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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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CIRCULATORY SYSTEM DEVICES PANEL

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November 3, 2021
9:00 a.m.

Via Zoom Videoconference

PANEL MEMBERS:

RICHARD A. LANGE, M.D.	Panel Chair
RANDALL C. STARLING, M.D.	Voting Member
JASON T. CONNOR, Ph.D.	Voting Member
JAMES C. BLANKENSHIP, M.D.	Voting Member
ROBERT W. YEH, M.D.	Voting Member
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RALPH G. BRINDIS, M.D., M.P.H.	Temporary Non-Voting Member
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KAREN WOO, M.D., Ph.D.	Temporary Non-Voting Member
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ALEX D. SHEPARD, M.D.	Temporary Non-Voting Member
JOAQUIN E. CIGARROA, M.D.	Temporary Non-Voting Member
ALBERT G. HAKAIM, M.D.	Temporary Non-Voting Member
MATT J. EAGLETON, M.D.	Temporary Non-Voting Member
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COMBINED PHYSICIAN PRESENTATION SPEAKERS:

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MARC BONACA, M.D.
American College of Cardiology

JOHN FRITZ ANGLE, M.D.
Society for Interventional Radiology

PHILIP GOODNEY, M.D.
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GUEST SPEAKERS:

GUSTAVO S. ODERICH, M.D.
John P. and Katherine G. McGovern Professor of Surgery
Distinguished Chair of Vascular and Endovascular Surgery
Director, Aortic Center
McGovern Medical School
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Memorialcare Long Beach Heart & Vascular Institute
Emeritus Professor of Surgery
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OPEN PUBLIC HEARING SPEAKERS:

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Indiana University School of Medicine

MATTIAS ANDERSSON, M.D.
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ART SEDRAKYAN, M.D., Ph.D.
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JENS ELDRUP-JORGENSEN, M.D.
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ERIC A. SECEMSKY, M.D., M.Sc.
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MEG SEYMOUR, Ph.D.
Senior Fellow
National Center for Health Research

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M E E T I N G

(9:02 a.m.)

DR. LANGE: Good morning, it's 9:00 a.m. Eastern Time and I'd like to call this meeting of the Circulatory Devices Panel to order.

I am Dr. Richard Lange, the chairperson of this Panel. I'm president of Texas Tech University Health Sciences Center in El Paso, where I'm also dean of the Foster School of Medicine. I'm an interventional cardiologist by training and now do primarily general cardiology.

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

For today's agenda, the Panel will discuss and make recommendations on the continued safety and effectiveness of endovascular stent grafts and how to strengthen real-world data collection on long-term performance of the devices, both for currently marketed devices and also for future technologies.

Before we begin, I would like to remind the public and panelists that it is a non-voting meeting, and ask our distinguished Committee members and FDA attending virtually to introduce themselves. Everybody has their video monitors already on, so as I call your names I'll ask you to unmute yourself before you speak and at that time, if you'll state your name, your area of expertise, your position, and also your affiliation, and I'll start with Dr. Starling.

DR. STARLING: Good morning. Thank you, Dr. Lange. Randy Starling, I'm a cardiologist at the Cleveland Clinic. I also have a master's in public health and epidemiology. My subspecialty is in heart failure and transplantation and that continues to be a very active part of my practice. Thank you.

DR. LANGE: Thank you, Randy.

Dr. Horvath.

DR. HORVATH: Hi, Keith Horvath, a cardiothoracic surgeon, senior director of clinical transformation at the Association of American Medical Colleges.

DR. LANGE: Thank you, Keith.

Dr. Brindis.

DR. BRINDIS: Good morning. Ralph Brindis, I'm a Clinical Professor of Medicine at UCSF at the Philip R. Lee Institute of Health Policy Studies. I'm a senior medical officer of the National Cardiovascular Data Registry with a career in cardiology, general cardiology, and interventional cardiology. Perhaps relevant for today, I also am on the executive committee of the VQI Patient Safety Organization.

DR. LANGE: Great. Thank you, Ralph, for participating.

Dr. Connor.

DR. CONNOR: I'm Jason Connor, I'm a biostatistician and president of ConfluenceStat, and Assistant Professor of Medical Education at the University of Central Florida College of Medicine.

DR. LANGE: Thank you, Jason.

Dr. Blankenship.

DR. BLANKENSHIP: Good morning. I'm Jim Blankenship, I am a practicing interventional cardiologist and Professor of Medicine at the University of New Mexico, where I'm also currently director of the cardiac cath lab and interim director of cardiology.

DR. LANGE: Thank you, Jim.

Dr. Yeh.

DR. YEH: Robert Yeh, I'm an interventional cardiologist at the Beth Israel Deaconess Medical Center, and Associate Professor of Medicine at Harvard Medical School. I direct the

Smith Center for Outcomes Research in Cardiology here, and we have expertise in the use of clinical trial and observational methods to evaluate medical device safety and efficacy.

DR. LANGE: Bobby, thanks for joining us.

Mr. Jarvis.

MR. JARVIS: Hi, I'm Gary Jarvis, I'm the Industry Rep to the Panel. I'm the VP of Clinical, Regulatory, and Medical Affairs for Alfa Medical.

DR. LANGE: Great. Thank you, Gary.

Mr. Conway.

MR. CONWAY: Paul Conway, I am the Patient Representative on this Panel. I'm a 41-year kidney patient, 25 years out on a kidney transplant. I serve as the chair of policy and global affairs for the American Association of Kidney Patients. Thank you.

DR. LANGE: Thank you, Paul.

Ms. Alikhaani.

MS. ALIKHAANI: Good morning. I'm Jacqueline Alikhaani from Los Angeles. I am a heart patient and volunteer patient advocate with the American Heart Association and also with UCLA, and I'm also an ambassador for PCORI, the Patient-Centered Outcomes Research Institute, and citizen scientist. Good to be here this morning.

DR. LANGE: Great. Jacqueline, thank you for joining us. I want to recognize Jacqueline, Dr. Woo, Dr. Barnes (sic), Dr. Cigarroa, that are on Pacific Time and it's about -- they joined us about 5:30 this morning, so thank you all. Thank you, Jacqueline.

Dr. Khaja.

DR. KHAJA: Good morning. My name is Minhaj Khaja, I'm an Associate Professor of Radiology at the University of Virginia Health System. I specialize in vascular interventional radiology as well as cardiovascular imaging, and I incidentally serve on the ACR, American College of Radiology's appropriateness criteria panel, as well, which may be relevant today.

DR. LANGE: Thank you, Minhaj.

Dr. Gravereaux.

DR. GRAVEREAUX: Good morning. Ed Gravereaux from Boston Brigham and Women's Hospital, I'm a staff vascular surgeon in the Harvard Medical School, an instructor.

DR. LANGE: Thank you, Ed.

Dr. Woo.

DR. WOO: Karen Woo, Associate Professor of Surgery at UCLA, I am a vascular surgeon. I'm also on the arterial quality committee of the Vascular Quality Initiative.

DR. LANGE: Great. Thank you, Karen.

Dr. Barnes.

DR. STARNES: Did you mean Starnes? My name is Ben --

DR. LANGE: I'm sorry, Ben.

DR. STARNES: Yeah.

DR. LANGE: It's a combination of Ben and Starnes. Ben, my apologies. Dr. Starnes, thanks for the correction.

DR. STARNES: So thank you, good morning. Ben Starnes, professor and chief of the Division of Vascular Surgery and vice chair of the Department of Surgery at the University of Washington here in Seattle. Good morning. My specialty is in aortic surgery.

DR. LANGE: Great. Ben, thank you. You can call me Rang, by the way, instead of Lange. So thanks, Ben. My apologies.

Dr. Shepard.

DR. SHEPARD: Good morning. Alex Shepard, I'm a practicing senior staff vascular surgeon at Henry Ford Hospital in Detroit, and a Professor of Surgery at Wayne State University School of Medicine.

DR. LANGE: Thank you, Alex.

Dr. Cigarroa.

DR. CIGARROA: Good morning. I'm Joaquin Cigarroa, I'm Professor of Medicine at OHSU. I am the chief of cardiology at the Knight Cardiovascular Institute and a general cardiologist with added training in interventional cardiology. Relevant to today, experience on the quality oversight for the NCDR registries.

DR. LANGE: Thank you, Joaquin.

Dr. Hakaim.

DR. HAKAIM: Al Hakaim, I'm a staff vascular surgeon at the Mayo Clinic in Florida, Professor of Surgery at the Mayo Medical School.

DR. LANGE: Al, thanks for joining us.

Dr. Eagleton.

DR. EAGLETON: Hi, I'm Matt Eagleton. I'm the chief of vascular surgery at the Mass General Hospital and Professor of Surgery at Harvard Medical School, and I have just a longstanding interest in endografting for aortic disease.

DR. LANGE: All right. And before we introduce the last person, I want to thank many of you that participated in yesterday's panel as well as today, so thank you very much.

And the last person to introduce is Dr. Zuckerman.

DR. ZUCKERMAN: Yes, good morning. Bram Zuckerman, cardiologist by training and currently Director, FDA Office of Cardiovascular Devices.

DR. LANGE: Thank you to all of you.

At this time I'd like to introduce Akinola Awojope, the Designated Federal Officer for today's Circulatory Devices Panel, and he will make some introductory remarks.

DR. AWOJOPE: Good morning, everyone, to our second day meeting. My name is Dr. Akinola Awojope, I'm the Designated Federal Officer for today's meeting. Now I will read the Conflict of Interest Statement to everyone.

The Food and Drug Administration (FDA) is convening today's meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the industry representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

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

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

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential 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. Subsection 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations on the continued safety and effectiveness of endovascular stent grafts and how to strengthen the

real-world data collection on the long-term performance of the devices, both for currently marketed devices and for future technology. The FDA intends to request the Panel input on the clinical outcomes that are most relevant to capture the real world along with the frequency and duration. And additionally, the FDA intends to seek input on data collection platform and how to synthesize and optimize real-world data collection.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Subsection 208 Part (b)(3) to Dr. Albert Hakaim, Dr. Alexander Shepard, Dr. Randall Starling, Dr. Matt Eagleton, and Dr. Robert Yeh.

I will start with Dr. Hakaim's waiver addresses his imputed employer's research contract from a firm that manufacturers endovascular stent graft. Dr. Hakaim's employer was awarded funding between 25 and $50,000 in total under the agreement.

Dr. Shepard's waiver addresses his imputed employer's research contract from the firm that manufactures abdominal stent graft. To date, Dr. Shepard's employer was awarded funding between 5,000 and $10,000 in total under an agreement.

Dr. Starling's waiver addresses his imputed employer's research contract from a firm that manufactures endovascular stent graft. Dr. Starling's employer was awarded funding between 50,000 and $70,000 in total agreement.

Now I will go to Dr. Eagleton's waiver addresses imputed employer's research contract from the firm that manufactures endovascular stent grafts. Dr. Eagleton's employer was awarded funding between 50,000 and $100,000 in total agreement.

Dr. Yeh's waiver addresses his imputed employer's contract from two unaffected entities to 31 (ph.) of the products at issue. Dr. Yeh's employer was awarded funding between 200,000 and $250,000 in total of an agreement.

The waivers allow these individuals to participate fully in the panel deliberations.

FDA's reason for issuing the waivers are described in the waiver documents which are posted on the FDA website for the public to see. The copy of the waivers may also be obtained by submitting a written request to the Agency's Division of Freedom of Information and the office is in Rockville, Maryland. I will share the address with you: 5630 Fishers Lane, Rockville, Maryland, and the zip code is 20857.

Mr. Gary Jarvis is serving as the Industry Representative, acting on behalf of all related industry. He is also employed by Alfa Medical.

For the record, the Agency noted that Dr. Rodney White, who is an invited guest speaker with us today, has acknowledged interests with affected firms in the form of institutional contract, research, consulting/advisory, and speaking services.

The next guest speaker, Dr. Gustavo Oderich, who is also an invited guest speaker with us today, has acknowledged interest with affected firms in the form of a research grant, speaking, and consulting/advisory.

Then, which is the last person in the guest speaker, Dr. Tara Mastracci, another invited guest speaker with us today, has acknowledged interests with affected firms in the form of consulting and scientific advisory.

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 the FDA participant has personal or imputed financial interests, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record purpose.

FDA encourages other participants to advise the Panel of any financial relationship they may have with any firm at issue.

The copy will be available for review and will be included as a part of the official transcript.

For the duration of the Circulatory System Devices Panel meeting on November 3rd,

2021, Mrs. Jacqueline Alikhaani has been appointed to serve as a Temporary Non-Voting Member. For the members and for the record as well, Mrs. Alikhaani serves as a consumer representative of the Cardiovascular and Renal Drugs Advisory Committee at the Center for Drug Evaluation and Research (CDER). This individual is a special Government employee who has undergone the customary conflict of interest review and has reviewed the materials to be consider at this meeting.

The appointment was authorized by Russell Fortney, Director of the Advisory Committee Oversight and Management Staff, on October 5th, 2021.

Before I turn the meeting back to Dr. Lange, which is our chairperson for the Day 2 meeting, I would like to make some few general announcements.

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

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

And the press contact for today's meeting is Shirley Simson.

Thank you very much, everyone. Thank you, Dr. Lange. Now I'll hand the meeting back to you.

DR. LANGE: All right, the last of the presentation was garbled. Can everybody hear me clearly? Great, I appreciate that. Let me repeat some of the things in the end.

First of all, our Consumer Rep, Patient Rep, and company representatives were all introduced, Gary Jarvis, Jacqueline Alikhaani, and Paul Conway.

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

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

And the press contact for today's meeting is Shirley Simson.

So those were the remarks that you may not have been able to hear.

At this time I'd like the FDA to start their presentation. I would like to 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, and that's me.

The FDA will have 30 minutes to present and at this time I'd ask the FDA, please, to begin their presentation.

DR. FAIRMAN: Good morning. For those of you who don't know me, I am a former Professor of Surgery and chief of the Division of Vascular Surgery and Endovascular Therapy for 20 years at the University of Pennsylvania. I am past president of the Society for Vascular Surgery, serving in 2018. Since July of 2020, I have been serving on the Vascular and Endovascular Devices Team as a medical officer here at the FDA.

This is our presentation outline for today. We'll begin with an overview of abdominal aortic aneurysms and therapies, we'll discuss the history and current status of endovascular abdominal aortic aneurysm repair, currently FDA-approved AAA endovascular grafts, benefits and disadvantages of EVAR, current realities, EVAR outcomes of interest, the current regulatory paradigm for EVAR devices will be described by Gordon Bryson, and finally, the role of long-term surveillance.

An abdominal aortic aneurysm results from structural deterioration of the aortic wall and gradual expansion of the aneurysm sac. Enlargement increases the risk of rupture. This results in an estimated 10,000 deaths each year in the United States.

To the far right is an MRI image of an abdominal aortic aneurysm, although CT angiography and ultrasound, also shown here, are the more common imaging modalities.

Risk factors listed here are from the SVS guidelines published in 2018 and these include age greater than 65 years, male gender, smoking, hypertension, and a family history of abdominal aortic aneurysms.

A few comments about medical management. Patients should be encouraged to seek appropriate medical management for hypertension, hyperlipidemia, diabetes, and other atherosclerotic risk factors. Smoking cessation is the most important intervention in a patient with an abdominal aortic aneurysm. Despite the benefits of statins in cardiovascular disease, durability to limit aneurysm expansion is lacking. An increased risk of rupture has been reported for patients who recently discontinued ACE inhibitors. Patients should be counseled that moderate physical activity does not precipitate rupture or influence abdominal aortic aneurysm growth rate.

Open surgical repair is an invasive and major operation performed either through a transabdominal or retroperitoneal approach.

EVAR is performed either through a surgical exposure of the common femoral arteries or more commonly today, percutaneously. The goal is to exclude blood flow from the aneurysm and depressurize the sac, leading to sac regression over time.

Endovascular abdominal aortic aneurysm repair was initially described by Volodos in 1986. Juan Parodi, in 1991, published his experience with retrograde deployment through the femoral arteries of a stent-anchored, Dacron prosthetic graft that would act to depressurize the aneurysm sac and thus reduce the risk of rupture. EVAR was born.

Early stent grafts were tubular or aorto-aortic, but we very quickly learned that the aortic bifurcation was not a secure zone for distal attachment of stent grafts. The first unibody bifurcated or aorto-bi-iliac stent was developed in 1993. Regulatory approval for the first abdominal aortic stent graft occurred in 1996 in Europe and in the United States in 1999.

EVAR has been widely accepted in the United States as approximately 80% of aneurysms are so repaired. This represents greater than 50% of the global market share. In 2012, approximately 47,000 EVARs were performed in the United States and the United

States EVAR endograft market has continued to grow by approximately 8% each year.

As you can see here to the right in Figure 3, open surgery rates have consistently declined from 2004 to 2015.

There are eight currently commercially approved and marketed EVAR devices in the United States. This table references the sponsor, device name, year of the original PMA approval, and the currently marketed iteration.

Design features of endovascular grafts are demonstrated here. The modern version of a stent graft design is a fully supported bifurcated modular graft.

Several designs have barbs to provide active fixation, as illustrated by this blue arrow in picture A to the left. Most current stent graft designs have suprarenal stents to inhibit downward migration and Type I endoleak.

Another device allows for extension of the proximal seal zone into the visceral segment by incorporating fenestrations into the design.

One device with suprarenal fixation is approved for use with adjunctive EndoAnchor fixation.

One device is designed for passive fixation, whereby the flow divider of the stent graft sits directly on the aortic bifurcation, as illustrated at the bottom left in Figure E.

One stent graft design has unique polymer-filled sealing rings intended to create enhanced seal in the aortic neck.

And finally, another device offers angulation control to achieve conformability and seal.

Failure modes impacting long-term device performance are listed on the left side of this slide:

- Iliac limb stenoses and/or occlusions;
- Stent graft migrations;

- Fabric tears;
- Fabric porosity;
- Stent or barb fractures;
- Loss of proximal or distal seal; and
- Modular stent graft separations.

The consequences of these failure modes are listed to the right, and I bolded those that I believe are most relevant and important:

- Lower extremity ischemia due to thromboembolic events;
- Endoleaks, predominantly Type I and III;
- Continued aneurysm sac expansion; and
- The need for re-interventions to prevent rupture.

The benefits of EVAR over open surgical repair are perioperative, and by that we mean 30 days or less, and include the following:

- High degree of patient acceptance;
- Shorter operative times;
- Reduced operative blood loss;
- Lower major operative complications;
- Elimination of intensive care unit stays;
- Reduced hospital length of stay;
- Rapid recovery;
- Selective use of local anesthesia; and perhaps most importantly,
- Lower mortality rates

The reduced 30-day mortality was clearly demonstrated in these landmark clinical trials, EVAR-I, Dream, and OVER.

A review of nearly 80,000 Medicare patients confirmed these results are

representative of current outcomes, with an overall perioperative mortality of 5.2% for open repair and 1.6% for EVAR.

The longer-term disadvantages of EVAR are listed here:

- Higher reintervention rates related to:
  - Device patency;
  - Aneurysm sac expansion; and
  - Endoleaks.

The perioperative survival advantage of EVAR is not maintained over time. Long-term survival is similar after 3 years.

There is a need for long-term imaging follow-up with radiation and intravenous contrast.

There's a higher risk of late aneurysm-related death post-EVAR.

And again, a review of nearly 80,000 Medicare patients through 8 years of follow-up demonstrated:

- Aneurysm rupture following EVAR in 5.4% versus open surgery in 1.4%;
- Aneurysm-related reinterventions after EVAR in 18.8% versus open surgery in 3.7%; and finally,
- Similar long-term all-cause mortality.

The longitudinal outcomes of EVAR are demonstrated here. This is a retrospective review of a 16-year EVAR experience, nearly 2,000 EVARs performed between 2000 and 2016 from the University of Pennsylvania. The overall reintervention rate was 7.5%. Reinterventions were performed as far out as 8 years following EVAR. Eighty percent of patients who required reinterventions underwent two or fewer reinterventions, whereas 13% underwent three and 7% underwent four or more reinterventions. The mean time to first reintervention is 2.3 years.

The most common causes of reintervention are illustrated on this pie chart to the right. Type II endoleak with sac expansion accounted for 55% of our reinterventions. This was followed by Type I endoleak in 23% and Type III endoleak in 10%. The most common cause of open conversion and explant was Type II endoleak and sac expansion.

Long-term disadvantages of EVAR are not specific to individual devices. Longer-term follow-up in three pivotal studies with 5-year published data show that clinical events continued to occur after 1 year, which is the typical follow-up duration necessary to support FDA approval of a new AAA EVAR device.

Current U.S. practice demonstrates liberal use of EVAR. Anatomic inclusion and exclusion applicability for EVAR based on device instructions for use approximates 50%. I would again ask you to recall, earlier in this presentation I mentioned that 80% of aneurysms in the United States today are performed with EVAR.

EVAR use with anatomies outside the instructions for use is predictive of sac enlargement and late rupture. And again, rates of readmissions and multiple reinterventions occur approximately 7% to 20% of the time.

For the data presented in this slide I would refer you back to the FDA Executive Summary, in particular, regarding the rates I'm reporting here. Follow-up imaging surveillance noncompliance approximates 60% with gaps 3 to 4 years after EVAR. Rates of sac enlargement at 5 years have approximated 41%. Endoleak occurs in one-third of all EVARs. Type I, II, and III endoleaks may develop years following EVAR. There is a need for long-term follow-up of patients with EVAR devices.

While Type II endoleaks are not device specific, they clearly are technology based. Persistent Type II endoleaks are reported to occur in 15% of cases. These may result in sac expansion in up to 25% and require multiple reinterventions. Delayed Type II endoleaks occur and may also result in sac expansion. In up to 60% of patients treated for Type II

endoleak, aneurysms continue to expand. Effective treatment of Type II endoleak remains a challenge post-EVAR.

I will stop here and introduce Gordon Bryson, who will be discussing the current regulatory paradigm for AAA endovascular devices. Thank you.

MR. BRYSON: Hello, my name is Gordon Bryson and I am a biomedical engineer and a lead reviewer within the Office of Cardiovascular Devices' Vascular and Endovascular Devices Team. I'll now present an overview of the current regulatory paradigm for AAA endovascular devices, as well as the unmet need for improved postmarket surveillance.

FDA's mission is to protect public health and promote innovations that make safe and effective medical products available to U.S. patients. This involves ensuring that there is adequate information to demonstrate reasonable assurance of safety and effectiveness while also avoiding a data burden so high that innovative devices addressing unmet clinical needs do not get to market in a timely fashion.

As part of FDA's total product life-cycle approach for AAA endovascular devices, part of this balance is consideration of both pre- and postmarket data when making regulatory decisions. As I will discuss in the following slides, premarket data typically consists of 1-year clinical data and supportive nonclinical data. And postmarket data consists of longer-term clinical data, usually to 5 years.

To support a premarket approval application for a new AAA endovascular device, FDA requires both nonclinical testing and clinical data. Nonclinical testing involves bench-top testing, in-vitro simulated use, and a large animal study. FDA also requires valid scientific evidence from one or more clinical resources to provide data that the device is safe and effective.

Recent premarket pivotal studies for AAA endovascular devices have the following characteristics: the clinical studies are multicenter, prospective, and single arm. Sample

sizes range from 150 to 200 patients at 25 to 40 investigational sites.

For two primary endpoints, safety is evaluated through 30 days and effectiveness is evaluated through 12 months. Secondary endpoints capture the rates of the primary endpoints through 5 years, including major adverse events and device integrity issues.

The primary endpoints are described here in more detail. Safety is evaluated with a composite of major adverse events at 30 days, including:

- Aneurysm-related mortality;
- Myocardial infarction;
- Stroke;
- Renal failure;
- Respiratory failure;
- Paraplegia;
- Bowel ischemia; and
- Significant procedural blood loss.

The effectiveness endpoint is a composite of technical success at the conclusion of the procedure and absence of device-related effectiveness outcomes evaluated at 12 months. The secondary endpoints continue to capture adverse events and device-related outcomes through 5 years, such as secondary interventions and aneurysm enlargement.

The evidence to support iterative device changes balances premarket and postmarket data requirements and they're targeted to address device performance that may be impacted by the changes. Some changes may be supported by nonclinical evaluations alone, such as bench-top verification testing to support minor changes to the delivery system. However, more significant interventions may require both nonclinical data and clinical evaluations. Examples of significant changes requiring new clinical data include an expansion of the indications of use or a change in the mechanism of delivery system. In

some cases a reasonable assurance of safety and effectiveness of a modified device can be demonstrated with shorter follow-up duration than would be required to support a new device.

FDA considers the balance between pre- and postmarket data from both new and modified devices, so post-commercialization surveillance is required for EVAR devices.

