessels and stents and other things. The number of those is pretty small, and I agree, you know, usually children of some age and pregnant women of some age are often excluded from the study, not from treatment, because later on you may use it, but I just think from the study, you want to find a good -- you know, a well-controlled group.

DR. ERKMEN: And I think a lot of the children are taken care of, you know, at specialized pediatric hospitals that aren't necessarily always study sites because there's only

a few patients at those sites, you know, over multiple years as opposed to more common age ranges.

DR. JENSEN: So we're not against it, and you could always ask for humanitarian exemption to use the device and the company could ask for that, but I mean, there is a big difference in using endovascular devices in, you know, babies versus children versus adolescents. When they get to adult size, usually 18 and up, they qualify, they fall into sort of that cohort but --

DR. GROTTA: But I guess I would just push it a little further. You have an 18-year-old pregnant woman comes in with a wide neck aneurysm rupture, and you got one of these devices; would you not want that person in this trial if she signed a consent?

DR. JENSEN: Well, I think we're sort of assuming, in that scenario, that there's no other way to treat the aneurysm except for the device.

DR. GROTTA: Right.

DR. JENSEN: And I don't know if that's necessarily true. I mean, there are ways of treating wide-necked aneurysms with other devices that are approved. I'm not quite certain -- it would have to be a very special case where only, we think only this device would work.

DR. GROTTA: I mean, we're talking about sort of new devices for aneurysms for which there isn't a good treatment, so --

DR. JENSEN: But it hasn't been established yet, and that's why we're studying it, right?

DR. GROTTA: Right, right. Well, anyway, I just -- I mean, that 18-year-old pregnant woman needs the treatment just as much as --

DR. JENSEN: And I'm not saying we wouldn't treat her. I'm just saying that we may not treat her with that particular device. Again, there are a lot of ways to treat patients

that are appropriate treatment with current technology.

DR. GROTTA: Okay.

DR. JENSEN: I just don't feel like we're necessarily withholding a treatment from a patient, which is sort of what, I don't know, I think your question is why are we withholding the treatment, and I'm not saying that we're withholding treatment of the patient.

DR. GROTTA: No. So I'll just go back to ischemic stroke trials because strokes don't occur in that population, and when they do, they're due to different causes usually and not necessarily something that -- and very rare. But subarachnoid hemorrhage is probably not that rare from an aneurysm in -- I mean, I don't know. How often do we see them in 20 -- you were just telling me that. I didn't realize the FDA looks at 21 years old as being an exclusion, so presumably in these trials, people under 21 would not be put in the trial. But, you know, is the cause of an aneurysmal -- or the cause of a subarachnoid hemorrhage from an aneurysm in a pregnant 20-year-old, does that occur? And if it does, is it really a different disease? I'm asking the question more than answering it, just raising it.

DR. JENSEN: Well, I guess, you know, for example, the stroke, some of the stroke device trials, it was 18 to 80 years old, right? So the pediatric population was excluded from them, but there were ways to go. You could use intra-arterial tPA to treat a clot. I mean, there were other ways to treat them rather than using the trial device. So I think we could probably make up any scenario where somebody's got something that only that device would work for, but knowing the armamentarium that we work with, I think that particular patient could still be treated with what's currently available.

Anything else?

(No response.)

DR. JENSEN: Okay, now I think I get to say I pronounce the March 1st, 2018 Neurological Devices Panel for the Medical Devices Advisory Committee adjourned. Thank

you very much.

(Whereupon, at 5:03 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

NEUROLOGICAL DEVICES PANEL

March 1, 2018

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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TIMOTHY ATKINSON

Official Reporter