Since marketing applications often have only 1-year pivotal data results at the time of marketing approval, follow-up of pivotal study subjects through 5 years is required. In some cases the conditions of approval require new post-approval studies to collect confirmatory safety and effectiveness data. This may include real-world data or additional clinical data on a subset of patients who experienced a particular type of event during the pivotal study, such as stent fractures, to better understand any clinical sequelae or effective follow-up measures. Additional information may be collected to support the translation of pivotal study results to real-world use. Finally, FDA requires manufacturers to publish an annual clinical update for physician users to report new findings from commercial use.

Another postmarket requirement is submission of medical device reports, or MDRs. MDRs describe suspected device-associated malfunctions, serious injuries or deaths. Mandatory reporters, such as importers and device user facilities, are required to submit MDRs, and voluntary reporters, such as healthcare professionals, are encouraged to submit reports.

This plot is an example of trends in EVAR device MDRs. In this figure, records over the last 5 years from all marketed AAA devices are organized by the time to event occurrence. Although most reported events are periprocedural, events continue to occur 5 years post-implantation and beyond.

MDRs have strengths and limitations. MDR advantages include that all stakeholders may submit reports. Coded information can be easily analyzed for trends. Reports usually

include relevant time points such as the implant date and the date of the suspected event. Reports can be submitted throughout the lifetime of the product, including longer term. And reports allow for entry of the device's narrative description.

MDRs have several limitations, including that it may be incomplete, inaccurate, untimely, unverified, or biased. Additionally, it is difficult to determine an accurate rate of events because events are known to be underreported and there is no denominator of devices implanted. Finally, trending of specific events such as Type III endoleaks is very time intensive because coded information is imprecise.

Overall, MDRs are helpful in monitoring device safety after marketing, but given the limitations, the current system does not provide for a robust means for EVAR device surveillance.

The current regulatory paradigm requires safety and effectiveness data for timely AAA device approval but may not capture important long-term real-world data. Further, as Dr. Fairman has mentioned, there is significant use of AAA devices outside the approved indications, so pivotal study data may not reflect real-world device outcomes.

The medical literature and the MDRs show that significant events requiring reintervention, such as endoleaks, continue to occur well beyond 5 years post-EVAR, which are not captured with adequate precision by pivotal studies. Real-world outcomes of iterative device changes implemented after marketing are also not captured in pivotal studies.

We are seeking input from the Panel on surveillance platform characteristics including key outcomes of interest, both clinical and imaging. Also, the Panel should consider how to maintain a high level of data quality and completeness so that this platform can meet the needs of all stakeholders. For example, data quality may be monitored by a central organization and follow-up compliance needs to be sufficiently high to be useful for

clinical and regulatory decision making.

FDA believes physicians and patients would benefit from knowing these long-term outcomes. However, we acknowledge the limitations of current database infrastructures in capturing these outcomes. The Panel will be asked to comment on the key outcomes that are clinically meaningful and feasible to capture from real-world data to provide needed information on long-term EVAR benefits and risks.

There are a number of resources currently available for gathering select real-world data which may be considered as the Panel develops recommendations. These include medical device reports, databases of singular or regional health systems, literature publications, and claims or registry based data.

My colleague, Dr. Li Wang from the Division of Clinical Evidence and Analysis, will speak more on these resources later in the day.

The Panel will be asked to discuss the key attributes that a real-world surveillance infrastructure should incorporate. FDA also seeks the Panel's input on strategies to incentivize relevant stakeholders to participate in real-world data collection on a routine basis.

There are several existing regulatory mechanisms to consider. A PMA condition of approval may require manufacturers to collect and report real-world data on the device and report to relevant stakeholders. Additionally, a postmarket surveillance order, also called a 522 order, may require manufacturers to conduct a scientifically valid postmarket survey to address a specific public health question. Five-twenty-two orders can cover multiple devices from different manufacturers if the public health question is identical for devices.

In summary of the current regulatory paradigm of EVAR devices, FDA utilizes least burdensome principles and balances pre- and postmarket data requirements in order to facilitate timely approval of devices with data demonstrating reasonable assurance of safety

and effectiveness.

The current approval requirements for a new EVAR device is 1-year safety and effectiveness data from a pivotal study and 5-year follow-up data on the pivotal study subjects after the device is marketed. New enrollment post-approval studies are also sometimes required.

Valuable data on how devices perform in the real world is underutilized, particularly key outcomes beyond 5 years, as is device use outside the approved indications. There are several mechanisms to facilitate real-world data collection.

I will now turn the presentation back over to Dr. Fairman to present the conclusions from FDA.

DR. FAIRMAN: I will summarize the last two presentations with this final slide.

Pivotal study outcomes at 5 years and long-term real-world data indicate significant adverse clinical events continue to occur post-EVAR.

There is uniform agreement that long-term follow-up is indicated post-EVAR.

While surveillance is critical to understanding long-term real-world device performance, clinical and imaging outcomes have been challenging to capture by current surveillance methods.

EVAR patients and physicians would benefit from knowing the rates of important clinical adverse events to an adequate degree of precision. For this, large numbers of patients followed post-market are needed.

A high-quality, robust post-market surveillance system is aligned with FDA's mission to protect public health and our total product life-cycle approach to device regulation.

Thank you for the opportunity to present today.

MR. BRYSON: I will now present an overview of FDA's questions for the Panel. Please keep in mind these questions as you hear from additional presenters.

Question 1: Please discuss the safety and effectiveness of endovascular stent grafts in the treatment of abdominal aortic aneurysms stratified by near-term and long-term outcomes.

Question 2a: Available long-term data demonstrate that adverse events continue to accrue post-EVAR. Please discuss which of the following real-world clinical outcomes should be assessed in a long-term EVAR surveillance system:

- All-cause mortality
- Aneurysm-related mortality
- Aortic rupture
- Aortic reinterventions
- Others

Question 2b: Although imaging outcomes are collected in pre-market and FDA-required postmarket studies, these studies have a modest sample size and it is challenging to collect serial imaging data in real-world surveillance. Please discuss the importance and feasibility of capturing the following imaging outcomes in real-world surveillance:

- Endoleaks
- Loss of device integrity
- Aortic enlargement
- Device migration
- Device patency

Question 3: Please discuss whether strengthening existing real-world surveillance is needed to evaluate long-term real-world EVAR performance.

Question 3a: If so, please discuss the key attributes that should be included in a real-world surveillance infrastructure to assure high-quality and clinically useful long-term EVAR device evaluation (e.g., enrollment strategies to address potential selection bias, data

monitoring and auditing, event adjudication, core labs, major endpoints, and statistical analysis plans).

Question 3b: Please discuss the frequency and duration of surveillance for patients post-EVAR that would be clinically meaningful and feasible to capture through a real-world surveillance infrastructure, including recommendations for patients who undergo aortic reintervention.

Question 3c: Please discuss strategies that can incentivize relevant stakeholders to participate in real-world data collection on a routine basis.

Question 3d: Please comment on how device manufacturers, healthcare systems, professional societies, individual providers, and other stakeholders should collaborate to maximize long-term follow-up compliance and data quality on EVAR device performance.

We would like to thank the Panel for their time in hearing this presentation and we look forward to your deliberations. Thank you.

DR. LANGE: I'd like to thank the FDA for that very clear presentation and we have about 10 minutes for brief clarifying questions the Panel would like to ask the FDA based on their presentation.

Dr. Starnes, Dr. Shepard.

DR. STARNES: Yeah, good morning. Can you please comment more on what the 522 process involves?

DR. JOHNSON: Hello, this is Carmen Gacchina Johnson, Assistant Director for the Vascular and Endovascular Devices Team, and my colleague is pulling up a slide specifically on the 522 process. So as outlined in this slide, this is a mechanism wherein postmarket surveillance is ordered by the Agency. The requirements which may be relevant to aortic endovascular grafts are highlighted here. To summarize, Section 522 of the Food, Drug, and Cosmetic Act provides FDA the authority to require manufacturers to conduct postmarket

surveillance if failure of the device would be reasonably likely to have a serious adverse health consequence and the device is intended to be implanted in the human body for more than 1 year. FDA may identify issues that are appropriate for postmarket surveillance at any point during the life cycle, including postmarket surveillance. In general, FDA has the authority to order prospective postmarket surveillance for a duration of up to 36 months unless the manufacturer and FDA agree to extend that time frame.

DR. STARNES: Thank you.

DR. LANGE: Dr. Starnes, does that address your question?

DR. STARNES: For the most part, yes.

DR. LANGE: Okay, great. And we'll have more time to discuss this.

I've got Dr. Shepard and then Dr. Khaja.

DR. SHEPARD: Thank you. Alex Shepard.

DR. LANGE: Then Mr. Conway. Go ahead.

DR. SHEPARD: Alex Shepard, Henry Ford Hospital. I have always been interested as to why lower extremity ischemia or limb loss is not considered a major adverse event as a primary safety endpoint for the EVAR trials. I don't know if anybody from the FDA could answer that question for me.

DR. JOHNSON: Thank you for that question and I will turn it over to my colleague, Dr. Fairman.

DR. FAIRMAN: Good morning, this is Ron Fairman. Alex, I would say that in all of the pivotal trials, lower extremity ischemia and limb loss is captured. Maybe not as a primary endpoint, but it's certainly captured as a secondary endpoint. And as you are well aware, lower extremity ischemia has rarely resulted in limb loss through any of the many pivotal trials that have been conducted in the United States. I hope that somewhat addresses your question.

DR. LANGE: Great. And Alex, we'll have more time to talk about whether we ought to be including it as well, to define one. Does that address your -- at least the FDA clarification address it, Alex?

DR. SHEPARD: Yes.

DR. LANGE: Okay, thank you.

I've got Dr. Khaja and Mr. Conway.

DR. KHAJA: Minhaj Khaja from UVA. My question to the FDA is regarding surveillance and in the prior question, is that surveillance clinical surveillance or are we just defining specific imaging surveillance and if so, what type of imaging?

DR. JOHNSON: Hi, this is Carmen Gacchina Johnson. So we are seeking panel input on both clinical and imaging surveillance, whether they are meaningful clinically and whether they are practical, and we're seeking your input on what the relevant endpoints are and how those can best be collected.

DR. KHAJA: Okay, thank you.

DR. LANGE: Great. So Minhaj, especially for the imaging part, I'll be calling upon your opinion with regard to these issues, so thank you.

Mr. Conway.

MR. CONWAY: Thank you, Doctor. Just to level-set at the beginning of the day here, so I understand the limits of the MDRs in terms of a passive mechanism for patients to report in. To the FDA, the question is this: What other current mechanisms do you have in place right now to capture patient-reported outcome or patient insight data relative to long-term surveillance?

DR. JOHNSON: Carmen Gacchina Johnson. Thank you so much for the question. There are not currently patient-reported outcomes that are captured in our AAA endovascular graft studies; however, we are certainly interested in capturing real-world

data from patient experience. Certainly a priority area for the Agency.

MR. CONWAY: Thank you.

DR. LANGE: Great, thank you. Any other clarifying questions for the FDA based on their presentation?

(No response.)

DR. LANGE: All right, seeing no hands, we'll advance to the next presentation. We'll now proceed to the Combined Industry Presentation. Again, I would like to invite the industry representatives to begin, they will also have 30 minutes to present, following which we'll have a brief time for clarifying questions, as well. So at this particular time, please begin your presentation.

DR. STARR: Good morning, and thank you for allowing us to come together to discuss industry perspectives today on data collection strategies for EVAR. My name is Jean Starr and I'm a vascular surgeon at Ohio State. I'm also the medical safety officer for Medtronic's aortic and peripheral vascular health operating units. I will be joined by Scott Williams, Director of Regulatory Science from Cook Medical.

During our joint presentation, I'll focus on the clinical perspective of endovascular aneurysm repair and Scott will focus on industry's proposal for strengthening real-world data collection on longer-term performance of endovascular stent grafts.

We are representing the efforts from the companies seen here that have developed endovascular stent grafts for the treatment of AAA disease.

First let me provide a brief background about aortic aneurysm disease and share how in my practice I discuss treatment options with a patient who has been diagnosed with an aneurysm.

Patients are usually asymptomatic until the disease progresses and ultimately may lead to aortic rupture and possible death. Many times aneurysms are found incidentally,

either on imaging examinations such as CT scans and ultrasounds, but can also be found on physical examination by their physician.

Up to 50% of patients with untreated aneurysms greater than five and a half centimeters will ultimately die of a rupture over a 5-year period.

The benefits of treating the aneurysm with open or endovascular repair outweigh the risks of observation when an aneurysm reaches five and a half centimeters in men or 5 cm in women; hence, intervention is recommended at this size or larger.

Patients are much more well informed today than in the past with the evolution of information platforms. Medical management can be appropriate in some patients who have significant comorbidities or other more urgent medical issues and for patients whose aneurysms have not yet reached the threshold for repair.

Endovascular repair is preferred by most patients given the shorter hospitalization and recuperation times. I always explain the caveat, however, of the necessity of lifelong clinical and imaging follow-up to monitor for aneurysmal disease progression and new aneurysm formation, as well as any complications that might arise. I always tell patients we'll be friends for life. However, in reality, patient compliance with follow-up is a complicated matter and often far from ideal.

We also discuss that based on available data, long-term survival is similar for endovascular and open repair despite the earlier advantages of endovascular repair. Open repair also has a lower reintervention rate and less frequent requirements for imaging and physician follow-up.

The first endovascular stent graft was approved in the U.S. in 1999. Over time, in collaboration with physician partners, endovascular grafts have become more flexible and modular, and delivery systems have become more user friendly. Improved migration resistance has aided in preventing distal migration. We have gained the ability to treat

patients with larger, shorter, and more angled aortic necks. Treatment for patients who have smaller arteries has improved due to the development of lower-profile delivery systems. These developments have led to more patients being eligible for endovascular treatment and furthermore, demonstrate the commitment of industry to improving patient care for those with aneurysmal disease.

Even with these innovations, the need for long-term follow-up remains important to ensure continued assessment of the safety and effectiveness of endovascular stent grafts.

We've accumulated a wealth of information to support safety and effectiveness of EVAR devices based on our IDE trials with midterm follow-up in the range of 2 to 5 years. Device improvements have allowed a broader population to be treated with EVAR, but more importantly have led to improved patient outcomes.

These are a few publications on the midterm outcomes of current generation stent grafts in which the physicians consistently conclude that modern stent grafts have been proven to be safe and effective in the midterm.

While EVAR has the advantage of improved short-term mortality and faster recovery with shorter hospitalizations compared to open surgery, it is well established that over time a portion of patients require a reintervention during their lifetime after EVAR.

With positive short- and midterm results, most societies now recognize that --

(Audio malfunction.)

DR. LANGE: I'm going to stop right here and ask audiovisual to stop so that the company's presentation is not garbled and we'll restart in just a moment.

(Pause.)

DR. STARR: A portion of patients require a reintervention during their lifetime after EVAR.

With positive short- and midterm results, most societies now recognize that EVAR

has become the preferred approach for the treatment of aortic aneurysms. While the publication of midterm outcomes have been encouraging, there's an opportunity to learn more about the long-term performance of these devices.

A recent publication in the *Journal of Vascular Surgery* examined the reintervention rates over the long term and how this rate may have improved over time with the introduction of newer device technologies.

In this study, Wanken et al. performed a systematic review and meta-analysis of the literature available. Three randomized controlled trials and 27 observational studies with a total of over 32,000 patients with implants from 1996 to 2014, representing a variety of endovascular grafts, were evaluated. Studies were excluded if they primarily evaluated patients with ruptured aortic aneurysm or off-label anatomies. The authors reported that the cumulative number of patients requiring a reintervention over 7 years has been cut in half, and this is driven in part by newer devices that exhibit lower reintervention rates. However, we agree with the authors that EVAR patients remain at risk for reintervention and should be followed indefinitely.

To summarize, device improvements have allowed a broad range of patients to be treated more safely over time. As a class, EVAR devices have been evaluated to be safe and effective after extensive testing in clinical studies with follow-up out to 5 years. Nonetheless, the potential need for reinterventions persists, supporting the need for long-term follow-up. And with an expectation for continued follow-up of EVAR patients, an opportunity exists to strengthen data collection and analyze long-term real-world data in a more systematic fashion.

The key objectives, as Scott will highlight, are to build off existing large sources of relevant data where possible. Our goal is to optimize data collection and allow for quick and reliable detection of safety and effectiveness signals.

Achieving improvement in aneurysm patient management requires a partnership and team approach. It's crucial for all stakeholders to be involved, including patients, their physicians, professional societies, advocacy groups, regulatory agencies, and device development companies.

Thank you, and I will turn the presentation over to Scott Williams to provide industry's perspective on how to strengthen real-world data collection and analysis.

Scott.

MR. WILLIAMS: Thank you, Dr. Starr, for providing the clinical background that speaks to the importance of lifelong follow-up, recognizing in particular the potential need for reintervention at any time.

Certainly, the need for long-term follow-up after EVAR is well recognized, for example, in device IFUs as well as society guidelines. And given the longevity of some patients after treatment, there is a need to enhance the collection and analysis of real-world data on long-term performance of these devices. There's been a lot of work already in this area which we hope to build on.

Before we provide some thoughts from industry and make recommendations for how to enhance long-term data collection, analysis, and surveillance, it is important to understand what surveillance mechanisms are currently in place throughout the lifetime of a device.

Currently, both short- and long-term mechanisms are utilized for surveillance of device performance. While many of the mechanisms shown here in the table tend to focus on follow-up through 5 years, other mechanisms such as complaint monitoring and assessment of physician-driven studies, publications, and presentations go on indefinitely. All of these information sources are reviewed on an annual basis and summarized in reports to FDA as a condition of PMA approval to support a continued assurance of safety and

effectiveness for as long as a device is on the market.

Postmarket surveillance and physician-driven data are often the primary sources for clinical data beyond 5 years and each of these has limitations. In fact, multiple think-tank meetings involving FDA, physicians, and industry have explored potential ways to strengthen active long-term surveillance, including through real-world data collection.

Beyond strengthening the surveillance framework for EVAR devices, longer-term real-world data collection is consistent with lifelong follow-up recommendations already in labeling and society guidelines for this patient population.

In addition, compared to premarket IDE studies, longer-term real-world data provides the opportunity for an assessment of device performance in a broader cross-section of patients and healthcare professionals --

(Audio malfunction.)

MR. WILLIAMS: -- the potential impact from off-label uses. It may also provide the potential to inform future iterative changes in device design.

So let's look now at what industry would consider to be most relevant to assess in a real-world setting to monitor long-term performance of EVAR devices.

Industry considered many possible endpoints and their importance to different stakeholders to propose outcomes that are clinically important, informative, and feasible. In doing so, we recognized that it would not be practical nor feasible to assess, long-term, all the same endpoints in a real-world setting as we routinely assess through 5 years under IDE studies.

Based on the assessment of the EVAR device literature and the patient population, industry proposes assessing three endpoints as part of long-term real-world data collection: vital status, reinterventions, and aneurysm rupture. These commonly reported and clinically relevant outcomes can be reliably collected in a real-world setting over 10 years.

They have been utilized as primary and secondary endpoints in several large randomized trials of EVAR versus open surgical repair and have been supported by outcomes of patient preference studies. In these studies, major complications including death and reintervention ranked as most important characteristics for patients, both treated and untreated, as well as their caregivers and providers.

Additionally, our recommended endpoints will provide a broad assessment of outcomes, capturing other key clinical events such as limb occlusion and renal occlusion that often lead to reinterventions.

Similarly, imaging-based endpoints such as endoleak, migration, change in aneurysm size, and device integrity may be particularly challenging given the relatively low follow-up rates acknowledged in society guidelines. However, the same endpoints will often be detected as the reason for reintervention or change in vital status and therefore can still be captured through the proposed endpoints.

To collect long-term real-world data on vital status, reintervention, and aneurysm rupture, we considered many possible options. Existing standalone data sources include independent registries, claims data, and patient implant data collected at the time of the initial procedure. We also considered combinations of these existing sources as well as entirely new data sources not in existence.

In assessing each option, we considered the robustness and accuracy of the data available both at baseline and during follow-up for the endpoints of interest through 10 years. We also gave a lot of consideration on how to make this effort successful, including the practicality of being able to both implement and sustain the efforts without substantial additional burden on hospitals and physicians with respect to resources and funding while still collecting complete and accurate data in a timely and efficient manner. A key objective was to take advantage of existing sources of data where possible in order to quickly assess

safety and effectiveness of EVAR devices. After careful consideration, our recommendation is to combine existing data sources using registries as a source for baseline and device-specific information linked to claims as a source for longer-term follow-up data on the relevant endpoints.

One example of an established registry in this device space is the Society for Vascular Surgery Vascular Quality Initiative, which can be linked to CMS claims. Similar approaches have been demonstrated in other therapy areas as well, including transcatheter valve therapy. When combined, the sources provide the necessary baseline and longer-term follow-up data.

Additionally, the data sources capture large populations of patients, healthcare professionals, and hospitals, thus supporting generalizability. Moreover, demonstration projects provide confidence regarding not only the ability to link the datasets, but also the accuracy of the results.

Many of us here are acquainted with the Society for Vascular Surgery Vascular Quality Initiative, or VQI, registry as a source for real-world evidence and we'll hear more about it throughout today. In brief, VQI is a collaboration between physicians and hospitals to improve the quality, safety, effectiveness, and cost of vascular health care. It was established a decade ago, now with several hundred participating hospitals and results on more than 64,000 EVAR procedures including detailed device-specific information. It is the largest prospective dataset with relevant patient-level information for this patient population.

With respect to longer-term follow-up, the architecture of the registry is somewhat limited due to having originally been established to collect outcomes through only 1 year. Therefore, in its current form, VQI will not provide stakeholders with the longer-term real-world data that we are seeking, necessitating linkage to CMS as the source for the longer-

term data.

The ability to link these two data sources, thereby narrowing the baseline patient- and device-specific information in VQI with the data from CMS, has been established through the work of the Vascular Implant Surveillance and Interventional Outcomes Network, also known as VISION. The VISION network has demonstrated the ability to link the VQI and CMS datasets and analyze the outcomes of interest including survival, reinterventions, and aneurysm rupture. This has been reported in multiple publications.

In addition, industry has collaborated with VISION, which recently completed the EDUCATe project comparing IDE results to patient data from VQI-CMS linked data. You'll hear more about this in the next presentation today and these results further support this framework. Importantly, results of these analyses will guide next steps such as follow-up on cause of events.

Success of this approach will depend on collaboration and coordination of our key stakeholders. The use of VQI linked to CMS represents more active, longer-term data collection analysis and surveillance in a real-world setting. Adoption and success will ultimately depend on equal input on the analysis plan and objectives to make sure of quality and reliability. Another key element of success will be the involvement of an independent statistical group to oversee data access and perform the analysis. And finally, we will establish well-defined roles, responsibilities, communication, and reporting.

In addition to the specific collaborative approach required for data analysis, we believe that understanding the longer-term outcomes of EVAR will require further collaboration amongst patients, industry, physicians, societies, hospitals, and healthcare systems. To that end, we recognize the ongoing efforts of many stakeholders and offer the following suggestions aimed at enhancing existing mechanisms to prove EVAR surveillance. FDA oversight and refinement of this collaborative surveillance plan will also be important.

In addition, FDA's input regarding the ability for these efforts to influence items such as device labeling will be important as we all continue to look for the best mechanisms to share information to facilitate care decisions.

We believe that this effort will provide additional information to increase patient awareness regarding the importance of yearly follow-up, remaining in contact with their physicians, and keeping an open line of communication.

Industry will continue to provide training and education related to our devices. For instance, device-related training must address how to implant a device, the device indications and contraindications.

Product labeling must address the permanent nature of these devices, the associated need for lifelong follow-up, and summarize available clinical evidence.

Finally, industry remains committed to ongoing analysis as part of our postmarket surveillance processes and to supporting society initiatives aimed at improving data collection schemes.

Physicians and societies play an important role in education and clinical evidence generation and publication. Contemporaneous updates to practice guidelines will impact patient outcomes by facilitating uniform treatment, follow-up, and reporting in the field.

Expanding upon and enhancing existing physician and patient education programs to offer more in-depth information and more frequent training that emphasizes the benefits and risks of treatment and the importance of lifelong follow-up will also impact patient outcomes. Enhancements to existing registries to extend follow-up and continued efforts to enhance data quality will facilitate data reporting. And publication of clinical data will improve access to important patient outcome information.

Hospitals and healthcare systems can also continue to enhance existing mechanisms to facilitate a surveillance system for EVAR devices. Offering quality driven incentives for

patient follow-up and adverse event reporting may facilitate availability of information specific to EVAR devices. Systematic adoption of UDI will facilitate data collection and analysis. Improvements in claims codes for identification of EVAR-specific outcomes will facilitate data collection.

Finally, improving or adjusting reimbursement consideration to help drive attention and focus on long-term follow-up data may help incentivize physicians. Importantly, we are all here because of a shared goal to improve patient care. A long-term surveillance mechanism will improve the ability to monitor patient outcomes and ultimately improve patient care.

In conclusion, EVAR patients may require reintervention at any time for a variety of reasons, supporting the need for long-term follow-up.

Industry proposes vital status, reintervention, and aneurysm rupture to 10 years as the most relevant endpoints to assess in a real-world setting for this patient population with AAA disease.

Additionally, linking established registries with claims as an initial step to enhancing long-term data collection is currently the optimal approach for timely assessment.

Industry is committed to working with the FDA and relevant stakeholders to determine possible next steps.

Thank you, and we look forward to the discussion.

DR. LANGE: Thank you very much for that Combined Industry Presentation, again, very informative, very professionally done, and with great clarity, so thank you.

At this time we're going to move on to the Combined Physician Presentation of slides, after which we'll have time for brief clarifying questions for either the Combined Industry Presentation or the Combined Physician Presentation. I'd invite the physician society representatives to begin, they will have 30 minutes to present and they may begin

their presentation now.

DR. DALMAN: Good morning. Thank you for inviting our assembled professional society representatives to contribute to this morning's discussion. On behalf of our group, I'm Ron Dalman, Professor of Surgery and Vascular Surgery at Stanford University and immediate past president of the Society for Vascular Surgery.

Joining me for our professional society consensus presentation today are, in order of appearance, Marc Bonaca, Professor of Medicine and Director of Vascular Research at the University of Colorado and chair of the American College of Cardiology PVD section leadership council; John Fritz Angle, Director of Interventional Radiology at the University of Virginia and the Society of Interventional Radiology representative; Phil Goodney, Associate Professor of Surgery and Vascular Surgery at Dartmouth University and chair of the Society for Vascular Surgery's Vascular Implant Surveillance and Interventional Outcomes Network with the SVS's Vascular Quality Initiative, or VQI-VISION. Also joining us this morning, M. Ashraf Mansour, Professor and Chair of Surgery at Michigan State University and president-elect of the Society for Clinical Vascular Surgery.

The Circulatory System Devices Panel of the Medical Devices Advisory Committee charged our group to provide input on the following topics:

Number 1: The overall safety and effectiveness of endovascular graft technology in the longer term.

Number 2: The clinical events associated with endovascular repair that are most relevant and feasible to capture in a real-world setting.

Number 3: The potential platforms available for real-world data collection.

Number 4: Ways to overcome low patient compliance in real-world data collection and the role of professional societies in ensuring compliance.

As a group, we firmly believe in the overall safety and effectiveness of endovascular

graft technology in the short, intermediate, and long term. That being said, improved endoprosthesis performance is also needed and improved long-term surveillance algorithms are essential to that improvement.

Dr. Bonaca will begin our joint response with the perspective of the American College of Cardiology.

DR. BONACA: Hi, my name is Marc Bonaca. I am the chair of the American College of Cardiology's Peripheral Vascular Disease Section and a practicing cardiologist and vascular medicine doctor, but here today I'm presenting as part of our collaborative multi-society group to talk about abdominal aortic aneurysm.

As you know, this is a silent and progressive illness characterized by high rates of rupture and mortality. AAA is a preventable cause of death with appropriate screening and intervention. And in fact, endovascular technology has really revolutionized how we intervene procedurally to prevent rupture in patients with AAA.

Because of hard work and collaborative work between clinicians, industry, and regulators, deaths attributed to AAA have declined dramatically and that is good news. But there is more work to be done and I think part of that is recognizing that AAA is a chronic disease. It begins with identification, which usually happens in the context of multiple risk factors and comorbidities. Treatment begins with assessment and lifestyle intervention, multiple medical therapies and medical management, and then multidisciplinary planning with shared decision making about the how and the when and the why to intervene.

As you can see in the middle of the slide, intervention is critical to prevent rupture, but then after intervention care continues and that may be the most important aspect of care where we focus on risk factor modification, education, and surveillance and in fact, surveillance is an area where we need to do better. Long-term surveillance is a gap right now and we all need to do our part. Patients, clinicians, industry, regulators, we need to

track who has these devices, where they were put in and why we need to remind patients and clinicians that they're there. We need to use technology like electronic health records to put in reminders and algorithms so that clinicians are reminded at the right time to perform surveillance. We need to do more education and other initiatives. We want to work collaboratively to make sure that we do a better job on surveillance and we hope that our industry partners will help with resourcing of some of these activities.

Now, as I mentioned, intervention is only part of the journey, and discussion of intervention really is part of shared decision making between patients and clinicians. In order to do this, we need to have data, we need to be able to discuss risk-benefit and the requirement to long-term surveillance. We need to be able to describe what are the outcomes, what are the possible risks over time and optimally, we should be able to personalize on this and talk about what patient characteristics are associated with higher or lower risks over time.

We at the American College of Cardiology are highly engaged in this discussion. We are the preventive cardiologists that are helping to make the diagnosis and optimize medical management. We are care team members, we are vascular interventional specialists, we are cardiovascular imaging specialists, and many others. We're engaged and we want to be a part of this multi-society and collaborative solution with industry and regulatory authorities.

In summary, the American College of Cardiology, as part of this multi-society statement, feels that robust long-term follow-up of data and on the risk-benefit and associated patient characteristics after AAA repair are critical for optimal care and shared decision making. We understand that data collection must be balanced with the practical realities, but optimally should be multidisciplinary, objective, precise with regard to key outcomes such as mortality, open and available for appropriate evaluation of publications,

and really engaging the majority, if not all centers. In this regard, the NCDR PDI registry has now been merged with the Vascular Quality Initiative registry and we believe this does present a good opportunity for long-term reporting.

Thank you very much for this opportunity. I now want to introduce Dr. Fritz Angle, who is the Director of Interventional Radiology at the University of Virginia and is going to represent the Society of Interventional Radiology. Thank you.

DR. ANGLE: Thank you, Dr. Dalman and Dr. Bonaca. It's a pleasure to be part of this FDA consensus panel on the detection and management of late EVAR failures.

Long-term clinical and imaging follow-up is standard practice for physicians implanting endografts due to the known rates of late aneurysm growth or rupture that are usually caused by endoleaks, which are due to either issues with anatomy, operator choices, or are related to the device.

The current discussion of increased awareness around late endoleaks does not alter our impression of individual patient need for lifelong imaging follow-up, nor does it change our impression of the clinical indications for EVAR. There are opportunities for multi-specialty consensus to further standardize the imaging type, frequency, technique, and of course the duration of long-term follow-up. Questions do remain about the most effective way to follow EVAR for long-term clinical events.

I see four methods for identifying trends in late EVAR failure. MAUDE or similar event reporting is probably the most useful due to the very low frequency of events and these events happening many years after device implantation. And imaging repositories such as the ACR's Imaging Network, clinical registries such the VQI, STS, or VIRTEX, that measures outcomes and reinterventions rather than imaging to detect late endograft or aneurysm changes. And more frequently now we're seeing advanced Medicare data analysis for CPT and ICD-10 related EVAR and reintervention.

An imaging database would provide the best follow-up and earliest detection of a signal. A prospective controlled imaging database of either imaging results or of the imaging would also provide standardized measurements of aneurysm size, endoleak type, and device anomalies. It would require tracking of patients to confirm imaging is done correctly and standardized interpretation is performed. Although the ACR's Imaging Network provides a model for this, scaling this to the national level has not been proven. The number of device events in the future will likely be small and the years follow-up required appears to be high. So although this may be a costly endeavor, it does provide a method to look back for not yet described threats.

Clinical registries collect adverse outcomes and reinterventions rather than imaging findings, which potentially introduces a delay in detecting recurring structural changes on imaging before they become clinically significant. Patient follow-up rates are a problem with all registries and multi-year follow-up is a bigger challenge. The rate of follow-up needed to capture a rare late EVAR failure with a potentially low-use device will need to be high, but this Panel cannot determine what the rate would be.

There are several methods of data collection for registries. VIRTEX and SIR uses automated report collection at participating hospitals by exporting society defined standardized procedure reports and imaging reports to a central database. However, the follow-up of clinical and imaging reporting templates have not been proven.

VQI has acquired massive baseline information on EVAR placements. Data entry is manual, but they have proven the value of physician incentives to get follow-up and to having a dedicated person to extract information from clinical records and enter it into a database.

Lastly, industry does appear to collect very reliable implant data, but follow-up is not routine.

Advanced Medicare analysis has been proven very recently with the paclitaxel data analysis. Here we proved that very infrequent events can be found using this type of analysis. This may overcome some of the clinical follow-up issues with registries as it uses very reliable data and also it's sustainable in the long run. However, it will not identify imaging anomalies which may mean, again, later detections as with clinical registries. And it will not track clinical parameters that help analyze root cause, which means it must be combined with some other type of clinical registry or other information to look for root causes.

A periodic reporting of national-level analysis will be needed, and this definition will need to be updated at least annually as the knowledge of EVAR and its complications evolves. Reporting should be no less frequent than annually, as well.

We will need to define accountability reporting of potential endograft issues and this will be challenging. It could be industry funded oversight panels, a multi-society panel, or a government agency.

We will have to define thresholds and what steps will happen based on those thresholds, and this also is untested. In other words, what size blip in a clinical or imaging finding leads to a mandatory clinical or imaging review?

Well, thank you for your attention. I would now like to introduce Dr. Philip Goodney, he is Professor of Vascular Surgery at Dartmouth. He is also the chair of the Research Advisory Committee within the Vascular Quality Initiative of the SVS. Further, he co-leads their development of the Vascular Implant Surveillance and Interventional Outcomes Network, or VISION.

Dr. Goodney.

DR. GOODNEY: Thank you, Dr. Dalman. I'd like to acknowledge those who helped to fund the work we've done in VISION, especially the Food and Drug Administration via the

U01 grant, shown here, to Dr. Art Sedrakyan. And for the next few minutes I'd like to provide an overview of VQI-VISION and describe how VISION data adds to the current state of evidence. Second, I'll outline how VISION can contribute in the future towards better long-term EVAR surveillance.

But first, some basic information about VISION. VISION, or the Vascular Implant Surveillance and Interventional Outcomes Network, was formed as a partnership between the Society for Vascular Surgery and the Food and Drug Administration's Medical Device Epidemiology Network, in an effort to advance evidence evaluation for vascular devices.

Our vision for the data in VISION is that it combines the clinical and technical detail available in registries about procedures, patients, and devices with the long-term generalizable information available, and follow-up using linkages to Medicare claims and other datasets, and this results in a national repository of linked clinical claims datasets for long-term outcome analysis. These are low-cost but high-value data for generalizable real-world effectiveness research.

We've a myriad of peer-reviewed publications documenting our ability to accurately measure long-term survival, reintervention, and late aneurysm rupture in VISION, including manuscripts published in the *New England Journal of Medicine*, *Annals of Surgery*, and the *Journal of Vascular Surgery*.

We use VQI-VISION data to examine reinterventions by device type, as shown in this figure which was shared on Day 1 of this meeting. On the X-axis are the years after the initial EVAR implantation and on the Y-axis is the rate of reintervention. You can see, shown in pink, that the early generation Endologix AFX device had a rate of reintervention of nearly 40% at 7 years after implantation although their contemporary endografts had rates approximately 15% lower, shown in the line in blue, and importantly, shown in the light green line, the late generation Endologix AFX device had a reintervention rate at 4 years,

which was similar to the comparator devices and lower than the early generation AFX devices.

Similar findings were evident when we performed analyses of late aneurysm rupture, again using VISION datasets. While late aneurysm rupture approached 10% at 8 years with the early generation AFX device, shown in pink, risks again were significantly lower among all other devices, shown in blue, as well as the late generation AFX device, again, shown in green.

We detected similar findings in propensity matched analyses as well as individual device-specific comparisons leveraging the clinical details available in the VQI registry with the information linked to Medicare claims.

This methodology also works well with data from clinical trials. In the Evaluating Devices Using Claims And Registry DaTa project or EDUCATe, we used data from Cook's IDE studies as a gold standard, shown in gray, and compared it to data using VISION's -- generated using VISION's methodology, shown here in blue. The data generated by VISION was statistically similar to Cook's trial data, even though it was collected at a fraction of the cost, and extended follow-up for several years longer than the data collected in the IDE studies.

So now I'd like to outline what's next, how VQI-VISION can contribute in the future towards better long-term EVAR surveillance.

Using the methodology previously described, VQI-VISION can build national device dashboards, shown here, for long-term EVAR surveillance. These device dashboards can serve as a near real-time signal detection system. They would have a key advantage. Because similar outcomes are measured and reported across devices, this would use comparison interpretation and benchmarking.

Finally, VQI-VISION already has a standing 35-member steering committee which

includes representatives from industry, the Food and Drug Administration, and multidisciplinary vascular societies, and we've met monthly since 2018 to discuss and review VISION projects.

Signals detected in VQI-VISION's device dashboards could prompt further clinical review in the VQI imaging evaluation and signal the need for further data collection, serving as an early warning and detection system. This would work within the registry to indicate the need for targeted secondary data element collection such as imaging and chart-level evaluation.

So in summary, it's been my pleasure to provide an overview of VQI-VISION and describe our methodology leveraging linked datasets for long-term EVAR surveillance. And further, in the future, with more contemporary data updates, a near real-time national EVAR surveillance program is a plausible next step for VISION.

Thank you. And I'll turn it now back to Dr. Dalman to provide a closing statement.

DR. DALMAN: Thank you, Phil.

To summarize, we, as a group, feel that the VQI-VISION methodology described by Dr. Goodney represents the most realistic option available now to capture real-world outcomes for aortic endografting procedures up to a decade or more after device deployment. We also feel that mortality and secondary interventions, identifiable through the VQI-VISION methodology, are realistic and relevant data points for evaluating long-term device performance.

Future iterations in the VQI data collection system may provide opportunities to obtain more granular surveillance from a smaller number of high-volume sites which we feel would supplement rather than replace VQI-VISION. Similarly, the American College of Radiology ACRIN model is scalable and could also augment VQI-VISION.

Incentivizing and ensuring patient follow-up is everyone's responsibility. Given their

unique role in the patient care continuum, we feel that the resources required to ensure augmented surveillance and patient education initiatives to identify unexpected device failures should be provided by the device manufacturers themselves as a requirement for market approval.

On behalf of the assembled professional societies, thank you to our colleagues on the Circulatory System Devices Panel for your commitment to optimizing long-term outcomes for patients with life-threatening aortic disease treated with aortic endoprostheses. Thank you.

DR. LANGE: Great. I'd like to extend my appreciation to the physician representatives and the societies they represent for their collective opinion and for their presentation, as well.

We have a sufficient amount of time for clarifying questions that could be directed either towards the industry representatives or towards the physician representatives and at this particular time, I'll open it up to the Panel to ask questions. So I've got Dr. Connor, Mr. Conway, Dr. Cigarroa.

Go ahead, Jason.

DR. CONNOR: All right, Jason Connor here. I guess my question is for Dr. Goodney. I just wonder, you know, merging data is always tricky and merging large claims databases and observational datasets is even harder. I wonder if you could speak to the challenges or maybe even some of your fears about trying to merge VQI with Medicare data, you know, things that you might not catch or the challenges you've seen so far. I mean, I think it's a great idea, I just know how hard that can be.

DR. GOODNEY: Thanks for your question, Dr. Connor, and we did our first matching exercises in 2012 with a grant from AHRQ to try to learn how to best accomplish the very process you describe and you're exactly right, there's a lot of ways to get this wrong,

whether you use deterministic methods or probabilistic methods. We found one of the advantages of the Patient Safety Organization setup of the Vascular Quality Initiative is that it allows us to collect identifiable information on patients who are entered into the registry, things like their name, their date of birth, their Social Security number or their Medicare identifier, which allows us to then do direct matching so it ensures 1:1 matching and we do this as part of our existing data use agreements with CMS, and we actually have two actively existing data use agreements that allow us to accomplish this.

So it allows us direct 1:1 matching exercises so we can track very carefully our matching success rates so we really know that Mr. Jones or Mrs. Jones, who had their procedure in the VQI is exactly Mr. Jones or Mrs. Jones who had his or her procedure in the Medicare claims so we know we have a direct 1:1.

We've learned over the years that you actually have to do this a couple of different ways, so we've done probabilistic matching methods, as well, and it turns out, even though those are a little trickier and you have to use a few less opaque ways to do it, those actually work reasonably successfully, too. So we matched all of the patients in the VQI registry, not just the patients who have aneurysm surgery, and our matching rates routinely exceed 90% in eligible patients.

So we've got a lot or practice at doing this for many years and I appreciate your question. It's something we've thought a lot about and we've been happy to have some modicum of success with it, but you're right, it is a bit of a challenge and did take some time.

DR. CONNOR: Yeah. And then a quick follow-up, if I can. How challenging is the things that come downstream in Medicare data that you're trying to match back to adverse events or their follow-up procedures, to identify the procedures that you're seeing in Medicare actually relate to the particular implant versus something else that's coming up in

a few patients? So you may be over-claiming as well as under-claiming, but it's a question about the over-claiming, you're assigning things that may not be related to that specific implant.

DR. GOODNEY: Another great question. I have a biomedical data scientist who, her job was to help us try to solve exactly that question in terms of whenever you measure something in two different ways you can find the events too commonly or you cannot find the events commonly enough with either dataset.

And it turns out that especially for certain events, and these are the events that I emphasized in our presentation, things like reintervention, things like late aneurysm rupture, those are pretty reliably coded within the VQI when the VQI does assess them in that 1-year window and then similarly in that 1-year window in Medicare claims, and we found about 85% concordance in those windows where the two datasets overlapped, if you will.

Once, of course, you get beyond 1 year you can enter data into the VQI directly, but you're not required to. So when we get beyond 1 year, we are specifically reliant upon the CMS input for our long-term outcome evaluation. And that's why we spent so much time trying to make sure that we can validate that outcome so that we know, when we find a reintervention in one, that it corresponds to the reintervention in another.

So the short answer to your question is it's about 85% concordant and we try to do our homework to get to that number. Thank you.

DR. CONNOR: Good. Thank you very much.

DR. LANGE: All right. The individuals that I've seen hands raised in this order: Mr. Conway, Dr. Cigarroa, Dr. Horvath, Dr. Brindis, Dr. Zuckerman, Dr. Hakaim, and Dr. Khaja.

So Mr. Conway.

MR. CONWAY: Great. Thank you very much, Doc. And this is a question for Dr. Goodney. I was interested in your presentation and in particular, I'm interested in the VISION steering committee since part of our discussion today is to determine architecture and long-range surveillance recommendations for FDA, things that work and don't work. Can you tell me how many patients are on the steering committee for the VISION?

DR. GOODNEY: Thanks for your question, Mr. Conway. You know, we have -- and that's a question we've actually thought quite a bit about, and in one of my other projects we just finished completing a 22-site randomized trial of a decision aid for patients to help them choose between open and endovascular repair. So patient-reported outcomes and involving patients in trials is something that's near and dear to my heart, that's called the true AAA, a randomized study of decision aid.

And on the steering committee calls specifically, we do not have patients attend the call. It happens from 8:00 to 9:00 at night every third Tuesday of every month, so it's kind of late. However, we have had over -- as the projects have evolved, and in several of those projects we have involved patients who had either in-line endografts or who are facing that decision about whether or not they should have an implant, we have involved them in the development of some of the grants that have evolved from the VISION dataset.

So while I don't -- you know, I've always struggled here a little bit because, I'll be frank, I don't want to this to be burdensome to our patients and telling them that they've got to -- if they're on the West Coast or the East Coast and they've got to meet at a late night conference call, I don't want to make that additive, but I have used their input iteratively over time, especially as the projects evolved, and I was particularly touched by Ms. Alikhaani's comments yesterday. I think it is invaluable to have patient input as you begin to develop your study designs so you make sure that the results of the studies that you do apply to patients and things that they care about. So we've not gotten it perfect just

yet, as you've outlined, but we have used it selectively.

MR. CONWAY: If I might be simple to suggest something, NIH and FDA and CMS include patients on many of the steering committees for the larger datasets and contracts that they have and you might want to try doing that. I appreciate your comments about including patients in the trial design and that type of thing, but having them on the steering committee might be helpful also, especially if VISION is looked towards by a federal agency as a potential source for architecture input for what we're doing.

DR. GOODNEY: That's a great suggestion, thank you.

DR. LANGE: Thank you, Mr. Conway.

DR. GOODNEY: Absolutely.

DR. LANGE: I've got Dr. Cigarroa, Dr. Horvath, Brindis, Zuckerman, Hakaim, and Khaja.

So Dr. Cigarroa.

DR. CIGARROA: Good morning, this is Joaquin Cigarroa and this is a question relative to VQI. I know that it has now merged with the ACC platform as of this January. Can you comment on the penetration of use across the country in terms of the number of sites and specifically relative to hospitals and the distribution of patient demographics? And what I'm trying to get at is will this be representative of underrepresented minorities. We've seen differential outcomes with regards to surveillance and follow-up following open repair and some suggestions, as well, with endovascular, in particular to black patients.

DR. GOODNEY: Ron, do you want me to answer that?

DR. DALMAN: Yeah, I don't see Jim. I don't see -- yeah, why don't you go ahead, Phil.

DR. GOODNEY: Thank you, Dr. Cigarroa, that's an excellent question and another topic that we have been quite sensitive to in the VQI. The penetrance of the VQI across

hospitals for aortic aneurysm surgery is a tough number to estimate directly, but I suspect it's probably -- you know, judging from the number of cases that are done in overall all-payer datasets or claims as compared to the number that we collect in the registry, it's probably somewhere between 30 to 50% of national practice. I can't offer you a publication to support that, but that's our estimate and it's a moving number from year to year, but we have followed it from year to year and we've seen an increasing representation of sites, of all of those sites that perform aortic surgery across the U.S., seeing that they are increasing in their proportion of those who are members of the VQI and it's an almost linear increase.

And then the second piece of data in terms of -- because we've been similarly concerned that the patients that we study in the registry may or may not be representative both overall and in certain important subgroups such as underrepresented minorities, patients who are very elderly, patients with certain chronic conditions. We wanted to make sure that we were as representative as possible.

We published a paper in *JAMA Surgery* just about a over a year ago which compared the care that's provided in VQI hospitals and in non-VQI hospitals, and one of the most important things we learned about in that project was that the demographics of the patients in both participating and non-participating centers, those who are part of the VQI as well as those who are not part of the VQI, when they're doing the same types of procedures and the same levels of complexity, seemed exactly similar. We did risk adjustment and used the usual modeling techniques, but at the end of the day that didn't change our results at all because the patient profiles were very, very similar, which I think gives us an insightful window into not just overall populations, but especially African American populations and patients of Hispanic ethnicity, the important subgroups that we want to make sure that we study, especially when there are gaps in surveillance because that's what we've seen in some of our VQI and some of the VISION analyses we've used to

see how commonly these grafts are indeed followed. That is a major area of challenge for us looking ahead and we've seen that our current lens through which we study these seems to provide us equal insight whether the data we garner from VQI seems similar to the patients that are cared for outside of VQI centers. Thank you.

DR. LANGE: Does that address your question, Joaquin?

DR. CIGARROA: Yes, sir. Thank you so much, Dr. Goodney.

DR. LANGE: Thank you so much.

DR. GOODNEY: Thank you.

DR. LANGE: I've got Dr. Horvath, Brindis, Zuckerman, Hakaim, Khaja, and Starnes and Jacqueline.

So Phil, you're a wealth of information. I'm going to ask you to kind of narrow the answers down just a bit because there are so many people that want to speak with you and the other participants, which is great.

DR. GOODNEY: Sure. Will do, sorry.

DR. LANGE: Thanks. Keith Horvath.

DR. HORVATH: Thank you, Keith Horvath. A quick question regarding VQI. How is it audited?

DR. GOODNEY: Thanks, Dr. Horvath. All data that was received from individual centers are required to submit a hundred percent of their cases, so when it's audited we ask for the billing records from each center and if you did a hundred carotids on your billing records, you should have submitted a hundred carotids for your case reports, and that's done for each individual aspect of the registry whether it's carotid surgery, aneurysm surgery and the like. There are targeted audits for centers that have data that lies outside of certain confidence bounds that makes -- for example, if you never reported an infection over 5 years, that flags individual center audits.

DR. HORVATH: So there's not a pre-specified percent of the participants that then undergo review on an annual basis, even to the level of chart review?

DR. GOODNEY: That's a great question. We've discussed that year over year in the registry and are developing plans for that. That's not a small endeavor, as you might imagine, and we want to be cognizant that we do that right. As the registry has evolved, we worked our way up to considering that at this point. Thank you.

DR. LANGE: Dr. Horvath, does that address your question?

DR. HORVATH: Yes, it does. I'll just add that knowing the Society of Thoracic Surgery national cardiac database, that they've worked out ways to do this, so there are examples from other registries that VQI might want to look into. As far as the auditing and the validating of it, I think, is absolutely critical.

DR. LANGE: Great.

DR. GOODNEY: It's a great suggestion.

DR. LANGE: We'll talk about that during our suggestions. Great suggestion.

I've got Dr. Brindis, Zuckerman, Hakaim, Khaja, Starnes, and Jacqueline.

DR. BRINDIS: Yes, Ralph Brindis. And just as a reminder, I serve on the VQI PSO executive committee and am also involved in MDEpiNet committees, also. So this question also is for Phil. Maybe one softball and maybe even an inside slider, so be prepared.

First, you discussed a little bit yesterday about your adjudication process. Key adverse outcomes, of course, are very important to the FDA and all of us, and maybe you can reiterate a little bit on that. But maybe the inside slider is the issue of delay of the CMS data, which can be 2 years potentially in terms of having the real-world monitoring, real-time monitoring process. And then also, the issue that I alluded to yesterday, the increasing CMS strategy to move from a fee-for-service environment to a Medicare Advantage environment and the challenges that will also lead to the VISION initiative, your comments

there.

DR. GOODNEY: Thanks. Again, Phil Goodney responding and I appreciate your questions, Dr. Brindis. First, in terms of the adjudication, I think I talked yesterday, there's Medicare Advantage and Medicare claims, so we've been doing claims-based research for 2 decades, is that it's great volume and it is longitudinal.

The difficult part is that it is possible sometimes to get small signals wrong, especially if the outcomes aren't adjudicated, and that's why we spent several years with chart-level reviews and tested our algorithms both in chart-level datasets as well as against clinical trials, as was alluded to in the EDUCATe project, to make sure that when we say we think a reintervention occurred, that we're certain of it, or when we think a late aneurysm rupture occurred, that we're certain of it, because that will -- as has been discussed, that will prompt or flag future downstream investigations which will be an investment of time and resources, so we want to make sure those are well treated.

You know, your second question alluded to the delay potentially in examining Medicare claims and you'll notice that our analyses extended to the end of calendar year 2018, we're preparing our data files through the end of calendar year 2019 at present and we'll continue to update those processes as the data are released from CMS.

There are ways to get even more recent data called the virtual -- VDRC seat or virtual data repository center, where you can actually get data that's delayed by less than 6 months and that's what I would propose to do as this project moves ahead. It's a more expensive form of Medicare data to analyze, but it would allow us to advance that delay from a year and a half or so to less than 6 months' time, hence the offering of a near real-time service. The analytics are all the same, you just get the data a little earlier and you have to do some data cleaning exercises. We've not done that yet just because it adds another layer of expense upon what is already an expensive project.

And then lastly, your question about the impact of Medicare Advantage. Fortunately, it seems like even though they say the Medicare Advantage patients shouldn't show up in the claims that we receive, we tend to find a lot of them, especially in our work, we've done this for a lot of years, our analysts are good at tracking of files. So we tend to not -- we've not seen a demarcation over the years in terms of the number of patients available to analyze, our matching rates have stayed high, number one.

And number two, I think part of the impact is, remember, Medicare Advantage is an HMO project that looks for low-risk Medicare patients and it's usually not the low-risk patients that are getting vascular surgery, so I think that Advantage has not penetrated into the vascular surgery crowd as much as we might have worried it might. But thank you for your question.

DR. LANGE: Thank you.

Ralph, sufficient?

DR. BRINDIS: Yes, thank you.

DR. LANGE: Thanks. Thanks for the softball and the slider. By the way, the Astros did not win yesterday.

(Laughter.)

DR. LANGE: All right. Dr. Zuckerman.

DR. ZUCKERMAN: Yeah, Dr. Goodney, great presentation. My question also has to do with near real-time data collection. As we saw with the case example yesterday, it's critical for patient information and the FDA, it's good that you see a vision forward, but how long would this take to accomplish and can you add anything else, because this is a critical component.

DR. LANGE: You talked about time and you mentioned cost, Phil, talk about that, as well.

DR. GOODNEY: Sure. And again, Phil Goodney responding. Thank you, Dr. Zuckerman, for your question. It's always been sort of a dream, if you will, of mine that we would have a VDRC seat, essentially a seat inside Medicare to look at their data as it evolves off the servers directly and we've had -- I had a colleague here who had a project that had several seats with four, so we have some experiencing working with it.

We've heard that it is difficult in terms of data cleaning work because the reason the datasets that you get from Medicare are delayed a little bit is because Medicare cleans them up for you and makes them sort of easy for the analysts to deal with. You have to have an analytic team that is prepared to do that cleaning for you and I'm fortunate here, we have a longitudinal team of analytic experts that have allowed us to do this for the last 20 years and I'm very proud of their efforts.

What we would propose would be likely, you know, depending on the rules of how many people can use the individual seats and how it lies within the data use agreement, but we would propose probably two seats in the VDRC network, but the price tag attached to that is about $35,000 per user per seat and then you have to pay it and that's just access to sit there and get the password to dial in. There are then data use fees, data use agreements, and a myriad of other costs in addition to the cost of these highly trained personnel to overlook and analyze the data.

So our budget, in rough terms, is in the six-figure-per-year range for this. We estimate a cost between 300 and $500,000 per year, all told, to basically take and start with VQI data and then link it to claims and then measure our late outcomes, all in the fashion that we've done it directly. The process, once we get inside of VDRC, would be identical to what we do now, that would be the advantage, that there would be nothing new. It's just we would get data earlier, we would have to clean it and then we would roll it through our existing pathway.

DR. LANGE: So Phil, to Dr. Zuckerman's question, how long would that take if you -- we told you to start it today?

DR. GOODNEY: If there was a blank check in front of me today, I would put in for the DUA and establish the seats and get my team to work on it and my presumption is we would -- you know, we could make the report cards I talked about, we can make the report cards with the old data tomorrow, we already have that data available, but with the new updated data, my suspicion is it would take us about 6 months to have some pilot versions of this. Those who have done Medicare claims analysis, if they were watching this discussion, would say I'm certain you're going to find some wrinkles in the data as it evolves and they would be exactly right, but we would try to work through those processes and stay involved.

DR. LANGE: Dr. Dalman, it looked like you wanted to address this, as well.

DR. DALMAN: Yeah, I just wanted to add that part of this discussion is going to have to be how is that paid for exactly, because it's not going to be a voluntary effort on the part of the Society for Vascular Surgery or the other assembled professional societies.

DR. LANGE: Ron, as I was watching I saw six people take their checkbooks out.

(Laughter.)

DR. DALMAN: Okay.

DR. LANGE: Dr. Zuckerman, does that address your question?

DR. ZUCKERMAN: Yes, thank you, Drs. Goodney and Dalman, very helpful.

DR. GOODNEY: And I'd be happy to discuss that at more length off line, Dr. Zuckerman.

DR. ZUCKERMAN: Thank you.

DR. LANGE: I've got Dr. Hakaim, Dr. Khaja, Dr. Starnes, Jacqueline, and Dr. Starling.

DR. HAKAIM: Great. This is Al Hakaim. This question is for either the industry

presenters and/or the physician presenters. You know, we've talked yesterday and today a lot about the data, but one area we may get to or may not get to that I think deserves some discussion is the barriers to imaging follow-up and I wonder, you know, I see patients here, the Mayo patients that are like VA patients that show up early or just late, but we see patients who either didn't know they had to follow up or in the emergency room with a ruptured aneurysm, they lost their insurance, they moved, they don't have a primary, more and more don't have a primary.

So there's really -- you know, the question is, is the onus on the physician, is the onus on the patient or should industry have a more active role in the imaging follow-up? You know, should the imaging be included in the cost of the device so there's no financial barrier? Because almost every -- not just with AFX, but almost every patient we see that needs an explant, they came to the emergency room acutely and they either never followed up, didn't know they had to follow up, etc. So I'd be interested in the perspective of the societies and industry.

DR. LANGE: I'm going to turn to the industry first, Scott, because you had actually said this is too onerous and wasn't a part of your follow-up, so I'll let you, industry, talk about that.

DR. STARR: Thanks. Thanks for the question, Dr. Hakaim. This is Jean Starr representing industry, and we certainly recognize that long-term compliance with follow-up, physician follow-up, let alone imaging is less than ideal and very inconsistent, especially in my practice, as well, and so we're recommending those endpoints now that we can reliably collect with the systems that we have in place. We certainly are open to considering that imaging follow-up as a next step to our proposal and however that needs to be done, however we can make it easier for patients to get to their doctors, to remember to get to their doctors, that could be a cooperation between hospital systems, it could be

cooperation with EMR, but certainly agree that those imaging follow-ups are important, but hopefully the endpoints that we've suggested here today can capture some of the imaging initially in the quickest way possible.

DR. HAKAIM: Thanks, Dr. Starr.

DR. LANGE: Thank you. Dr. Hakaim, does that address your question?

DR. DALMAN: I could also add just briefly that in our presentation we also emphasized that follow-up is everybody's responsibility across the entire care continuum. You know, VQI has mechanisms to send reminders to try to reach the 80% 1-year follow-up as part of 9 to -- I forgot, it's 9 to 21 months, I think, is the follow-up window. But in reality, the whole concept of device development, marketing, implementation and follow-up needs to be one circle and it needs to be considered in the cost of doing business, I think, to ensure the appropriate follow-up and I think that's the consensus of our physician society representatives, as well.

DR. LANGE: Great.

DR. HAKAIM: Thank you. Yeah, I think that's -- yeah, that's fine, I think you can do it.

DR. LANGE: We'll be talking about this, we'll be talking about this in our discussion.

DR. HAKAIM: Okay, thank you.

DR. LANGE: Great. Dr. Khaja, Dr. Starnes, Ms. Alikhaani, Dr. Starling, and Dr. Blankenship.

DR. KHAJA: This is Minhaj Khaja, UVA. I had a couple questions, number one being about for the VQI-VISION's program, you're using the endpoints of reintervention, for example, and late aortic rupture without really incorporating and looking back at the imaging to see if there is some sort of signal. My question really is why not have the imaging portion as part of that from the beginning and teaming up with ACRIN, for example, which does lung cancer screening? That is one part.

And the secondary part that's very similar is the inclusion of cardiovascular imaging, interventional radiologists, as well, into this group because there are not, at least as I saw, there are not those members on the steering committee of VQI-VISION, which those providers and myself perform these procedures, as well as Mr. Conway mentioned earlier, patients. And so that would really allow for capturing all of these patients because a large group subset of patients may not be included, especially in that you sort of have to buy into this program. And so I really think that that is something that should be considered and discussed, so I just wanted your thoughts on that.

DR. GOODNEY: Thank you. Again, Phil Goodney from VQI-VISION. Thank you for your comments and suggestions, Dr. Khaja. First, in terms of why not collect imaging data right now, I couldn't agree with you more, I think we view it as more of a "walk before we run" sort of concept in that right now there's not much being collected in an organized fashion, so we wanted to start sort of with the low-hanging fruit, the pathways that we've already established, which can work to identify patients where these adverse events have occurred and that would then trigger the need to go back amongst those sample patients, so instead of collecting all the imaging, collect the imaging on the patients where events have occurred or where a signal might be detected.

I think the ultimate goal, as outlined in the ACRIN program, was something, as Dr. Dalman alluded to in his presentation, would be a goal for several -- you know, within a few years of evolving the program, to start more broadly collecting imaging because now that the technology has evolved to allow us to collect that information at scale, it only makes sense to start to include that, but it's just a matter of which iterative step to take first. So I think that would be the process there.

Second, in terms of multi-society involvement, I was privileged to be on SIR's -- some of their guideline development committees and have worked with many of your colleagues

in interventional radiology across different projects and I would welcome the opportunity to involve you in our steering committee meeting, I think it would add to the multidisciplinary nature of our work, so I think it's a great idea.

DR. LANGE: Great. It's not very often that you have people signing a disclaimer to get on a committee, Phil, that's good news.

I've got Dr. Starnes, Ms. Alikhaani, Dr. Starling, Blankenship, Eagleton, and Mr. Conway, and that may take us up to the 15-minute filler time. So again, I'll ask our -- brief clarifying questions and we'll have more time for discussion, and brief answers just so we can get everybody participating.

So Dr. Starnes.

DR. STARNES: Yeah, Ben Starnes from Seattle. You know, we heard from Dr. Jean Starr this morning that our devices are safer and more effective. We also heard from Dr. Fairman that only 50% of EVAR is conducted on label. So my question is for either Scott Williams or maybe even Phil Goodney could weigh in on this.

Industry, in my mind, has a responsibility to police the initial use of their devices, but there's an inherent conflict of interest there. I mean, should we make the reporting of anatomic data and IFU compliance a condition of PMA approval for these new devices?

Scott Williams?

MR. WILLIAMS: Yeah, this is Scott Williams here. Thanks, Dr. Starnes. I think that you raise a good point and as we think through this longer-term surveillance plan that we would put in place, certainly there's the need to generate a lot of data and evidence to further inform labeling. Whether right off the bat there would need to be a condition of approval to follow the recommendations for imaging in the IFU as they are in the IFU's today, there are recommendations and we're somewhat reliant on clinician judgment to follow those recommendations while also considering society guidelines on follow-up.

DR. GOODNEY: And this is Phil Goodney, just for the response as well from the registry side. As you know, Dr. Starnes, we already collect some aspects that would inform IFU adherence, things like neck diameter and diameter of the distal seal zone, neck angulation, aspects that would allow us to inform IFU adherence. So I think we have first steps in place, but certainly some room to grow. Thank you.

DR. LANGE: Ben, keep that, I think it's open -- I want that to be part of the discussion, that's a really good point and I'm glad you brought that up. Thank you.

Ms. Alikhaani.

MS. ALIKHAANI: Yes, this is Jacqueline Alikhaani. I really like what I'm hearing about your efforts and considerations for collecting data from the providers and hospital systems and payers, but I'm also wondering about have you thought about or done any work towards considerations for getting input directly from patients and getting PROs directly from the patients?

What I'm talking about is something that -- we had a work group with the American College of Cardiology that included FDA and many others, Dr. Zuckerman was there, I was there, and we had a great discussion that included how we can take advantage of technology more through phone apps because being that AAA is a chronic condition and there are considerable daily quality of life issues that can come into play and that's always important, and when the patient leaves the doctor's office, what happens between the next doctor's visit.

A lot of good information could possibly be captured through phone apps and I know that there's standards issues there because I'm on an IEEE standards development committee and we just got one of the first standards developed for healthcare formats, mobile apps, because believe it or not, there are tens of thousands of apps but very few standards and so first, things have to be standardized. But I think, for those patients who

want to do that, I think that would be really helpful because there's a lot of good data that can happen in between the doctor's visit that you could be missing out on.

DR. LANGE: So Jacqueline, I see Phil shaking his head, nodding the entire time you're talking. So Phil, you get 30 seconds to answer this.

DR. GOODNEY: Ms. Alikhaani, if you could -- we submitted a grant to do exactly that, we're so excited about that exact process because you're right, you need to have a safe way for the data to travel from your phone and you have to have a safe place for it to stay once it arrives in the registry. We've worked very carefully to develop, and have developed, a phone-based application that could be used in this instance. We submitted an application to the NHLBI to test exactly that within VQI. So if you could call up the study section that's going to judge the veracity of our grant and show them how excited you are, I'd be very appreciative.

DR. LANGE: I'd call that shameless advertising, Phil.

(Laughter.)

DR. LANGE: I've got Dr. Starling, Blankenship, Eagleton, Mr. Conway, and then we've got to go to our next presentation. So again, brief questions and brief answers.

DR. STARLING: Yeah, thank you. Starling. So my question is in the context of another registry that I'm familiar with, which is the INTERMACS registry, which has some similar characteristics to what I'm learning about VQI, and I applaud you for your website, which I found very informative.

So in the context of transparency, our biggest problems we face are missingness of data, adjudication, and then finally, access. So I'm specifically interested in how accessible is this data to independent investigators with respect to projects. Thank you.

DR. GOODNEY: Thank you. In terms of missingness, we have had an auditing committee dedicated to the evaluation of missing data. Since our inception, this is a key

topic discussed -- again, this Phil Goodney with VQI-VISION -- it's discussed in each of our biannual quality assurance meetings. We don't do a perfect job, but it's something that we aspire to do. I'm not a believer in imputation strategies, we'd rather have the real data, so we ascribe to try to do that as best we can. Our missing data rates vary by procedure, but in general have been acceptable to allow us publication in some fairly competitive journals. So we try to do a good job there.

Adjudication of outcomes similarly were alluded to and our plans are evolving for both adjudication of participation and adjudication of the outcomes that are reported. They're adjudicated by the time that they're entered by specific health techs, but we are looking at ways to do a better job to measure them, as was alluded to by the previous question.

And then finally, data access. So it also turns out I'm chair of the research advisory committee and we look over every application for people to use this data that is collected as part of the Patient Safety Organization, and a key component of that data collection is that the data is not used for competitive marketing and is used for quality assurance and quality research. So we're certain that anybody who applies to use the data will use it for those purposes.

We have involved collaborators who are not VQI members. If they bring to bear a project that we think will improve the health and safety and the care delivery to patients with vascular disease, then we have, as I said, a committee that looks at those applications every month. Generally, we receive on the order of 30 to 50 applications from both our members and non-members, which we look over and approve datasets when appropriate.

DR. LANGE: Thank you. So Randy, does that address your question?

DR. STARLING: Yes, thank you.

DR. LANGE: Okay, great. And the last three, Dr. Blankenship, Dr. Eagleton, and

Mr. Conway.

Dr. Blankenship.

DR. BLANKENSHIP: Thank you. This is Jim Blankenship. We've heard something about the cost associated with potential registries and so a question that would be oriented, I think, towards industry, there are some frontend costs to this. For instance, as cath lab director, I'm well aware of the costs of entering data into the ACC's NCDR registry, which are considerable, it takes manpower to do that and then of course, one has to subscribe to the registry, which is also expensive. Those factors might limit participation in the VISION registry, and is there any thought that there would be support from industry to subsidize the cost at the front end of actually entering patient data into a registry and then supporting the registry?

DR. LANGE: Phil's listening to this answer with great interest.

Scott.

MR. WILLIAMS: Yeah, I think one of the appeals of looking out to the VQI and the CMS linkage is there's a wealth of data already there on some of the current technologies that we could potentially look at and then going forward in terms of incentives, we've thought a lot about maybe to just help paint a broad picture of where this plan might play out, if we could show very quickly slide TQ-5.

You know, where we are today, and at least where we're pretty forward, is shown here in Step 1, trying to get some alignment on what the relevant framework would be and what the relevant endpoints would be to assess long term. Necessarily, there are many steps that would have to follow today and including, most importantly, Step 2 and the planning, talking about what sort of data analysis protocol, the involvement, the timeline. And I would importantly note, through all these steps shown here, it would involve all stakeholders including patients, industry, FDA, physician societies, VQI, CMS, and

independent statisticians to do the analysis, as well. So this was kind of the big-picture vision and we're really just today trying to kick it off with Step 1, and I think some of those cost things would come into Step 2 and planning to really figure out the breadth and scope of the work out of this.

DR. LANGE: So is that a yes or a no, Scott?

MR. WILLIAMS: Yes, industry is open to considering what we need to do in our part.

DR. LANGE: Terrific. I really appreciate the commitment, thank you.

Jim, does that answer your question?

DR. BLANKENSHIP: I think that's an important point and I guess we'll have to see, so yeah.

DR. LANGE: That sounds great.

Dr. Eagleton and Mr. Conway.

DR. EAGLETON: Thank you, this is Matt Eagleton. This is probably addressed to Phil a little bit. Phil, it sounds to me like with the VISION we can identify patients from VQI that have events that are captured in the CMS database, but there seems to be probably a lot of information that's lost between VQI potentially and when that event happened, which was discussed briefly here, is there a way to report back to the physician that performed the event, that their patient had an event and then try to collect additional information that? Do we move backwards in that direction and put the main onus back on the physician?

DR. GOODNEY: Thank you. Again, Phil Goodney, VQI-VISION. Thanks, Dr. Eagleton, and a great question. We were fortunate to do a project that did just that, in collaboration with the FDA. So we looked for patients who had a certain type of endograft, treated a certain way in the VQI data, and then looked back for it and asked the sites to feed us back further information about how that graft was implanted. This was done as part of a potential label expansion for the Gore IDE graft. And it turned out that worked really well

because we already have sort of the sites, the places that enter the data already have a person there and e-mail that, you know, they'll answer and a pathway to sort of seamlessly contact the treating physician. So the advantage, we think, of detecting the signal using the claims and then marrying it back to the infrastructure, the network that already exists in the VQI, would facilitate that conversation.

So for example, if Phil Goodney 5 years ago put in an endograft that some patient presented down in Boston and unbeknownst to me had a reintervention, that would get flagged in the CMS claims and then could allow identification of me, since I already am part of the VQI network, it would identify my site and my coordinator as someone who would then do the homework of going back and looking at what interval imaging had been obtained, potentially if there was a root cause -- and this is what we had talked about in the ACRIN, to then submit follow-up imaging and follow-up interventions, to then look more deeply into that deep dive. So VQI-VISION would be the first step in that process and one of the advantages is the pathways through which that data would flow already exists. Thank you, Dr. Eagleton.

DR. LANGE: Thank you.

DR. EAGLETON: Thank you.

DR. LANGE: Mr. Conway, you have the last question before we go to our next presentation.

MR. CONWAY: Great, I'll make it quick. To Mr. Williams, in your presentation earlier today you talked about the fact that there had been several meetings with FDA regarding long-term data collection and I'm interested in whether or not patients were involved in those meetings or not.

And a second thing, can you characterize for me very quickly what you see industry's role and commitment is to patients and gathering patient insights going forward? You in

part answered that in terms of the answer given to Dr. Blankenship, but I'm just kind of interested in your perspective. Thanks.

DR. LANGE: Thank you, Paul.

MR. WILLIAMS: Yeah, Scott Williams. Thanks, Mr. Conway. The meetings referenced earlier were actually arranged through VISION, hosted at FDA, and I don't recall -- I'm going to have to ask Phil to help me out here, Dr. Goodney, whether patients were involved in those meetings. I don't believe so.

DR. GOODNEY: There were no -- we did not, as part of VISION, invite patients to those meetings but, as I alluded to earlier, Dr. Conway or Mr. Conway, we had involved patients in some of the projects that were discussed then. You know, patients travel and we have involved patients traveling to other meetings before and it's -- you know, it is -- I know we're short on time -- it's a big step, and especially a big ask for many of these elderly patients, and I always want to be cognizant of those -- what we were asking them to do, you know, a transcontinental flight for some of our more elderly folks, I worried sometimes, was risky for them, but it is something that we've put into context and I wholeheartedly agree with your suggestions as outlined before.

DR. LANGE: Great.

MR. WILLIAMS: And Mr. Conway, just to make sure I addressed -- Scott Williams again -- addressed your second question relative to involving, if I understood you correctly, patient input and insight to this plan going forward, was that your question?

MR. CONWAY: Yeah, actually from your perspective, the commitment of industry to patients and the role of industry in collecting some of those patient insights. I was pleased to see your inclusion of some of the patient preference studies, especially PREFER, so I'm interested in what your perspective is on industry's commitment. We've heard from the medical professionals, but I'm interested in what industry has to say.

MR. WILLIAMS: Yes, Scott Williams. We're very committed. Obviously, patients are first and foremost at the front of the total effort and so we're very eager and interested to have them involved as stakeholders providing input, if there are relevant endpoints we're not considering, that need to be considered to help patients be better informed in their care decisions in the future.

DR. LANGE: Okay.

MR. WILLIAMS: Thank you.

DR. LANGE: Mr. Conway, does that address your question?

MR. CONWAY: Sure does. Thank, Doc.

DR. LANGE: Great, thank you. I'd like to thank everybody for participating, a great participation and a lot of great information, as well.

We're going to now proceed on to the FDA's Office of Clinical Evidence and Analysis, the OCEA presentation. They will have 20 minutes to present and may now begin their presentation.

DR. WANG: My name is Li Wang, senior epidemiologist for the Office of Clinical Evidence and Analysis, Clinical Evidence and Outcomes Research Team. I will be speaking about the aortic abdominal aneurysm, or AAA infrastructure for real-world data or RWD, and real-world evidence or RWE.

First, I will give an introduction to real-world data use in the regulatory space and transition to an overview on the growing need in the evolving AAA ecosystem, which will include the common challenges that surround real-world data usage in the AAA space. Next, I will speak about prominent cases where real-world evidence was utilized both in the AAA space and in the general cardiovascular space. A high-level characterization of AAA-specific sources will be presented and I will speak to potential considerations for successful use of real-world data and real-world evidence, and conclude with key takeaways.

Using real-world data for regulatory submissions allows us to understand the device performance in a real-world setting to inform benefit-risk profiles. The process of utilizing real-world data provides opportunities to obtain patient perspectives in new ways. There are efficiencies to be gained both in time and cost reduction, and real-world evidence use better aligns evidence generation with new device iterations and development.

There are many potential regulatory uses for real-world evidence in the total product life cycle. For example, data from real-world evidence can be hypothesis generating for evaluation in a prospective clinical study. It can inform prospective trial design or be used as the control arm for a clinical trial. Real-world evidence infrastructure can serve as a framework for data collection both in the pre- and postmarket, and it can be used for identifying safety signals for medical devices. Evidence from these postmarket uses can further support expansions of indications.

We recently published 90 illustrated examples highlighting a breadth of real-world evidence sources used for regulatory purposes. Of those 90 examples, 65 were leveraged for premarket submissions and of those, about 20% leveraged real-world evidence as the sole source of clinical data, about 60% featured real-world evidence as the primary source of clinical evidence, and about 20% leveraged real-world evidence as a supplementary or secondary source. I have provided the title of this document at the bottom of the slide, which can also be found at fda.gov.

Earlier, FDA has presented on the evolution of the AAA ecosystem. As EVAR has become extensively more prominent than open repair for AAA treatment, evaluation of the device space must evolve, as well. To reiterate, there is a growing need for evaluation in the long-term performance of AAA devices, defined in this presentation as greater than 1-year follow-up, as periprocedural survival advantages of EVAR are not maintained over time. There are increased reintervention rates related to patency, aneurysm sac expansion,

and endoleaks.

As mentioned in the previous FDA presentation, endoleaks occur in approximately one-third of all EVARs. Current realities in the published literature show that EVAR devices are also often being used outside of the approved indications for use. Also, surveillance imaging noncompliance is approximately 60% 3 to 4 years after EVAR.

To better understand and identify the different evolving questions that surround the AAA devices, there is a need for more reliable follow-up to evaluate the long-term events and outcomes. Current surveillance mechanisms aren't adequate to obtain an accurate profile of real-world usage of these devices, especially when identifying key long-term outcomes. For AAA device evaluation, questions around ensuring patient privacy protection and navigating or modifying preexisting data use agreements need to be further explored to streamline real-world data usage.

To better understand the potential utilization and challenges of real-world evidence, I will present case examples highlighting variables of success as well as high-level challenges in utilizing real-world data.

A case example of success with leveraging real-world data in the AAA space for regulatory use is Medtronic's Endurant II and IIs. Real-world data from the ANCHOR registry, which is a multicenter, postmarket, non-interventional, nonrandomized prospective study with 5 years' post-procedure follow-up was used in premarket approval for expansion of indication. This registry continues to be used for the devices' post-approval study.

This example expresses the advantages of using registries for regulatory use by being a sole source of clinical information for premarket approval, a mechanism to capture both clinical and imaging outcomes, as well as a mechanism to provide ease of central governance of patient data. It's also a success because it's utilized both in the pre- and

postmarket. However, even with this success story, challenges remain in using registries. Examples of this can include adequate definition enforcing of registries for outcome measures and low imaging compliance in order to ascertain specific device-related outcomes such as endoleaks.

Another example of success for leveraging real-world data are the transcatheter valve therapy registry post-approval studies. Here, manufacturers of transcatheter aortic valve replacement devices conduct their long-term safety follow-up in post-approval studies using a real-world data combination methodology, linking the TVT registry and Center for Medicare Services claims. Linkage allows for the assessment of safety outcomes through 5 years post-procedure. The TVT registry has been used to support 25 regulatory decisions, specifically as an infrastructure to address postmarket data collection as a condition of PMA approval.

Linking data from more than one real-world data source can be a practical way to comprehensively evaluate a research question. Multiple data sources used in the TVT example allow better capture of device performance in the total product life cycle. These data sources allow for a more representative or real-world capture of device use compared to a traditional new enrollment study. Efficiencies that can be gained are time efficiencies from a reduced need for site selection and initiation, as well as a reduced need for site-level patient follow-up. Collaboration in the precompetitive space between multiple stakeholders such as manufacturers, FDA, academic and professional societies contributed to the development and success of the TVT registry.

It should be noted that combining multiple real-world data sources has its own challenges such as navigating data use agreements and interoperability. It's also important to recognize the advantages and disadvantages of each data source and how these contexts influence resulting analyses. Additionally, IRB and ethics approval to ensure patient privacy

can be more difficult when engaging multiple entities. These are some of the more significant challenges of navigating the real-world evidence landscape.

In the prior discussion for the Endologix endovascular graft, real-world data was used for surveillance and postmarket safety studies to provide additional evidence for elucidating whether or not there was a specific device-related safety concern for Type III endoleaks.

Kaiser Permanente integrated clinical database provided long-term data defined as greater than 1-year follow-up and high granularity for surveillance. Another study provided an alternative type of evidence by using CMS Medicare claims data. Harvard Beth Israel Deaconess Medical Center was able to assess long-term device safety on a national scale. These are just some examples of how real-world data can be leveraged to further assess device performance.

As you can see from these previous examples, in general, each real-world data type has its own advantages and disadvantages and this holds true for the AAA space. Generally, databases that collect device information are important sources to identify specific devices that are often not positioned as standalone sources of evidence as they don't capture outcomes.

EMR and EHR data sources are great compilations of granular data, but there is great variability in each different EHR system, both content-wise and interoperability-wise. Registries are a great source of granular standardized data, but often are expensive and lack long-term follow-up. Claims data is a great source of long-term follow-up data, but data can be specific to ICD and CPT code definitions and lack device identification. Other sources such as hospital visit details and lab results are great supplemental data sources, but aren't sufficient standing alone.

When asking your meaningful question, you must choose the relevant data source or

sources to your question and evaluate important data analytic characteristics such as linkage, data quality, and standardized definitions and the proper analytical methodologies in order to provide externally validated findings.

For the next slide, I will be focusing on real-world data sources specific to the AAA device space and identify characteristics unique to this ecosystem.

Here is a high-level assessment of the largest AAA-specific data sources, the data characteristics that FDA has found of interest for the evaluation of AAA devices. We have worked with respective data sources, which are blinded here, to identify core data characteristics and information directly provided to FDA by each respective source.

This table was not designed to compare pros and cons of each source, but rather to look at the AAA ecosystem as a whole on larger entities. Each column represents a different data source. Green represents that the data source confidently captures or embodies the data characteristics. Orange represents that the compliance or data completion for that data characteristic is less than ideal and has great variability. Red represents that this data characteristic is not currently captured.

The first table represents the non-outcome related data characteristics and you should interpret it by assessing the table by rows. By looking across the row, we can see where there are gaps in data collection. As you can see, one of the biggest gaps is the identification of specific devices. The majority of the current infrastructure for AAA devices does not currently collect unique identifiers.

In addition, clinical and anatomic characteristics are important and can be better captured. Looking at the follow-up duration, longer-term follow-up is needed to evaluate outcomes that may appear later in the total product life cycle.

Here we're looking at specific outcomes of interest for the evaluation of a AAA device, which in this table are stratified into clinical outcomes versus imaging outcomes and

by 1, 3, 5, and 10 years. We see that for clinical outcomes, aneurysm-related mortality, aneurysm rupture, and stenosis are difficult to capture and may not be capturable based on what's available in source data. Other outcomes that are difficult or not currently captured are endoleak and device-specific outcomes such as loss of device integrity, occlusion, and migration.

In addition, being able to capture subtypes of outcomes such as endoleak Type I, II, and III is important. As you can see, it can be more difficult to capture imaging outcomes versus clinical outcomes. The common challenge for imaging outcomes is low imaging compliance, which contributes to the lack of outcome capture.

Compiling the areas where real-world data collection can be potentially improved, there is a need for identification of specific devices as it can be difficult to identify brand, device iteration, and specific individual devices for analysis purposes. As reiterated throughout this Panel, longer-term follow-up is needed of patients.

Based on the previous table specifically, surgeon outcomes could be more consistently captured throughout the duration of the total product life cycle, such as aneurysm-related mortality, stenosis, the different endoleak types, and most device-related outcomes. Noted by the outcome-specific table, a majority of the outcomes that are challenging to capture are imaging outcomes and this can be due to a low imaging compliance.

And when looking to utilize or improve regulatory usage of real-world evidence, there are various elements to consider in using real-world evidence and of utmost importance are the data relevance and reliability -- in the FDA 2017 CDRH RWD/RWE guidance, which is listed at the bottom of the slide.

How well the data caters to the regulatory questions at hand and the data quality, consistency, and other aspects of reliability are essential to consider first and foremost.

Other common elements to consider for successful regulatory usage of real-world data are data governance, a process of managing the availability, usability, integrity, and security of data, and data flow, incorporating data harmonization, which may include the process of combining separate databases into a unified system and/or interoperability which may include the ability of systems to create, exchange, and consume data with cleared shared expectations of the content, context, and meaning of the data. Standardized definitions, an integral part of data interoperability, are important when evaluating any research question and common data models, or CDMs, are very useful in transforming data for fast access, easily interpretable data ready for analysis.

To recap, overall challenges to the AAA real-world data utilization consists of the following considerations. Readiness to access data can be impacted by important considerations to patient privacy protection, and navigating preexisting data use agreements may need further exploration. Many outcomes necessary for the evaluation of AAA-specific devices are impacted by a lack of longer-term follow-up and low imaging compliance.

Potential solutions to these challenges that have been implemented in other clinical areas of practice can be establishing data use agreements early with robust data sources or utilizing third-party entities with existing contracts for data extraction and analysis. This connects -- and streamline processes.

For more thorough data collection, efforts such as TVT have used multiple data sources to complement each other to provide a more comprehensive picture of a total product life cycle. In improved imaging compliance, one can focus on prioritizing imaging compliance with select designated sites as opposed to tackling the ecosystem as a whole. In addition, efforts such as the TVT registry post-approval studies and many others were examples of multistakeholder collaborations where manufacturers, relevant government

agencies such as FDA, professional societies representing relevant physician specialties, and academic experts such as real-world data experts were brought together to develop a real-world evidence methodology. This may be a viable method to consider as we continue addressing how to move forward in the AAA space.

So in conclusion, there have been very successful incorporations of real-world evidence in the regulatory space, each used in a variety of contexts such as postmarket studies and surveillance and premarket approval.

The existing real-world data infrastructure provides multiple modalities for data capture. This includes significant AAA-specific infrastructure such as a registry, which other clinical areas may not have developed. The aforementioned registries have the ability to capture both imaging and clinical outcomes, as well as representing real-world device use.

As noted in the case examples, as well as the high-level assessment of current AAA-specific real-world infrastructure, the current infrastructure has challenges and these key areas include navigating data use agreements, low imaging compliance, more reliable long-term follow-up, and ensuring patient privacy protection.

In the preceding slides, we have presented the current state of the AAA real-world data infrastructure and noted what data is currently being collected, areas of strength as well as opportunity. We are seeking input from the Panel on what outcome data and duration of follow-up should be collected, as well as ways to overcome current challenges in the AAA EVAR real-world data infrastructure. We ask the Panel to consider the presented information as they provide recommendations.

We look forward to hearing your thoughts and perspectives as we tackle this important endeavor together. Thank you.

DR. LANGE: Thank you to OCEA for that presentation and we have 8 minutes for clarifying questions. Again, we'll have deliberations later.

Dr. Shepard.

DR. SHEPARD: Thank you. Alex Shepard from Henry Ford Hospital. I just wanted to add on to the points about image availability and the lack of compliance with image follow-up. As we heard from Dr. Oderich yesterday, it's not just a question of getting the images, it's a question of the quality of those scans. Sometimes you can tell the aneurysm sac size, but if there's no venous phase or delayed imaging, you can't tell whether there's an endoleak. If there's an endoleak present, it's oftentimes difficult on poor-quality scans, so what sort of endoleak is present? So I think this calls into question the need for a core lab analysis and independent review of some of these scans, which obviously is going to add to the expense of any surveillance protocol. Thank you.

DR. LANGE: That's a comment. Any question directed to the speaker at all, Alex, or just that comment for future --

DR. SHEPARD: Just a comment, I'm sorry.

DR. LANGE: Okay. That's okay. Any clarifying questions for the presentation?

Dr. Woo.

DR. WOO: I have a question for Dr. Wang. You mentioned some data sources and we talk a lot about the Medicare claims data, obviously, but as we've already discussed, that doesn't capture everyone. There are other claims data sources such as Optum and other private insurer claims. Have those ever been looked at in terms of this purpose?

DR. WANG: Dr. Woo, thank you for that. For looking at alternative RWD sources such as alternative claim sources, it really depends on the evaluation of, as I had mentioned before, relevance and reliability and FDA has had previous experiences with alternative claims outside of Medicare, but it really depends on the question being asked and how well that RWD source fits the question being asked. And as I mentioned before, each of the RWD sources has its own strengths and challenges and then aligning those strengths and

challenges with the question that you're asking regulatory-wise, safety-wise, device performance-wise, is key.

So when it comes to the evaluation of AAA devices, then it depends on, you know, we have to think about that particular source such as Optum or Truven or any other of those alternative claims to really determine is it relevant to the question at hand and then if it's relevant, how reliable is the data and how that data is being captured. Does that answer your question?

DR. WOO: Sort of.

DR. LANGE: Yeah. So I'm going to pin you down. Again, relevance and reliability are important. Have you done it using alternative non-Medicare databases?

DR. WANG: Sorry, could you repeat that?

DR. LANGE: Have you used alternative databases of current registries?

DR. WANG: So in my particular experience, we have evaluated other RWD sources, but it again depends on the question being asked. Maybe some of my other colleagues can answer to their experiences, but again, it really depends on the question being asked and with those submissions that use RWD, generally, we ask those on these relevance and reliability questions on how to characterize those sources.

DR. JOHNSON: Hi, this is Carmen Gacchina Johnson. Maybe to answer the question specifically to the AAA space, we did not specifically investigate alternative care-based registry or information systems. The three examples that were presented, were presented because they were large regional or national databases and infrastructures already established in the AAA space.

DR. LANGE: Dr. Woo, does that answer your question?

DR. WOO: Um-hum.

DR. LANGE: Great. I've got Dr. Goodney, who raised his hand, Mr. Conway, and

Dr. Yeh.

Dr. Goodney.

DR. GOODNEY: Just a brief response to Dr. -- this is Phil Goodney, VQI-VISION. A brief response to Dr. Woo's question. We use New York All Payer datasets to run similar analyses, Karen, to see if our methodology worked well in those datasets and a short answer is it worked just fine there. The results were essentially identical to what we found in regular claims. Thank you.

DR. LANGE: Okay. Thank you, Phil.

Mr. Conway and Dr. Yeh.

MR. CONWAY: Thank you, Doctor. Just a follow-up on Dr. Woo's question just so I have a full understanding here as we're going forward for the rest of the day, also. What about the VA database and Tricare, have those been looked at for potential?

DR. JOHNSON: Hi, this is Carmen Gacchina Johnson. Absolutely. And you may have seen in your -- the Executive Summary provided by FDA, there is an ongoing coverage in the VA and Harvard researchers. Unfortunately, that data analysis is not far enough along to be able to present at panel. However, we have an ongoing coverage there and look forward to being able to present that data publicly in the future.

DR. LANGE: Great. Great question, Paul, thank you.

Dr. Yeh.

DR. YEH: Mine was just a bit of a response to Dr. Woo's question because we had collaborated with FDA and OCEA during the peripheral vascular drug-coated balloon controversy and we had used -- actually designed with them a study using Optum data, in collaboration with Medtronic. So those data were useful in that situation for a mortality endpoint because mortality is captured well in Optum, particularly Optum commercially insured Medicare Advantage patients. But we did find there's substantial missing of both

mortality data and also claims data because in the commercially insured patients, unfortunately, there's a lot of insurance switching that happens; that doesn't happen in Medicare fee-for-service patients and so the follow-up, it's very hard to get 5-year follow-up from an Optum database, people have almost invariably switched insurance in a large number.

DR. LANGE: Great. Thank you, Robert.

This brings us up to the lunch hour, which is only 40 minutes, so we'll take a break. In the meantime, Akinola, in the link I could not find the presentations that the industry or physician representatives made, so if you would e-mail those presentations to the FDA panelists so if they want to look at those over lunch to help guide their discussion, that would be very helpful.

DR. AWOJOPE: Okay, I will get in touch with you, sir.

DR. LANGE: That would be great, Akinola, I appreciate that.

We will reconvene at 12:30 Eastern Time, 9:30 Pacific Time. So thank you all very much. And by the way, during this time, please hold no discussions about any of the content we've discussed or will discuss, thank you.

(Whereupon, at 11:50 a.m. a lunch recess was taken.)

AFTERNOON SESSION

(12:31 p.m.)

DR. LANGE: Good afternoon, it's 12:31 Eastern Time and I'd like to resume the panel meeting. We'll proceed with the guest speaker portion of the meeting. Public attendees are given an opportunity to address the Panel, to present data, information or views that are relevant to the meeting agenda.

We have three speakers. The first two, Dr. Gustavo Oderich and Dr. Tara Mastracci, will provide prerecorded presentations followed by Dr. Rodney White, who will give a live presentation. Each speaker will be allotted 5 minutes for their presentation.

Please begin with Dr. Oderich.

DR. ODERICH: I would like to thank the FDA for the opportunity to present. These are my disclosures.

We all know that we have a little bit of a problem with the late outcomes of EVAR, particularly compared to open surgical repair. Freedom from reintervention or rupture was significantly lower among patients treated by EVAR as compared to open repair beyond 3 to 4 years.

Andy Schanzer also pointed out that even though technology might be getting better, physicians are becoming more and more aggressive when using these devices outside of the instructions for use.

And you can see here the lowering freedom from sac enlargement in patients who were treated in the more recent experience compared to at the beginning of the EVAR experience.

There is a number of reasons why EVAR fails, and it's not always the device or the patient or the physician. Often it is a combination of these three factors and I would like to

illustrate with some examples that I had the chance to treat over my career.

First, physician is often to blame on why EVAR fails. The combination of poor judgment, perhaps sometimes with the desire of using a new technology, can lead to EVAR failure. Take, for example, this patient treated in 2009 for actually a small infrarenal aneurysm with a very short neck, and this was immediately after the Talent device became commercially available for a 1 cm neck indication. It's not actually surprising that the physician encountered, during this procedure, a Type Ia endoleak years after the patient was referred to me for treatment of this Type Ia endoleak and I actually waited several years until the aneurysm reached about 6 cm and then eventually we treated the aneurysm with a fenestrated graft.

Other times the problem is clearly the device. Now, we were all excited when the AneuRx became commercially available and quickly, this actually became the stent graft of choice. After all, it was also one of the only few devices that was commercially available. You can see the excitement of some of the first publications in this issue of *Endovascular Today* from 2000, outlining the new gold standard. A few years past this excitement, several centers have noticed the issue of device migration. You can see here the cumulative event rate of 67% in 4 years.

Now, one would think that actually physicians and engineers would learn from the fact that the device didn't hold with radial force alone and you needed active fixation, but in fact, the same experiment was then repeated with another device and then again almost one and a half decades after with another device. So trying to reinvent the wheel and repeat the same experiment, I think, clearly doesn't work.

Other times the problem is the patient. Now, you can see that we again were all excited when a large device became available so we could treat more patients with the same type of approach. Thirty-six millimeter devices quickly became widely used, first with

some excitement about how well this device performed but then, as time went by, we saw patients like this one that I treated initially with what I thought was an acceptable landing zone, but then after a few years with a Type Ia endoleak, and again we can see many, many publications outlining the problem of large-neck devices.

So in conclusion, device-, patient-, physician-related factors directly affect mechanisms of EVAR failure.

Patients can go undetected for years or decades with totally ineffective repairs before clinically significant events such as reintervention, rupture, or death takes place.

And the reporting of EVAR failure is inconsistent and mostly up to single-center retrospective reviews, which vary widely and are mostly not reported for community based outcomes.

Thank you very much for your attention.

DR. MASTRACCI: Thank you so much for the opportunity to speak at this meeting. These are my relevant disclosures.

In preparation for the meeting, I was asked to focus on three separate points and I'll address them all in this slide deck. The first one, and what I see as probably the most important, is to discuss the overall safety and effectiveness of EVAR.

I think the first couple generations of endovascular devices probably had some engineering flaws and have since left the market. Since that time, though, the modern devices that we're using have proven to be pretty good and, in fact, if you look at any large series of people explanting or converting failed endografts, what you find is that there is a broad assortment of different grafts that fail in different anatomy.

And in fact, anatomy is probably one of the things we've learned the most in the 27 years to predict poor outcomes. An unfavorable neck anatomy is probably one of the best predictors of failure, as is something called a hostile neck.

And so really, when we talk to vascular surgeons, the question should not be which devices fail or in what anatomy will devices fail because we know the answers to those things, but really what's motivating the judgment behind putting devices in places where we know they're going to fail.

So we did a bit of research to try and figure this out and what we did was we looked at all of the EVARs done at an academic teaching center in London, England, and we made two cohorts, one from a very early cohort, 2008 to 2010, and one from a later cohort and there were about equivalent numbers of patients.

And we really wanted this to be heavily imaging intensive research. So we had three consultant vascular surgeons score all of the CT scans that were available using the modified anatomic severity grading score and we did things that I think are really valuable, like measure the intended length of seal, the actual length of seal, to see what the technical skill of the surgeons implanting the device were.

What we found is between the two cohorts there was actually an impressive operative strategy change in that given the same anatomy, a lot more patients were provided a complex endovascular repair like fenestrated repair in the later cohort and this despite the fact that there was really no difference in the medical demographics or the health of the patients themselves. We also found that what people considered anatomy suitable for infrarenal EVAR changed.

Now, I think it's really important to note that there was no difference in the number of off-IFU treatments provided. In fact, in both cohorts the surgeons were on IFU most of the time.

However, if you look at the anatomy based on the ASG, you'll see that there was a statistically worse anatomy in the early cohort compared with the later cohort for infrarenal repair and most of the time, in the late cohort, if patients scored poorly in anatomy, it was

because of distal landing zones and much more rarely the proximal landing zone unless, of course, it was a rupture.

The technical skill, you won't be surprised to know, was absolutely equivalent. There was no statistically significant difference between surgeons being able to land a device accurately. Somewhere between 80 and 90% of the sealing zone they wanted to achieve they did achieve. The difference, though, is that the neck length and the sealing length that they were aiming for was statistically significantly different, the neck lengths were much longer in the later cohort and as was the sealing zone distally in the later cohort.

And the complications over 3 years are, as you would predict, much higher in the earlier cohort with less landing area, and the number of reinterventions followed suit. And you can see that these reinterventions largely involved reclaiming the sealing zone for the patients.

And these decisions impacted survival because after about 6 months the all-cause mortality in the early cohort was much worse than that in the later cohort.

We've published this paper and provided a curve of what a successfully decreasing sac shrinkage should look like and, in fact, provided a way that surgeons can plot their own patient's shrinkage over time to see if they're matching that curve.

The second thing you asked me to address is clinical and imaging outcomes and what are most critical. I really think you need to have detailed anatomic data including measurement of landing zones, and I think we should bring machine learning into this wherever possible.

From a clinical outcome point of view, all the usual suspects, but include sarcopenia and frailty because it's incredibly important, and social deprivation. We actually took that early cohort of patients and looked at the impact of social deprivation. I'm very pleased to tell you that there was really no difference in their presentation or perioperative outcomes.

But over time it was clear that people who were in more deprived groups were less likely to get EVAR and in fact, that they're all-cause mortality was much worse, as well. So if we had addressed the deprivation status, we probably would've had better outcomes.

Thirdly, the strengths and limitations of platforms for data collection, I can speak most expertly to the UK National Vascular Registry, which is the national registry in the United Kingdom. In the last couple of years they've started to include device-specific data including whether or not the IFU was followed, and they publish their statistics every year. I think having a platform that you don't have to pay to participate in is incredibly important to getting pragmatic results.

Thank you.

DR. WHITE: Thank you, it's an honor to present today. I'm going to address the same topics that the other reviewers have talked about. Next slide, please.

You've already heard that outside the IFU indications are where we frequently have problems. And next slide, please. Where we've really -- next slide.

Where these have worked well, where you've got 5-year surveillance to look at this and other prospective registries, so I think we have ways to collect this data. Next slide.

The real-world imaging is part of our emphasis here today and I think you've heard we need thin-cut CTs. I frequently tell patients at some interval to get one from the chest all the way through the abdomen because these patients have other aneurysms that can be addressed and can be screened at the same test.

We've learned over time that CT is good for measuring, as I'll show you in a minute, and then the ultrasound -- next slide -- can be very useful. This is an example of a patient with an endoleak on the CT all the way on the right. Or on the left, I'm sorry, and then the two color flow images that demonstrate that leak. Next slide.

The other parts of this are, previously, we never looked at surgical grafts at follow-

up, so when clinical indications for these were first in the postmarket setting, it was set out that everybody would use 30 days, 6 months, and then annually. Next slide.

And there's still interventions that do that. But I think, and this is my own personal pattern for doing this, but what I try to do is restrict the contrast, use the colored flow, then, whenever we can, and particularly restrict contrast after device stabilization is demonstrated and that usually can be within 2 to 3 years. And then beyond that, actually have the patients be able to get ultrasounds, it makes it less really cumbersome for the patients and if we can broaden that surveillance interval, it makes it easier for the patients to come back. Next slide.

My personal experience continued then with using M2S, I think this was a very familiar pattern for people and it's very easy to select the data over time. Next slide.

This one really looks at what I think are critical measurements, the volumes, the diameters, iliac and the access vessels and then angle and lengths of tortuosity. Next slide.

This is an example over 12 years so we can see in a patient and if you look at those right-hand panels, those were done with non-contrast CT and you still can get information that's relevant and be able to continue the surveillance. Next slide.

I think this is the most important one, and Jacqueline emphasized this yesterday, is patient involvement. From the patient compliance, which is usually a very significant limitation, it can be very hard to get these folks back and I think this has to be started from the time of the initial encounter. We need to talk to other patient relatives, close associates, get reliable phone numbers, and I think even I use my cell phone, people don't like to do that, but patients don't abuse it and if they get a call from you and they recognize your number, they're likely to pick it up. When I get a call from a doctor's office, it's automated and I'm thinking it's a spam call. So we need to have names and numbers, give patients copies of the images and get them very closely involved from the very beginning

and that will help this compliance problem.

With that, I'll stop. And thank you very much.

MR. VEIZIS: Sorry, Dr. Lange, you're muted.

DR. LANGE: Thank you very much, Jim.

Thanks to all the presenters. We have a couple minutes for any clarifying questions.

Dr. Khaja and Mr. Conway.

DR. KHAJA: Dr. White, I really enjoyed your brief presentation. You know, can you tell us a little bit more about how you engage the patient's family? And then also, how important it is to have imaging performed at the same institution?

DR. WHITE: Yeah, I think engaging the family -- and again, this happens at the time of that initial encounter, particularly in the hospital. What I try to do is have the nurse that's going to do the follow-up exams get to know those patients, that way the patient feels they have an advocate and if there's somebody they can call and recognize again when there's a follow-up contact, they're more likely to come in than not. And I think if it's -- you know, we send out letters and we do a lot of things, but it's very hard sometimes to get these folks back, so that to get that level of compliance that will have them feel like there's an advocate. And again, like I told you, I give a lot of the patients my own cell, we worry about that, but it's really not abused by the patients and if they have a problem, I want to know anyhow, I'm going to find out in the end after they've had difficulty. So I think making it easy, have your name show up on their cell phone or somebody who's their patient advocate is very important.

The second part of that, same-center imaging doesn't necessarily have to be the case, but a protocol that outlines interval, you know, short-interval, high-contrast CT imaging is a critical component that we frequently, and I heard this yesterday, don't get good images. So having again a way, a protocol, and disseminating that to the centers

where the patients are going to follow up, we obviously would like to get it back. That's not an easy thing to overcome and that standardization of the protocol and your communication is very important.

DR. KHAJA: Thank you.

DR. LANGE: Mr. Conway.

MR. CONWAY: Thanks, Doctor. Paul Conway.

Dr. White, a quick question for you. Thank you for articulating a patient advocate viewpoint and a patient engagement viewpoint. I'm particularly interested in contrast and non-contrast. So in terms of your approach on non-contrast, is that for ease of process and burden on a patient? Or is there also a medical component of that, of not exposing patients over time to more contrast load, for any potential adverse issues with contrast load? Thank you.

DR. WHITE: In particular, that's the biggest issue, is the large contrast load. I showed you those patients where we've gotten annual follow-ups out to 12 years but over time that is, as you know, a significant issue and so we try to limit that. You don't get information about endoleaks and that sort of thing, but if it's already been demonstrated that the aneurysm is shrinking down and there's no other issues, then you can look at the device conformity. On the non-cons you can do all the reconstructions and still get significant information about everything you want to do for the surveillance.

DR. LANGE: Dr. Khaja, I saw your hand raised again.

Thank you, by the way, Dr. White, for responding.

Dr. Khaja and then Dr. Blankenship.

DR. KHAJA: Yeah, I just wanted to -- this is Minhaj Khaja.

Just to make a comment regarding that, again, I agree that a contrast-enhanced study is ideal with a non-contrast phase followed by a CT angiogram phase and then a

delayed venous phase, and this is all captured in the multidisciplinary appropriateness criteria by the ACR for the follow-up of abdominal aortic aneurysms, including vascular surgery, cardiology and so on and so forth, and this is all spelled out. And I do agree that getting contrast-enhanced or non-contrast ultrasounds at time points when things are stable, as well as non-contrast CTs are very beneficial, but if there were a change, then you would move on to a contrasted study.

DR. LANGE: Dr. Blankenship and then Dr. Connor.

DR. BLANKENSHIP: Thanks, this is Jim Blankenship.

So we've certainly heard a lot about the importance of clinical follow-up and imaging, but on the other hand we've heard that a lot of these complications are asymptomatic, although one can suspect that making sure that patients have stopped smoking and minimized risk factors is important.

So my question is, is there any standard among vascular surgeons about whether there is, say, annual clinical follow-up with a practitioner? And if so, is that specified and should it be the surgeon or an advanced practice provider or a general practitioner and should that be part of guidelines if it's not part of guidelines?

DR. WHITE: I'm not sure that's in the guidelines as to who should do the follow-up, but as long as it's somebody who's going to ask the relevant questions. The other important part of this is some of these patients over time get debilitated to where they have very much difficulty to be able to come in to the office and do an encounter. So one of the things we've learned over the last year and a half is if you can get them to a relative or use Zoom on their own, you can do those kind of interviews.

So there's ways to get this information and be able to see how the patient is doing on an interview and then figure out with them what's going to be easiest if they do need imaging at that interval, to get them to someplace close, arrange for them even to get to

the hospital, be picked up and fast-forwarded, making it easy. So easy access is the big part of this and I think you can actually make that, but it takes a lot of trained folks and even again, the nurse and PA and NP advocates that are going to follow these folks and get to be their friends and get the information, as well.

DR. BLANKENSHIP: I would just like to follow up and commend you for your idea of giving them your cell phone, I think that's a level of engagement and that is really commendable and we should all aspire to that, so that's a model for us all. Thank you.

DR. WHITE: Yeah. And again, I think a lot of people are afraid of doing that, but I've got to tell you my own experience is it's not overused and when a patient has a concern or something's happened, I'm going to find out after two to three other encounters or not at all. So to get a call and be able to handle it is an easy way to do it and it saves -- you know, it personalizes the interactions and the patients respond better and we're trying to increase compliance and that's one way to do it.

DR. LANGE: Dr. Connor.

DR. CONNOR: I have just a super brief comment, that I appreciate the first two speakers listing their conflicts of interests, but the total time on screen of their slides was less than one-half of a second, combined. So if they're going to show conflicts, I'd appreciate you giving us time to digest it.

DR. LANGE: Thank you. Well put, Dr. Connor. Many of us did not pass our speed reading course.

DR. WHITE: That's why I took mine off, I showed them yesterday and then today was going to be over 5 minutes and you were going to cut me off, so I haven't yet finished the presentation.

DR. LANGE: It just takes one meeting with me to get me down, Rodney, and you got me. All right.

DR. WHITE: You got it.

DR. LANGE: We're going to move on now to 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. Mr. Awojope will read the Open Public Hearing Disclosure Process Statement and then I'll introduce the speakers.

DR. AWOJOPE: Hello, once again. Like I said, my name is Akinola Awojope, Dr.PH, doctor's in public health. I'm also the Designated Federal Officer (DFO) for today's meeting.

Both the Food and Drug Administration and the public believe in the transparency process for information gathering and decision making. To ensure such transparency at the Open Public Hearing and the guest speaking session of the Advisory Committee meeting, the 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 speakers and the guest speakers, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you might have with any company or group that may be affected by the topic of this meeting for today. 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 today. Likewise, the FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of your financial relationships at the beginning of your statement, it will not preclude you from speaking.

Thank you very much. Now I'll hand it back over to Dr. Lange, our chairperson. Thank you very much once again.

DR. LANGE: Great. Thank you, Dr. Awojope.

The FDA has received seven requests to speak. Each speaker will be given 5 minutes

to speak. The first six presentations are prerecorded and then Dr. Meg Seymour will conclude this Open Public Hearing with a live presentation. So at this time, please proceed with the Open Public Hearing.

DR. LEMMON: I would like to take the opportunity to thank the FDA advisory panel for allowing me to speak on Day 2 of endograft surveillance. My topic is entitled "Going Forward and Looking Back to the Past." I'm Gary Lemmon, I'm Emeritus Professor of Vascular Surgery at Indiana University, currently associate medical director at the SVS PSO. I need to disclaim that the views, opinions, and recommendations of this title and topic are my own and should not be construed or thought of as an endorsement by the Society for Vascular Surgery or the Patient Safety Organization. I have no other disclosures.

In order to understand endografts we need to look back to the past. In a 1999 *JVS* editorial written by Dr. Emerick Szilagyi, he was very prescient in understanding that all endografts will fail eventually. They are a temporary solution at best, resulting in aneurysm remission due to the lack of secure fixation. They all have predictable failure patterns. This mandates a lifetime of patient monitoring and there is no guarantee from rupture after EVAR placement. However, not all EVAR reinterventions are bad.

Inertia has developed, however, on early reports of endograft malfunction and in the September 28, 2017 communication from the FDA, it quotes: "There appears to be an increase in Type IIIa and Type IIIb endoleaks with EVAR." This was from 2017 and this, over 4 years ago. The report also stated that "We are bringing this potential complication to your attention to remind and encourage you to report Type IIIa and Type IIIb endoleak events to the manufacturer and the FDA." Unfortunately, that is 4 years ago and we achieved little progress since.

And as you know, reporting should be done through the MDR and *Federal Register* for device adverse events which include serious injury, death, or device malfunction within

30 days. All Type III endoleaks are included under this MDR.

What is needed going forward is a change. If a patient has an EVAR, they should undergo inclusion in a lifetime surveillance club that should be housed with data and extension of the VQI registry that is not available only to VQI members but applicable to all implanters. It should provide, just like having a battery checked on your pacemaker, information about survival; image type of surveillance, whether it be CT or ultrasound; size of the aneurysm and subsequent change; endoleak presence and type, if any; any reintervention done at the EVAR zone of repair; and new aneurysm treatment for above or below that area should also be identified. And this should be incentivized through governmental and industry support to allow for enthusiasm for the patients and physicians for this information. It also should be transparent for patient portal search features for an informed safety net of our community.

Monitoring for adverse events should include all ruptures, including those with rupture and survival or death. It should include emergency repairs for event rupture or limb loss, explantation of any endograft whether it be from open conversion or through other means, and it should include direct aneurysm sac pressurization, known to occur with Type Ia, Ib, Type IIIa and b endoleaks. A signal detection should be monitored and annual registry report for each unique device identifier to an oversight committee, the FDA, and the device manufacturer. This should hopefully occur with an overlap from a DELTA program on the VQI registry database.

After all, it's about the patient and we should be doing better than leaving them hanging out to dry. Thank you.

DR. ANDERSSON: Hello. Thank you for the invitation to attend this meeting. My name is Dr. Mattias Andersson, I'm a vascular surgeon in Sweden and my research is focused on complications of EVAR, especially post-EVAR rupture.

Our research group recently published a study in *Journal of Vascular Surgery*, a population-based study of post-EVAR rupture during 15 years. In that study we used Swedish national registers to assess the instance of post-EVAR rupture among all EVARs performed in Sweden between 2001 and 2015.

Following this publication, we were contacted by the FDA with an inquiry about the possibility to use the Swedish national registers to study device-specific complications of EVAR. I would like to start by giving a short background of the registers and then talk about how they can be used.

First of all, all individuals in Sweden have a person-specific identification number used in the national registers, such as the National Patient Register, the Cause of Death Register, and the Swedish National Registry for Vascular Surgery, the Swedvasq registry. Through the personal identification number, the merging of data from these registers is possible while maintaining all patient specific data.

The Swedish National Patient Register is considered to give an accurate description of patient-related diagnosis and treatments in 85 to 96%. The Cause of Death Register, data based on death certificates, has been shown to present 77% agreement with the cause of death expected upon reviews of medical records. Both registers are maintained by the National Board of Health and Welfare and reaches national coverage exceeding 99%.

The Swedvasq registry reflects hospital statistics in 96% with almost 100% coverage of primary AAA procedures. The brand and type and size of devices are recorded. All reinterventions following EVAR should be registered in Swedvasq.

But there are some limitations connected to the use of these registers. Concerning the Swedvasq registry, complications leading to reinterventions are registered. But of course, we know that the degree of registration of reinterventions has not been validated and importantly, untreated complications are only registered at 30 days.

The National Patient Register is limited by the precision of the ICD codes. Some diagnosis codes and intervention codes used to detect EVAR complications and reinterventions in the register are also used for events not related to the EVAR reconstruction.

Precision of the Cause of Death Register is limited, especially in patients deceased outside the hospital environment, since autopsy rate in Sweden is only 6%.

We got into possibilities to use the registers to assess device-specific complications after EVAR. It's our experience that the registers are highly useful to identify patients who had a primary EVAR and to estimate survival. With careful selection of inclusion and exclusion criteria, some complications and reinterventions may be assessed and they will be device specific.

In order to maximize the detection of complications and reinterventions and to minimize the risk of over- or underestimation, validation of the register data through review of patient medical records may be performed. This is possible since medical records are also traceable through the personal identification number. This addition to the registry information is time consuming, but strengthens the validity of the data.

We recently used this method to create a database of complications and reinterventions in 1,800 consecutive standard EVARs at five Swedish vascular centers. We've already submitted one article on mechanisms and anatomical causes of post-EVAR rupture, and we also started working on another study on all complications and reinterventions of the cohort. A similar approach could be used to reliably assess real-life device-specific complications during EVAR.

Thank you for your attention.

DR. SEDRAKYAN: Thank you for another opportunity to share a perspective and some other results from Medical Device Epidemiology Network national and international

initiatives. Today, my partners again are Dr. Phil Goodney and Dr. Adam Beck.

And just a reminder that MDEpiNet is a global public-private partnership that is known for building Coordinated Registry Networks. Our Coordinated Registry Networks include a variety of data sources, and aside from registry data and claims data, we also leverage EHRs and patient-reported outcomes. But importantly, claims data alone can make some significant contributions to medical device research and surveillance and that's what I will focus my presentation on today.

Within VISION, that you heard about yesterday and also will hear about today, we do data linkages but we also have significant resources and continually update our claims data sources in order for us to leverage this for research.

And in that kind of analysis using Medicare data, we recently completed this investigation of endovascular leak tears of the aorta for abdominal aortic aneurysms and over the past 18 years documented both early benefits and potential late harms associated with this technology, particularly related to some reoperations that occur more often after EVAR compared to open surgery.

But it's really important to understand that these effects are changing over time. The effect of EVAR and its association with higher mortality does not exist in a later time period. There's significant improvement of EVAR over time, particularly in patients age 75 and over and in males. Similarly, there's significant gains in the improvements in EVAR compared to open related to reoperations, and that's a much stronger gain among the elderly patients over 75 and among females.

So these results from the United States are really important to also compare to the results from our international partnership registries and countries. The International Consortium of Vascular Registries that we launched 7 years ago and I highlighted yesterday, helps us do these harmonized investigations and we create datasets that will enable us to

look at the data in a similar way.

And an example study that I just wanted to highlight, published in the past year, looked at the volume outcome relationship after EVAR and open surgeries and documented a much stronger volume outcome relationship after open surgery, but really an absence of such effect for endovascular repairs of the aorta. Similarly, we looked at the early outcomes of EVAR, early benefits of EVAR, and documented that countries that use this technology more often have much lower postoperative mortality.

So again, when we look at the data from the United States, and in this instance, our partner registry and partners from Australia, and we did very much harmonized analysis of early and late outcomes, we have seen some similarities but also some differences. In Australia, the early benefits are stronger after EVAR, but also the late events occur more often.

In a study previously completed using German all-payer claims databases, we have seen a slightly different pattern and much longer period of early benefits but again, after 2 years or more we start to see again higher rates of mortality associated with EVAR. Again, these three major country data sources can be brought together and looked at in a similar way to better understand international performance of EVAR.

So we believe that these outcomes of EVAR are improving over time and we document that using national claims data sources.

We do believe that continuous national and international evaluation of long-term outcomes will help us understand global performance of this technology, particularly in the subgroups where there's potential for harm.

Thank you very much.

DR. ELDRUP-JORGENSEN: Ladies and gentlemen, on behalf of the Society for Vascular Surgery and Vascular Quality Initiative, I would like to share our perspective on

optimizing real-world data. I have no disclosures.

There is increasing recognition of the value of real-world data in monitoring device performance that requires high-quality data and long-term follow-up. The Vascular Quality Initiative was organized under the Society for Vascular Surgery and is a voluntary clinical registry that collects granular clinical data including comorbidities, anatomic characteristics, procedural details, and significant outcomes out to 1 year. The VQI has over 800 participating centers and strong collaborative relationships with other organizations including the NCDR and American Heart Association.

We are pleased to report that less than half our membership consists of vascular surgeons and there's strong representation from interventional cardiology and interventional radiology. About one-third of our hospitals are academic, one-third are teaching hospitals and almost 40% are community hospitals, representing a true real-world experience.

The value of VQI is the granular clinical detail capturing outcomes out to 1 year. On the downside, VQI is a voluntary registry and subject to issues such as data missingness and length of follow-up. From our perspective, VQI supplies most of the data and infrastructure required for real-world evidence, but we need to build on this foundation.

Strategies to improve VQI data and length of follow-up are the following: mandated device approval requiring a post-approval study in a registry for a predetermined period of time. Another consideration would be a national coverage decision requiring registry participation. Alternatively, we can enhance the current VQI registry by adding customizable data fields and time points or using the registry to build a vascular research collaborative. Let me explain a little more.

In the vascular research collaborative, or VRC, we propose creating a subset of VQI centers, maybe 40 to 50, that have the following characteristics: high-quality data entry,

longer follow-up, experienced trials, and populations underrepresented in medicine, as well as the broad representation from specialties and hospital types. Or to express it colloquially, VQI on steroids.

The 50 centers would be selected based upon important criteria. VQI has developed a site selection tool (SST) that allows us to identify sites on preselected criteria such as volume, data completeness, follow-up for populations underrepresented in medicine. By entering preset criteria, we can filter out the appropriate sites. SST allows us to identify sites by percent of long-term follow-up, discharge medications, ethnicity, race, or gender.

The vascular research collaborative would be focused on high-quality data and longer follow-up out to 3 to 5 years. Such an effort would, of course, require additional expense and financial support.

The vascular research collaborative would provide high-quality real-world data that would add value to industry, FDA, professional societies, and most importantly, our patients. Such data could be used for device improvement, device surveillance, regulatory guidance, signal discernment, and addressing important scientific questions. Real-world data from the VRC could be used for addressing real-world problems such as endoleaks and paclitaxel devices.

Thank you for your attention.

DR. SECEMSKY: Hello, my name is Eric Secemsky, I'm a practicing interventional cardiologist and the Director of Vascular Intervention at Beth Israel Deaconess Medical Center, and I will be making a comment on real-world evidence for the evaluation of aortic device safety.

These are my disclosures.

So as we know, there have been many concerns about cardiovascular devices that have emerged post-approval and two main themes that come out of this, one is that

premarket randomized trials are not effective mechanisms to evaluate rare or infrequent safety signals, and second, that we really lack a systematic approach to evaluating post-approval safety, in particular for medical devices where we often rely on voluntary reporting.

Now, the 21st Century Cures Act really created the mechanism for us to start incorporating the use of real-world data to generate the real-world evidence needed to help satisfy post-approval study requirements including the evaluation of safety.

Now, in 2019 we met at an FDA advisory panel to discuss paclitaxel-coated devices and I'll use that as one of my two case studies on use of real-world data for evaluating the safety of these devices.

As we know, there was a meta-analysis that showed increasing risk with increasing time associated with paclitaxel balloons and stents. Yet, there were many limitations to this analysis. In addition, a randomized trial was thought to be infeasible due to the large study sample that would be required to power for mortality up to 5 years of follow-up.

As such, we were engaged with the FDA to create and design an opportunity, a safety analysis evaluating paclitaxel-coated devices using real-world Medicare insurance data. This invoked a number of statistical approaches including the use of inverse probability of treatment weighting and sensitivity analysis to evaluate for unmeasured confounding, and we approached this like randomized trial data with a predesigned published methods paper and filing at clinicaltrials.gov.

We were able to show in the SAFE-PAD study of over 158,000 patients with follow-up extending out to 5 years, that there was no harm associated with drug-coated devices and in numerous sub-analyses of important patient subgroups, as well as seven sensitivity analyses for the impact of residual confounding for performance of consistency of the safety signal.

More recently, and as people saw yesterday at Day 1, we presented data on the AFX unibody endograft. In this analysis we leveraged the use of a specific CPT code for the unibody endograft 34804 to identify these devices and evaluate long-term risks associated with them. And in this analysis we saw that in the full study period there was a greater risk of the primary outcome with unibody grafts compared with non-unibody grafts with an adjusted hazard ratio of 1.19.

In addition, we were able to look at very specific secondary outcomes including endograft extension, graft relining, late aneurysm rupture, and then conversion to open repair, which was unique as these outcomes are very relevant to the development of Type II endoleaks and were numerically and statistically different between unibody and non-unibody endografts.

So I want to just make a comment about the opportunity to leverage real-world data for safety concerns such as this. There are alternatives to insurance claims databases or registries, with or without linkage, and we know that registries do provide granular data and anatomical characteristics and device types and there is an infrastructure in place, but we know that registries tend to suffer in terms of long-term follow-up. Now, this is partially improved with linkage to insurance claims data.

Because of this approach, however, is that registries tend not to represent all centers in the United States performing these procedures. And in addition, there's a possibility for selective nonconsecutive enrollment, it's dependent upon volunteerism, and there's also a large burden of cost and time associated with this approach.

We'd like to present an alternative opportunity to use insurance data through the use of a limited device file. So what a limited device file would like is that for every endograft implanted in the United States, industry would submit the graft type, the demographics of the patient, and the date and location of implant. Then linkage can be

performed with insurance data just using this simple form and limited data to identify that patient and passively follow up the patient throughout time. This reduces cost, improves generalizability of findings, and also prevents the nonconsecutive enrollment of patients. And this could also include patients that have already been treated in the past, as well as future implants. Lastly, it allows industry partners to maintain ownership of the data, which is critically important.

So in conclusion, real-world evidence has an opportunity to play a significant role in device safety evaluation, both by providing timely evaluations of device safety at lower cost and representing real-world practice.

And limited device files with linkage to insurance data can provide a cost-effective, flexible approach to evaluating the safety of aortic implants as well as other medical devices.

Thank you very much.

MR. WALTHAM: Hello, I would like to talk to you today on behalf of Cydar Limited about software as a medical device, Cydar EV Maps, which could form part of the solution regarding data collection and a better understanding of endovascular device performance and outcomes.

Cydar is a UK-based medical technology company that has developed Cydar EV software as a medical device intended for use to assist image guidance during endovascular aortic surgery.

Cydar EV is FDA cleared and currently in use. The software is in continuous development and improvement with sequential releases offering additional functions and capabilities. Cydar EV Maps, currently under FDA review, significantly involves capabilities to assist in planning, sizing, and reviewing endovascular cases. Cydar EV Intelligent Maps supports clinical decision making by providing artificial intelligence-driven analytics from

completed case data and has been submitted for breakthrough device consideration.

Cydar has introduced the concept of a surgical map, a dynamic interactive patient-specific surgical plan that integrates patient features, clinical events, and outcomes data and analytics.

In terms of the software design, a cloud-based approach was adopted early on to meet development and computing power needs. This also means users always have access to the latest version. Authorized users securely access the system anywhere, anytime, through a web browser.

The cloud software device is connected to the hospital PACS image archive system and operating room image equipment. During normal clinical use, Cydar EV aggregates processed CT data, user inputs, and intraoperative imaging to Cydar vaults, which are cloud data repositories for each hospital.

Pseudonymized data is processed on the compute cloud, a specialized compute resource hosted in remote data centers with high-performance graphics processing unit machines.

Before a case, clinical users plan the endovascular procedure using several tools, some using artificial intelligence to increase efficiency. They create a preoperative map consisting of selected vessel anatomy, vessel rings, and virtual wires using processed preoperative CT data.

During surgery, the device provides information, in addition to the fluoroscopic images, that assist the surgeon with the intention of improving the efficiency and accuracy of the procedure to improve patient outcomes.

Cydar EV Maps further integrates the cloud data platform to process and aggregate preoperative, intraoperative, postoperative, and longer-term follow-up image data. Cydar EV Maps could provide a data collection platform solution to aggregate an unprecedented

quantity and quality of real-world data regarding endovascular device use.

After a case, the system provides a signal cloud platform where authorized users can securely review all case imaging in one place anytime and from anywhere. Cydar EV Maps will be able to provide analytics derived from these data, for example, patient-specific anatomical and disease morphology and technical outcome measures. These analytics will be valuable to clinicians, providers, device manufacturers, and payers.

Cydar has also submitted a further development of the device, Cydar EV Intelligent Maps, for consideration for breakthrough device designation. This device will provide multiple artificial intelligence-driven comparator analytics derived from matched completed case data to assist new patient decision making.

In the future, Cydar also intends the device will collect electronic medical records and other data collection tools, for example, VQI registry data. Linkage to clinical outcomes will enable further analytic insights into how patient factors, clinical decisions, and technical outcomes are related to longer-term clinical outcomes.

Cydar EV is FDA cleared, GDPR, and HIPAA compliant. It is already in use in several U.S. and European hospitals with data analytics on more than 3,000 aneurysms and hundreds of reinterventions. Every time Cydar is used, more data is added to the global pool of completed case data.

Cydar EV could provide a powerful platform to aggregate and analyze high-quality data to improve endovascular patient outcomes. Cydar would like to work with the FDA and medical device companies to incentivize and optimize real-world data collection.

Thank you.

MR. VEIZIS: I guess we need to introduce our live presenter.

DR. LANGE: Great. So Meg Seymour, I believe, is the last presentation and it will be a live presentation.

Meg, the floor is yours.

DR. SEYMOUR: Thank you. And thank you for the opportunity to speak today on behalf of the National Center for Health Research. I'm Dr. Meg Seymour, a senior fellow at the center. We analyze scientific data to provide objective health information to patients, health professionals, and policymakers. We do not accept funding from drug or medical device companies, so I have no conflicts of interest.

We are concerned about the conflicting data on EVAR devices and the reliance on 5-year studies that include different iterations of a device. These are high-risk devices and FDA should require clinical trial data for the approval of revised versions of the device. The FDA's Executive Summary discusses some long-term clinical trial data following patients up to 5 years post-EVAR procedure.

However, the FDA clearly noted that many devices have undergone modifications and that the clinical trials include the data on products that are no longer on the market, with more recent iterations including fewer years of follow-up data. Real-world data can be useful, but not when it includes numerous devices that don't specify the data for each different device. Let's simplify what is happening.

A newer version of a device is assumed to be better. With no clinical trials required by the FDA, it can takes years before any problems with the modified device are clearly documented. That revised device may be revised again, once again without clinical trials, and that new version of the device is also assumed to be better. This creates a cycle in which a lack of clinical trials for each modification makes informed consent impossible for patients and informed decisions by surgeons is also impossible. How many patients are harmed before new data on new versions of these devices have enough follow-up information to be useful?

The death rate for EVAR patients is high, they're high-risk patients, and this is

therefore a high-risk device. Clinical trials should be required for each time a high-risk device is revised because of the problems, ensuring that the new device isn't as bad or worse than the previous version that was recalled or withdrawn. Moreover, FDA should not allow devices to be approved for all patients with a particular medical need and the device is only effective for a very small subsample of patients.

As you consider conflicting data, we want to raise the question about how conflicts of interest may affect findings. As Dr. Menard stated at yesterday's meeting, many of yesterday's public speakers did not mention if they had financial conflicts of interest. We know that the FDA does not require such disclosures, but when physicians discuss their clinical experiences or provide data to the FDA's advisory panel, it is important that conflicts of interest are disclosed just as they are at medical conferences. Thank you.

MR. VEIZIS: Sorry, Dr. Lange, you're muted.

DR. LANGE: I'm sorry, thank you very much. Meg, thanks for your comments and to the other speakers, as well, in the open public forum. The floor is open for any of the panelists to ask questions of any of the presenters.

Dr. Brindis, I see your hand first.

DR. BRINDIS: Yeah, it jumped up. So thanks, everyone, for those presentations. I have a question for Dr. Jorgensen about the VQI registry. First of all, I was very intrigued by the tiered approach that you were talking about, VQI on steroids, actually is something proposed by John Laschinger when he was at the FDA.

My two questions are related to is it easy for VQI to identify when an EVAR is put in that doesn't follow an IFU? And also, maybe you could comment more in depth about the issues of auditing, what you're doing presently and what your plans are for the future so that we can be able to assure the FDA of high-quality data.

DR. ELDRUP-JORGENSEN: Thanks very much for those questions, Dr. Brindis. We've

had a number of applications and interest about looking at whether devices conform to the IFU or not, and there is some criteria that we do collect that can identify off or on IFU, for instance, neck length, neck diameter, taper, but we don't collect other information such as iliac artery diameter and so on. So although we could pretty well identify if a device was on or off IFU, it would not be 100%. But as we upgrade our registries and revise them every couple years, that's something that we're going to plan to consider.

Your other question was with regards to the data audits. Data accuracy and integrity is critical to any registry and very much so is one of our highest priorities. There are three components to accuracy: completeness, consistency, and correctness. We audit every site every 3 years for completeness of data entry by comparing it to claims data to make sure that centers are not cherry-picking cases, excluding cases that didn't do well or including inappropriate cases, and so we do that match.

A couple of years ago we had a large internal effort looking at consistency, the data that goes in is what the data comes out and as a result, we incorporated a number of quality control measures.

We're just beginning. About a year and a half ago we started a major effort towards data accuracy or correctness. We've gone through what we call the Phase 1 and Phase 2 and we're about to enter into a Phase 3. The initial effort was a survey to show data accuracy, we found we were in line with other major clinical registries, but this will be a major focus for us moving forward as it's so critical to the data that's used by industry and FDA.

DR. LANGE: So Ralph, based upon your knowledge with VQI, I'd call the second question a softball and the first question I'll call a knuckle ball, okay?

Alex. Dr. Shepard.

DR. SHEPARD: I'm very excited, Dr. Jorgensen, by your description of the VRC. I

guess I would ask if you could let the Panel know how much this is going to cost and your thoughts on how this would be funded going forward.

DR. ELDRUP-JORGENSEN: Thanks very much for that question, Dr. Shepard. There's been a lot of interest in the VRC and a number of our participants have expressed interest in participating, but collecting this high-quality data, especially out to a 5-year time period, is going to require some support. We've had some preliminary discussions with NIH and PCORI and they're not willing to support the infrastructure per se, but are willing to look at individual applications. We just submitted an application by one of our participants to the NIH to address an important scientific question.

In terms of the expense, we're in the process of putting together a budget for that, but one thing that I would say is that it's going to be a lot cheaper than a traditional post-approval trial where you have to start from scratch and you have to develop case report forms. It will be a fraction of what industry would require to pay for their own industry supported trials. By having so much of the infrastructure in place, we just need to add on a few more additional data elements, lengthier time points, and I think it would be extraordinarily cost effective. There have been a number of publications by us and the FDA as well as the cardiovascular registries showing a significant ROI on registry based trials.

DR. LANGE: I've got Dr. Starnes and then Dr. Khaja.

DR. STARNES: Yeah, I have a comment and then a question. My comment is for Megan Seymour. Megan, I can assure you, the process of becoming a special Government employee is onerous. I filled out so much paperwork for the FDA and I think the FDA knows more about me than my family does. So that's the comment.

The question is for Eric Secemsky and that is, Eric, how hard is it to link unique device identity to insurance data?

DR. SECEMSKY: Eric Secemsky. Thank you, Dr. Starnes, for that question. You know,

the UDI, I'm a little bit less familiar with linking the actual UDI to the insurance claims, say, without some supporting data about the patient and the implant site. And so in that proposal that I made, the flexibility that is involved includes being able to potentially match based on probabilistic matching and using characteristics like the date of implant, the site of implant, and familiar basic characteristics that are HIPAA compliant. Again, the leverage on that mechanism here is that it's flexible, so we want more than just the device itself, we could augment what is collected in Medicare by also supplying some basic anatomical details or the characteristics in a single data dump.

And again, what we would propose is complementary to what VQI is doing. I think the VQI matched registry is very important but would again allow for an opportunity to enroll more patients, a broader patient population and more devices, so that would make sure we have power to evaluate safety signals in a larger number of devices and then also, it would be a flexible platform that would be able to adapt to new devices as they emerge and other demands that might come up. So just an alternative or complementary mechanism, but I think it has some strengths and we haven't talked too much about the limitations of registry based only approach.

DR. LANGE: I've got Dr. Khaja and then back to Dr. Shepard and then Dr. Blankenship.

DR. KHAJA: This is Minhaj Khaja again. So more of a comment, but to Dr. Jorgensen about the VQI again, if industry and the FDA were to come together such as in the PRESERVE trial for IVC filters, for example, maybe we would be able to fund this and get more high-quality data, as well as provide the VQI software to smaller sites that may not be able to purchase it themselves. So just a comment.

DR. LANGE: Thank you, Dr. Khaja.

Dr. Shepard and then Dr. Blankenship.

DR. SHEPARD: Yeah, Alex Shepard from Detroit. Dr. Secemsky, perhaps you mentioned this already, but we heard from Dr. Goodney this morning that with the VISION marriage to VQI data with CMS data, that it took about 2 years and he was hopeful that with some further financial support this could be dropped down to around 6 months. Perhaps you mentioned it for the sort of analyses that you're doing, but what's the lag period between the time the data is available and, you know, that we can get answers? And sort of a follow-up to that, with the limited devices file approach that you mentioned, is the advantage of this is that it's faster, it's more -- or is that it's more granular or that it's both? Thank you.

DR. SECEMSKY: Eric Secemsky. Thank you, Dr. Shepard, for the questions. So for the first comment and kind of piggybacking off of what Dr. Goodney mentioned this morning, there are virtual seats at Medicare that allow us to access data with usually about a 6-month delay. And so we currently already have one active seat at our center which we use for another project and we have very deep knowledge and sophistication using the seat. And so we are able to get access to data, typically within the 6-month delay, depending on again what source we go through. Again, we used a different mechanism for the presentation that we provided yesterday. But again, the acquisition of registry data takes more time potentially than a quick cloud-based deposit of this device implanted in what patient and where and when and then we'd be able to find them in the Medicare set when that dataset catches up.

The second question, I think that the main strengths of this approach again is several-fold. First off, it's very passive and so it's cost efficient and it's lean. It requires again some participation on accessing some sort of information about the device that was implanted and some characteristics of the patient, but very minimal requirements from the upfront implant data and then everything happens in passive follow-up similar to the

Medicare data that you saw yesterday.

And again, I think the strengths in our standpoint looking at this is it's going to be more nationally representative. The data that we presented yesterday was from more than 1300 sites. I'm not sure how many actually particularly in the aortic registry for VQI, but I think it's a fraction or a percentage of that, I should say. And also it allows for us to really be able to control all patients who have implants being represented in this dataset, including potentially underrepresented patients who are treated at centers not participating in the VQI.

So again, I think the strength here is it's a little bit leaner and faster, it's complementary to the VQI, and I think there are strengths to the VQI proposal as well, and there's a lot of important data that the VQI collects that we probably wouldn't want to go through, it would slow down this process to go into this in detail, but it would be a complementary approach that would allow a little bit more of a representative or larger population, more devices, a little bit more flexible, and potentially more cost efficient.

DR. LANGE: And so this will frame our discussion about databases and knowing that it's not an either/or, but using complementary data will be the point of our discussion.

I've got Dr. Blankenship and then Mr. Conway.

DR. BLANKENSHIP: Yes, Jim Blankenship. Again for Dr. Secemsky. On the limited device file proposal, you can link to CMS, which certainly we know we can do that, but you also mentioned other insurances and I think you mentioned state insurance databases. My question is, are there -- there's likely significant numbers of patients who kind of fall through the crack, for instance, people who change insurance or reduce insurance or maybe states where they don't have a state insurance database.

DR. SECEMSKY: Eric Secemsky again. Thank you, Dr. Blankenship, for that question. Great comment. You know, I think that we really rely on Medicare data, it's worked very

well for commissions, particularly, in fact, older patients who are more often insured by Medicare. We heard earlier about the increasing use of Medicare Advantage, which makes some of this with linkage and also, there are private payers and patients who were treated earlier in their life. So we are continuously looking and trying to leverage opportunities to use other datasets. We have an all-payer claims database in Massachusetts that has not been, from my understanding, successfully reached before, but it's something we've been deeply looking into. California has one similarly. And then I think brought up earlier in the session was some private companies that collect EHR data and other insurance data. So I think we need to continue to explore opportunities to fill in those gaps.

I will say that one reason why I do think using the limited device file approach, even with CMS to start is important, is again, we're going to see a lot of patient dropout from any type of registry or study that requires insurance linkage if we only include a selection portion of those patients who then have mixed payer makeup. And so again, using the Medicare dataset at least, although we will lose some patients, it's a much larger and broader insurance database. But great question, Dr. Blankenship, it's something that we're incredibly interested in looking to work with other datasets because it is important for this type of work moving forward.

DR. LANGE: Great. I've got Mr. Conway.

MR. CONWAY: Thanks very much, Doc. For Dr. Secemsky. In your process, have you tried using Department of Defense Tricare data or VA data? Do you already have that going or is that something that you've looked at and said to use/not to use?

DR. SECEMSKY: Eric Secemsky. Thank you, Mr. Conway, I appreciate the question. I think the VA database typically requires someone who's a federal employee or a VA employee to be able to access. So we were able to work synergistically with a colleague for the paclitaxel evaluation, we published a paper out of the VA dataset, we have a close

colleague who helped run some of the cardiovascular research that comes out of the VA system. So I think it's an incredibly important dataset and it's valuable and I think that the issues with the dataset always is access and I think we can get it outside of the VA. Now, again, there are insurance databases that they can do something very similar and I would hope that they would consider that.

DR. LANGE: I saw Dr. Woo's hand.

DR. WOO: Yes, Karen Woo. For Dr. Secemsky. Do you envision collecting any data other than the device and like the date that it was implanted? Because oftentimes what happens when we do these cases is the industry representative actually fills out a piece of paper that has quite detailed information about the case planning and it seems like a lot of that information could be helpful. Is that something that would be possible to collect in your proposed registry?

DR. SECEMSKY: Eric Secemsky. Thank you very much, Dr. Woo. Absolutely. You know, I think going back to Jens's comment, this would be Plan A or the Plan A on steroids. And so I think that we kind of gave the base approach where we can continue to identify which device was implanted and with better granularity than what we presented yesterday to its approach, but there is absolute flexibility in terms of the other data that can be acquired. And so I think that we talked a lot about the anatomical considerations, which are critically important.

So in my mind, this would be, again, the opportunity where not only the basic limited patient information, but the brand and device type and then also some specific anatomical considerations that are deemed important would be able to be transmitted in the same mechanism through a simple cloud-based survey and then again, we'd be going through the same linkage but have some augmented variables for adjustment and for consideration for evaluations moving forward. So great suggestion, Dr. Woo, I think that's

something that we absolutely have considered and would build into this, if that was a mechanism deemed complementary to the other mechanism preferred today.

DR. LANGE: Dr. Shepard.

DR. SHEPARD: Alex Shepard from Henry Ford. Dr. Secemsky, I asked Dr. Jorgensen about cost and I guess now I have to ask you the same question, what would be the cost of this ongoing project?

DR. SECEMSKY: Eric Secemsky. Thank you, Dr. Shepard. You know, I think the costs here are a little bit more lean, it would require us to be able to collect these data and link them, this is something that our center actively does. Again, we have a virtual seat so we have experience there, we probably need another one to do a project like this.

But it would be hard for me to throw out a budget without being more informed, but I would think this would be a very lean proposal, it would be, again, much more passive and a little bit less manpower than like containing a little registry of some sort or alternative mechanisms. So I could absolutely follow up with some more details if there's an interest, but again we would be looking at a lean mechanism here that would be hopefully sustainable for as long as there's a need.

DR. LANGE: So Eric, I'm don't want to pin you down. When you say lean, give us a range. You're talking 50 to $100 or are you talking 5 to 10, 20 to 50, 100 to 500? Just kind of give, if you can, just kind of a ballpark.

DR. SECEMSKY: Eric Secemsky. I don't want to put my foot in my mouth here. You know, I think Dr. Goodney kind of proposed what the costs were to have a virtual seat in Medicare when you have an active DUA already, and so that's typically around 35 to 50,000 and then there's a renewal fee. But between that and then being able to collect the data, this would be a couple hundred thousand dollars on a yearly basis, but just the same and it's not less than -- more than 10 to $50, less than a million dollars.

DR. LANGE: Eric, I appreciate you ball-parking that. The six people that previously wrote checks to Phil have ripped them up and now are making their checks out to you.

DR. SECEMSKY: It's meant to be complementary and not replace what Phil proposed. Again, I think there's a lot of value of the data that was shown, so this would be a complementary mechanism here.

DR. LANGE: Great. Randy, I see your hand up.

DR. STARLING: Yeah, thank you. Starling. So first a comment. It seems to me that there's kind of two levels here, one is the patient, and what I'm hearing is that longitudinal follow-up and imaging is very important and maybe the onus to that responsibility should be on the provider. But as far as gauging safety signals with this EVAR therapy, it would seem that you can model a finite population or sample size that would be required, whatever database we're talking about here, to track the safety signals rather than trying to capture everyone. Any comments in that regard?

DR. SECEMSKY: Eric Secemsky. Dr. Starling, is that directed at me?

DR. LANGE: Correct.

(Cross-talk.)

DR. STARLING: To you, and I think to VQI leadership.

DR. SECEMSKY: Okay. I would just make the comment that the number of devices tracked, you know, we saw pretty full representation of what was available in Medicare without too many exclusions. Again, we excluded ruptures and aortic aneurysms outside of the abdominal location and for up to 2017 we had about 25 to 3,000, depending on the timing, of unibody devices placed in the AFX2 era. So I think we'd have to go back and do a formal power calculation to get to the answer, which is absolutely doable. But I think that as more device iterations are occurring and more devices come on the market, I think that power is absolutely going to be a concern for detecting a signal and it should be taken into

account with the proposals. And so I think that the Medicare would potentially be sufficient, but we can give you a more granular number, but we're now looking like we have 80,000 unibody grafts available already and these are still a portion of the market, which is a diverse market.

DR. ELDRUP-JORGENSEN: This is Jens Jorgensen. From the VQI perspective, we think that a sampling methodology might be effective. To get this high-quality data is going to require a fair amount of resources and support to do and so we're trying to provide a cost-effective approach. At the same time, in the interest of signal discernment, we're working with Fred Resnic at the Lahey clinic using his DELTA methodology, digital extraction and longitudinal trend analysis, and we are in the process of integrating DELTA into VQI to hopefully allow us to measure early signal discernment. With our current ability to incorporate global unique device identifiers into our registry, it allows us to look at individual devices with this software application.

DR. LANGE: Thank you, Jens.

I've got Dr. Zuckerman and then Dr. Starnes.

DR. ZUCKERMAN: I just want to make a general comment. There's been a fair amount of discussion regarding cost and I would instead ask the Panel really today to figure out what is the system that we need and then, in subsequent interactions with some of the groups here, industry and FDA, we can talk more about cost. That is really the key question in Question 3. As we saw yesterday, we couldn't even identify particular devices. We need a better national system here and I'll be looking to Panel members to help define the basic structure of that system and what questions should be asked. It is interesting that we've had several proposals and they may be complementary. Certainly, during the panel discussion I would like to hear more discussion about how these different approaches might be complementary. Thank you.

DR. LANGE: Thank you. Thank you very much, Bram.

Dr. Starnes.

DR. STARNES: Yeah. So you know, I listened to Mr. Waltham's presentation from Cydar with some interest and an idea came to me. If we can link the device to the patient and the patient to the institution, is it possible, leveraging artificial intelligence and the use of your imaging interpretation, once there is a device event, to go back retrospectively and to pull those CT scans from the preoperative phase and throughout the patient's surveillance phase to understand the mode of failure, why it failed, and get some information that way? Is that possible?

MR. WALTHAM: And thank you for the question. This is exactly what we're interested in, we're very interested in understanding why devices are failing and so looking at the decision making that is going on during the patient treatments. And as has already been pointed out, there's an awful lot of data and information that is not being collected at the moment and that is around how decisions are made, what the plan for the case is before it's even done, and then actually what happens during the case, what devices are chosen, what component sizes are chosen, how the devices are placed in the anatomy and so on, and then linking all of that together to learn, for future similar cases, what the best decisions are going to be to improve patient outcomes.

So we've already developed prototypes where we can use machine-learning computer vision to do exactly that to identify when devices are being introduced on the fluoroscopy image, to identify what those devices are, sort of whose devices, which manufacturers they are and so on, and so a lot of things about disease and patient morphology and anatomy that goes way beyond just a clinician entering the neck diameter or neck length or angulation or any of those very basic things. You know, we're using AI computer analytics to assess the anatomy and the disease, collecting what happens during

the case, and then we'll be able to link that postoperatively to when failure occurs in devices, to look back and understand why they fail.

DR. STARNES: My question really is can it be done retrospectively, can you go backwards?

MR. WALTHAM: Yes. Yeah, because we're aggregating the analytics from the processed preoperative CT data from all of the fluoroscopy because we're connected to the imaging system, so we're aggregating data from all the events that happen during surgery and then the postoperative follow-up, the initial postoperative CT and any subsequent CTs. We're collecting those in a patient-centric vault which we can then link it all together and look at the whole patient care pathway and try to understand why the devices have failed and then obviously use that information to then improve future decision making based on a sort of global aggregation of patient events.

DR. LANGE: Dr. Sedrakyan, I saw your hand up.

DR. SEDRAKYAN: Thank you for the opportunity. I just wanted to highlight that the very reason we built, in collaboration with VQI and SVS, VISION-CRN, which is Coordinated Registry Network, is to bring all relevant data and technologies in in a coordinated fashion and build from existing BAAs and DUAs that are already in place. That can take years and years to establish. And for example, to link with the all-payer New York State data that Phil highlighted, it took us 2 years to get the agreement from the state to get that data in and then link with vital statistics to get mortality data. The same is even more difficult in California. It's not like a 1-month or even like 6-month process to get data alternatives to Medicare, but we have all these processes already in place in VISION.

Second, to start something, in my opinion, a new registry that is considered here, I think it's an enormous task. Just a single business associate agreement to get device data from a site, I don't know who is going to do that anew. VQI already has the relationship in

place to build from. So I just wanted to bring a little bit of logistics and reality of how this can be done to help with the decision making.

DR. LANGE: Art, thank you.

I'm about to conclude the Open Public Hearing session to be officially closed. We're a little bit ahead of time, but I'm sure we'll -- I'm not sure that will sustain. Here's what the rest of the afternoon is, we have a 15-minute break shortly. We have a 2-hour period set aside for deliberations and that's specifically for the Panel to ask any of the presenters anything that will help them form their answers to the FDA questions.

So what I'm going to do in preparation for that, I'm going to ask the FDA, Akinola and Jim, to put the questions back on the screen, I want to roll through them before we take our break so that the panelists can be thinking about it during the break and then when we reconvene, to ask any questions that they need to clarify, that would bring clarity to any of their questions that would help answer the FDA questions. So could we put up the original FDA presentation?

DR. AWOJOPE: I can. Jim?

MR. VEIZIS: We're going to go ahead and run that shortly.

DR. AWOJOPE: Thank you.

DR. LANGE: Great. And I'm sorry, I know I'm taking a little bit of license here and I don't want the FDA to read them, you'll put them up and everybody on our Panel has passed their reading test in the third grade, so there are some faster than others, but everybody did pass. Actually, put it up a little bit longer, they're not that quick yet. So that was just like a disclosure slide, Jason. All right, if you'll go forward one slide, okay, let's just pause it there so that everybody can read it.

(Panel review of Question 1.)

DR. LANGE: Proceed to the next question, please.

(Panel review of Question 2a.)

DR. LANGE: Thank you. Next question, please.

(Panel review of Question 2b.)

DR. LANGE: Next question, please.

(Panel review of Question 3.)

DR. LANGE: And next slide.

(Panel review of Question 3a.)

DR. LANGE: Next slide, please.

(Panel review of Question 3b.)

DR. LANGE: Next slide.

(Panel review of Question 3c.)

DR. LANGE: And I believe that's the last one. Move forward just so I can be sure. No, I'm sorry.

(Panel review of Question 3d.)

DR. LANGE: Great. So Jim, if you'd be kind enough, we're going to set a 15-minute timer, then we'll come back and convene the panel deliberations. This will be a time for everybody on the Panel to ask any questions they have before we go into the FDA questions. All right, thank very much. I'll see you back in 15 minutes.

(Off the record at 2:05 p.m.)

(On the record at 2:20 p.m.)

DR. LANGE: Welcome back to the FDA panel. We will now begin the panel deliberations. Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair, that's me. Additionally, we request that all persons who are asked to speak again identify themselves each time and this will help the transcriptionist identify the speakers. During this next session we will

open the floor to panel questions and I will lead off. The first question -- I'm sorry, Paul, I'll get you right after me. The first question, I'd like to direct it to Phil Goodney. Phil, specifically the VQI is designed to provide very robust 1-year follow-up. We talked about a longer follow-up in terms of what we'll need. Talk to me about the logistics of that. Is it currently set up to provide just as robust a follow-up? If not, what needs to be done and what is the appetite for the centers that are enrolled to do so? So Phil.

DR. GOODNEY: Thank you very much for the question, Dr. Lange. And it's Phil Goodney from VISION-VQI. So as it stands at present, patients in centers that are entered into the VQI registry are committed to a 1-year follow-up entry after their procedure, so a year after their aneurysm repair we ask the sites to commit toward seeing the patient and entering their long-term follow-up information directly, so done as a keypunch function.

What we are currently doing, and what we have been doing since 2012, is extending that 1-year follow-up using Medicare claims, using the methods that I have described previously. So that's already been happening and that happens ad infinitum, so essentially it's for however long the patient lives after their linkage. If they live for 1 year or 3 years or 10 years, we collect follow-up passively through the Medicare claims and have done so, as we specified before.

There have been initiatives to add further in-person follow-up visits and that's what Dr. Jorgensen spoke about and those have been piloted in various stages across the registry and there has been -- you know, as you might imagine, the in-person data entry is more work and more expense than the passive collection mechanisms that we have used already and set up via our data linkages to the Medicare system and to some other state claims datasets, and I'll sort of emphasize the time and effort that we took to marry those two data sources because as it stands presently, Medicare data alone makes it very difficult to identify many of the important clinical characteristics that Dr. Oderich and many others put

into place, how large the aneurysm was, what exact type of implant they had, you know, a bifurcated implant, and Medicare claims is a pretty broad bucket of information. In the registry, we already collect that information through hundreds of variables that help us to inform that risk adjustment. So the short answer to your question is, is that we already do it essentially for as long as a patient survives for those outcomes that I mentioned: reintervention, late aneurysm rupture, and long-term survival. We also measure how often they have their surveillance scans and we publish that information, as well.

DR. LANGE: Great.

DR. GOODNEY: Does that answer your question, Dr. Lange?

DR. LANGE: It does. So I've seen several hands and I've got Mr. Conway, Dr. Cigarroa, Dr. Eagleton, and Dr. Yeh.

So Mr. Conway first.

MR. CONWAY: Great. Thank you very much, Doc. To Dr. Goodney. And I'm not certain if this question is better for you or for Dr. Jorgensen, but you were given a little bit of a nudge earlier today on the issue of transparency and so not necessarily just for patients, but for patient stakeholder organizations that are national, how do you envision transparency in terms of if an organization wanted to inform their membership of things that they're seeing about EVARs in your data, is there any type of anticipation of providing that?

DR. GOODNEY: Again, Phil Goodney, VQI-VISION. So thank you, Mr. Conway, a great question and something that we tried to think about in the construction of our steering committee when we formed it. Once we started to see that we could collect this information, that we could study it and that we might find important information that would be important to our multistakeholder panel, we made sure to make our steering committee have that constituency. So that's part of the reason why we have

representatives from the Food and Drug Administration, representatives from each of our individual device manufacturers, they attend the calls that I spoke about, they hear about the ways that the data is being constructed, they hear about the projects that are being initiated and then finally, hear about those results. So we try to make sure that this information won't show up blindly out of nowhere, that people will have some anticipatory guidance about it and make sure to inform their important team members when that information does arise. And we used that very same pathway when we found the signal for Endologix here, for example, we talked with their state and with their industry representatives to share our results and what our concerns were.

MR. CONWAY: Yeah, but could --

DR. LANGE: Jens, did you have your hand up, as well?

DR. ELDRUP-JORGENSEN: If I could respond in part to Mr. Conway's question, I would like to do so. I didn't have time to get into the full details of the VQI, but one of the unique aspects of our organization is members are required to participate in biannual regional quality meetings where they get together to look at their data, their outcomes are benchmarked on regional and national benchmarks, and we also discuss compliance with professional society guidelines, we measure how an individual provider or their center complies with guidelines and the impact it has on their outcomes.

And I just wanted to let Mr. Conway and Ms. Alikhaani, in particular, know that we value patient input. We've just started a pilot project to collect patient-reported outcomes, we have a patient advisor sit on that committee and engage in our discussions, and we're starting to collect patient-reported outcomes using paper forms, tablets, and also smartphones and we really want to get patients engaged more in VQI as we move forward.

DR. LANGE: Great. Apropos to that, I'll get to Dr. Cigarroa, Eagleton, and Yeh in just a second. Minhaj Khaja provided an appropriate use criteria drafted by an organization and

he sent it to Akinola.

Akinola, if you want to send it out to the members in preparation for our discussion later, please do so.

Dr. Cigarroa, Dr. Eagleton, and then Dr. Yeh.

DR. CIGARROA: Good afternoon, this is Joaquin Cigarroa, and the question I would like to direct to a co-panelist, Dr. Brindis. And as we think about longer-term follow-up, which is clearly necessary in this particular situation, and we think about active versus passive information flowing into this long-term follow-up, are there lessons to be learned from NCDR as we've gone from attempts at the initial hospital outcomes to further follow-up in the PCI registry, for example, that would be important for us to contemplate as we consider the VQI and longer-term follow-up necessary?

DR. BRINDIS: Ralph Brindis. Thanks, Joaquin, for that question. So it's been a challenge, long-term follow-up, and it's about carrots and sticks or centers appreciating internal value. Some of our patient-reported measures, the SAC questionnaires and such things and the PCI registry have not been uniformly used, some centers find value, some do not. The biggest inducement so far is the TVT registry and having a stick, and actually Jens referred to it earlier, which is the concept of a national coverage decision with a CED, because that is actually strongly encouraged, people like to be covered and paid to be able to fully submit the 1-year data and again, for our patient representatives, that includes patient-reported outcomes at 1 year, which is amazing, related to TAVR. But eventually, national coverage decisions go away, so that's going to be challenging for us with the TAVR registry and how that will play out. And I personally don't think that CMS would put in a national coverage decision or a CED related to EVAR since the horse is already out of the barn. That's my own personal thought.

DR. LANGE: Ralph, thank you.

Joaquin, thank you for the question.

DR. CIGARROA: Thank you.

DR. LANGE: Dr. Eagleton and Dr. Yeh.

DR. EAGLETON: I'm going to ask a fairly simple question that I want to direct towards Ron Fairman and Scott Williams from industry, and I think Ron gave us a fair amount of clinical information this morning in a brief period of time. We've seen that reinterventions occurred at a mean of about 2 years from the University of Pennsylvania data, but they're also occurring up to 8 years out. So when we start to develop a plan for long-term outcomes assessment, how long term are we calling this? And what are our recommendations going to be based on our clinical outcomes and what the device companies are seeing?

DR. LANGE: So Ron, you first and then I'll turn it over to Scott.

DR. FAIRMAN: Sure. So --

DR. LANGE: I'm sorry, this is Dr. Ron Fairman.

DR. FAIRMAN: Again, thank you, it is Ron Fairman. I think that was the most concerning thing that we saw when we did the 16-year retrospective review of our EVAR experience and the incidence of reinterventions really didn't change over time. I think one of the things we haven't really focused on today is technology dependent outcomes which are not device failure modes, and I brought that up briefly in my presentation about Type II endoleaks because in our clinical experience, aneurysm sac enlargement in the setting of failed Type II endoleak treatments was in more than 50% of our explants, that was the cause. So I think for me I'm talking about 10 years, that's what I'm talking about.

DR. ZUCKERMAN: Yeah, Dr. Eagleton, let me underline Dr. Fairman's comment and thank you for answering or asking the question. This is the reason why we have FDA Question 1. As you pointed out, the benefit-risk assessment changes with time and we'll be

very interested in hearing from you and other esteemed vascular surgeons on this Panel, the right length of time. But from the FDA perspective, we would posit 10 years based on the current data, which really challenges us to build this national infrastructure that we're talking about. Sorry.

DR. LANGE: And you've got Phil Goodney's shortest comment, it was a one thumbs up for that.

So I'm going to let Scott address it, then I've got Dr. Yeh and then Dr. Shepard.

MR. WILLIAMS: Yeah, Scott Williams. And industry is in agreement with the proposal for looking at that longer-term information out to 10 years, as well.

DR. LANGE: Well, we may have Question 1 answered in fairly short order, so it's great to get -- Scott, thank you. Ron, thank you. Phil, thank you as well.

I've got Dr. Yeh, Dr. Shepard, and then Dr. Woo.

DR. YEH: Robert Yeh from Beth Israel Deaconess. I think this is a question probably for Dr. Goodney or Dr. Jorgensen. You know, I'm just looking through some of the prior publications on AAA from the VQI and I see at least in one, Phil, I think you're the last author, a hundred and sixty-eight participating sites in the study in *Circulation* you had last year. Is that approximately the number that you have now of sites that are submitting their data for AAA? And just for perspective, in the Medicare analysis we have about 1200 sites submitting, doing AAAs, more than 10 during that same time period.

And then following that, if that is, what are the -- how do we get more sites to participate in VQI and is there a mechanism to mandate participation -- maybe this is a question for Bram -- via 522 or related to Ralph's prior comment, is it unrealistic actually to create an NCD for this, to mandate participation in something like the VQI linked registry so that it can be a sort of a comprehensive type of solution that would really, I think, be more

desirable?

DR. LANGE: Great question, Bobby.

DR. ELDRUP-JORGENSEN: This is Jens Jorgensen, VQI. I'll begin by answering and let Phil fill in. I think that we're now at over 300 sites that are participating in the registries. We have both the EVAR registry and a separate open AAA registry, the open AAA doesn't have quite as many sites. But you know, although it may not have a huge penetrance, this large volume of data, I think, provides adequate analysis.

I mean, many people use the National Inpatient Sample for studies where it's only covering about 10%. So I think the volume of the data and the fact that we can show good participation from a variety of specialists and a variety of centers allows us to provide meaningful evidence. With regards to encouraging participation, I'm all for it and interested in hearing other views.

DR. LANGE: So is this the point where Phil picks it up, Jens?

DR. GOODNEY: Sure.

DR. LANGE: Okay, Phil, tell us how to do that.

DR. GOODNEY: All right, sure. So just following up, so the difference between the 300 and the 168 -- again, Phil Goodney, VQI-VISION. Thanks for the question, Dr. Yeh. The difference between the 300 and the 168 simply had to do with our need to comply with Medicare's state use agreements and number of patients in the numerator and denominator of the rates that we would report.

So I'll echo again this thought that we do have 300 centers out of a potential 1600. What we see when we look at -- I mean, we look similarly at bland claims data, the non-enriched data, and what we see is there's a lot of centers that will do a few EVARs and perhaps different devices skewed towards those centers, but there are fewer centers that do a lot of EVARs and the advantage that we think our approach has is the clinical detail,

you know, how large the aneurysm was, was it symptomatic, the exact device, not just the claim that it was a bifurcated device because remember, a bifurcated device could be a Cook, could be a Bolton, could be a Gore, could be a Medtronic. There's not really much granularity to our -- when we looked at plain Medicare claims. Many of the factors that drive the need for reintervention really are impossible to find with Medicare data alone. And so that's why, over the years, we have driven towards our hybrid approach, if you will, where we take all the clinical detail, you know, what was the iliac extent of the aneurysm, was there an endoleak at the end of the case, all of the details that really enrich the models that will help predict the need for reinterventions, marry that then to the simple long-term follow-up metrics that we validated so we can be sure of what we would find in the long term.

So you know, I applaud your group's work, you guys are obviously expert in this and you're absolutely right that the advantage of a strict claims-based approach is generalizability. However, our tack over the years has been to leverage the additional detail that really we already have put into place both in terms of the upfront description of the procedures as well as the ability to be precise in what happened to the patients afterwards. Thank you for the question.

DR. ZUCKERMAN: Okay, Dr. Lange, if I could interject here for a moment because now we're talking about FDA Panel Question 3 for the panelists, you know, what is the ideal system, and first we have to ask ourselves what questions need to be answered. But I would agree with Dr. Brindis's comments that there's not going to be, in the NCD, anytime in my lifetime for this area. What we're really talking about is a medical device ecosystem that needs to change its culture, and we've seen tremendous cooperation at this panel meeting and in preparation and certainly, the FDA will continue to try to guide that cooperation as opposed to using so-called punitive measures like 522 studies. We think

that we can develop a better system if everyone understands that we're in the same sandbox. But we do need to define what are the questions, where do we need the granularity perhaps proposed by one system as opposed to a broader, less granular scheme for other types of questions and I would look again to the vascular surgeon specialists to help us with those points in Question Number 3.

DR. LANGE: Great. Thank you, Bram, for that clarification.

I've got Dr. Shepard, Dr. Woo, Dr. Horvath, and Dr. Khaja.

DR. SHEPARD: Thank you. Alex Shepard from Detroit. I just wanted to change the focus slightly and maybe re-address what industry's responsibilities are in all of this, and this kind of piggybacks on what Dr. Starnes mentioned this morning and then Dr. Woo a little later in the panel meeting. Dr. Starnes talked about the importance of staying within the IFU with the implantation of these devices, and the data we even heard presented today from a high-quality institution where I'm presuming that they stayed within the IFU, a 7.8% risk of reintervention at 8 years versus a 33% risk of reintervention at 10 years using real-world data, it would just suggest to me that a lot of these implanters are not staying within the IFU and what is the role of the device manufacturers in terms of making people stay within the IFU.

And to Dr. Woo's comments this morning or earlier this afternoon when she talked about the fact that we have pre-op imaging data on all of these patients, the device representatives for most of the companies participate in the device planning and sizing worksheet that's drawn up on every patient. It seems to me that that would be a rich source of data as a baseline for these patients going forward. And I might add that if the device manufacturers realize that this information is being tracked, they might be a little more selective in whom they allow their devices to be implanted. Thank you.

DR. LANGE: Thumbs up from Dr. Starnes on that. Alex, great comment and that will

come into our discussion, as well. Thank you.

Dr. Woo, you have the next question.

DR. WOO: Yeah, my question is a logistics question, I guess, directed towards the VQI contingency and also, Dr. Secemsky. And I'm involved with VQI and I'm actually also on the VISION board, which I didn't state before. But in order to enter the data into VQI, because it's a PSO, there have to be agreements with the hospital, but those things take a really long time and that -- but that is what protects the patient privacy.

Logistically speaking, like if we were to try to convert the VQI platform into an all-comers platform where the industry could input that data and all patients could be captured, maybe not to the same detail that we currently expect from people who sign up to participate, but is that something that could be possible, given what Art said previously, where we have all those agreements in place for data sharing and all of that stuff? Would that be possible?

DR. ELDRUP-JORGENSEN: Jens Jorgensen, VQI. I'll begin to respond, Karen, and then turn it over once again. Every couple years in our strategic plan we have a question about whether we should remain as a Patient Safety Organization or give that up, you know, it has advantages in terms of confidentiality and allows people to share their data, it allows them to share their patient safety work product, including bad outcomes and complications, without fear of discovery, and so based upon on those and as you pointed out, it does have some limitations in how we handle the data. But the conclusion that we have reached every couple years is that it is to our benefit to our membership and to our patients to be a Patient Safety Organization. And so in the near future, anyways, we'll continue under that, that structure.

DR. GOODNEY: I'll just add briefly that the updated site total for the EVAR sites actually is up to 457, Jens. The registry folks just told me. But in general, Dr. Woo -- again,

this is Phil Goodney, VQI-VISION. In general, we have spent the last -- since the last decade essentially trying to ensure that while those linkages are accomplished, that we protect the very roles and important patient confidentiality measures that you described. And at every step we've seen that it's almost always harder than we thought it was going to be to either get the business arrangements in place or make sure the linkages were accurate, but with some time and effort, you know, we're proud of the work we've done, we're obviously honored to have you on our board and we think that our results speak for themselves in terms of the sensitivity, specificity, and accuracy with which we accomplished all those goals. I'll leave it to Dr. Yeh and Dr. Secemsky to talk about their ideas, which certainly sound novel, but what we've tried to rely upon are the track records of our experience in this, in which it usually is pretty timely and pretty expensive, so I would just offer our experience as the proof that we can accomplish it.

DR. LANGE: So Phil, about 30 minutes ago we were at 300 institutions, now we're at 457, I feel like it's a telethon. The next three people enrolled get a free t-shirt and a mug that says VQI.

DR. GOODNEY: Business is getting better by the moment. My team updates as they call.

DR. LANGE: Great.

DR. GOODNEY: And I think we have one other brief comment. It does speak to the moving landscape and the need, I think, as more vascular surgeons have seen more of these problems emerge, they recognize the need for the detail and the need for the long-term follow-up, and I think it has encouraged many as EVAR becomes more well understood and its problems become more well understood, more surgeons are anxious to participate in what we can offer. Thank you.

DR. ELDRUP-JORGENSEN: I will just add that I'm -- Jens Jorgensen, VQI -- that I try to

be careful when I'm in a public forum and I said over 300.

DR. LANGE: So noted, Jens.

I've got Dr. Horvath and Dr. Khaja.

DR. SECEMSKY: Dr. Lange, do you want me to respond?

DR. LANGE: Oh, I'm sorry, Eric. My apologies. I'm sorry, I did not see you there. Go ahead.

DR. SECEMSKY: No problem. Yeah, sorry, I was dropped off for a moment. Eric Secemsky from Boston. Dr. Woo, I'd say I caught the majority of it, I was watching on the live feed so I was a little bit delayed. But you know, I think again, the unique part of what we propose as a complement to what VQI is doing is that the companies would not necessarily have to involve the institution in this collection of data. So these companies often already are collecting these data, we know that for other devices in the cardiovascular space, like Abiomed does for the Impella mechanical support device, these data are collected as part of the implant process, so very often these data exist already.

And how we envision this, again, this does not necessarily have to involve our center or me in particular, but how this process would work would either be a data coordinating center where the companies would send in these files and would provide linkage or there is always the possibility that companies can link on their own and then provide that linked analysis.

So there are definitely platform mechanisms here which again would be something unique but would allow for some of the nuances involved in the contracting and also the institutional side to be in many cases avoided. I will note also, though, that there are many centers like ours, and I will comment on ours, but there are many centers like ours and we are facile in contracting and we have DUAs in place. These are complicated, but these are also part of the business that we all do on a daily basis. So I think that there are very

sophisticated centers that already have a lot of these systems in place and know how to contract and really do that contracting with these companies, so I will say that those hurdles are there, but they are things that can be achieved and may already have been.

DR. WOO: Can I just ask a clarifying question? Karen Woo. So how is the patient privacy protected in your model? I know how it works in the VQI model because I'm familiar with it, but how does it work in your model?

DR. SECEMSKY: So you know, there would be no identifying information, so it's almost like what I think Jens brought up, the National Inpatient Sample, you can get the age, the demographics, the location of the patient but not any identifying information, and so you can do matching based on these characteristics. Again, if we know what device is placed at a center for a patient of a certain age and the gender, then you can provide those linkage mechanisms for identifying that patient and following them.

So there are ways to do this in a HIPAA-compliant way that does not require identifying information for the patient and it would be similar to how there are other publicly available datasets that provide some granularity but not specifics like date of birth or Social Security number, tax ID number, etc.

DR. LANGE: Dr. Goodney, do you want to respond, as well? Then we'll go to Dr. Horvath and Dr. Khaja.

DR. GOODNEY: Just a brief response to Dr. Secemsky. You know, as I alluded to earlier, we've done both deterministic matching as well as probabilistic matching, meaning we've used actual identifiers versus probabilistic ones and over the years both worked reasonably well. What I have found is the engagement one gets with one's community, meaning that how strongly people listen to any recommendations we've had, always seemed to ring a bit more true when we say we know for sure that these are indeed the patients we're studying as opposed to well, you know, we've got a 97% chance that we

think this is Mrs. Jones and sometimes you have to do it that way, I don't disparage that strategy. But the PSO structure of our registry allows direct identification, which we found to be helpful in the impact of our findings. Thank you.

DR. LANGE: I'm going to give an editorial comment here in just a second. If you're not from Texas, you don't know Blue Bell ice cream. Blue Bell ice cream, it's not only the closest way you can get to heaven, it's the fastest way you can get there. And when I stand in front of the Blue Bell ice cream freezer, I agonize for 15 minutes over which flavor I'm going to get and I narrow it down to two and eventually I take two home because they're both complementary, I don't have to compete. And I think what we're going to describe or come to today is we've got some great ways to analyze data and to follow up and fortunately, they're complementary and they'll be cooperative, as well. So Question 5 is going to talk about your favorite ice cream, so I expect the FDA to answer that.

I've got Dr. Horvath, Dr. Khaja, and Dr. Connor and Jacqueline.

DR. HORVATH: Thanks, Keith Horvath. A question regarding VQI. What is the cost to the participants and is that at the provider, the practice, or the institution level? And then another somewhat related question is, does participation in VQI allow the participants to be in MIPS, do they get that quality bump if they're participating in VQI?

DR. ELDRUP-JORGENSEN: Jens Jorgensen, VQI. The cost of our subscription to any individual registry is about $2500. We have a suite of 14 different registries and so it would be 14 times 2500. But you know, as I suspect most of the people on this Panel are aware, the cost of subscription is fairly nominal compared to the cost of data collection. You know, if you're putting in about 500 to 1,000 cases per year, you're talking about one FTE. Many people now find it more cost effective to outsource it to a data extraction service and that will cost -- cut that cost in about half with no loss of accuracy. Actually, there will be an improvement with accuracy. And I'm sorry, I forgot your second question.

DR. HORVATH: Yeah, do participants get MIPS --

DR. ELDRUP-JORGENSEN: Oh, yeah.

DR. HORVATH: --- quality bonus as a result of participating?

DR. ELDRUP-JORGENSEN: Yeah, that's a very timely question. There are individual providers, there are practice groups that subscribe and there's sometimes divisions or it can be a hospital, so their cardiologists and radiologists can all subscribe under one. What we have found is that most of our membership had MIPS and MACRA under an ACO and so there was no benefit to them. It was costing us much more to do that, we could've paid them off, so we dropped that as a benefit, it was just too expensive for us to maintain it, the rules seemed to be changing a little bit every year. So the short answer is no.

DR. LANGE: So Dr. Horvath, the question you didn't ask is 5.99 a half gallon, that's the other cost.

(Laughter.)

DR. LANGE: Dr. Khaja and Dr. Connor --

DR. HORVATH: I thought it was priceless, based on your description, that sounds like it's priceless.

DR. LANGE: Dr. Khaja, Dr. Connor, and then Jacqueline Alikhaani.

DR. KHAJA: Thank you, Minhaj Khaja. I just wanted to applaud both Dr. Secemsky and Dr. Goodney and the VQI teams, as well, for these. Now, hearing that there's 457 different groups involved in this, are we able to target, as Dr. Jorgensen mentioned, sort of the VISION on steroids, the groups include the underrepresented minority patients, the patients -- I mean, I've worked at two centers where we've had VQI. I'm an interventional radiologist, by the way, and I do EVARs and TVARs every week. So I would say that we don't live and die by the VQI, but we use it because it's a heart institution. And so two parts, making sure that we capture all the people who are doing these procedures, which includes

interventional cardiologists; some thoracic surgeons; some, obviously, vascular surgeons and a large portion of IRs in keeping also -- and the academics as well as private practice, and then catching the rural population, underrepresented minorities. Is there a way that we can do that better?

DR. ELDRUP-JORGENSEN: Jens Jorgensen, VQI. That's a critical issue that you've brought up and as I suspect you're well aware, populations underrepresented in medicine are traditionally underrepresented in registries, clinical trials, and all areas of medicine. We just submitted an application to the NIH for a registry based randomized clinical trial at which we promoted using our site selection tool so that we could identify sites based upon the percentage of populations underrepresented in medicine. We have a number of safety net hospitals that participate in VQI and we wouldn't have any problem ensuring that there is appropriate representation of African Americans, Hispanics and others who are traditionally underrepresented.

Using the site selection tool, we can look at volume, we can look at discharge medications, long-term follow-up, geographic distribution, age, gender, and we really hope to be able to base our selection of sites not only on the traditional criteria, but some of these other very important criteria.

DR. KHAJA: Thank you. I'd also add, though, for the physicians that are involved, it would be important to have underrepresented minority physicians, for example, or smaller groups in rural settings, things like that. I mean, that's very important, as well.

DR. ELDRUP-JORGENSEN: Fully agree. We also agree that we should have good representation of different specialists such as cardiology, radiology, and we do have that on our executive committee and others.

DR. LANGE: Thank you, Jens.

Dr. Connor and then Jacqueline.

DR. CONNOR: Yes, thank you. Jason Connor. So I have a question, and maybe this is more for the panelists and my colleagues on the Panel here. So I'm curious, just so I can get a sense of this as a non-doc, like what fraction, if any, of patients who you might treat for aortic aneurysms do you use open procedures or as your default just to use one of these devices?

And then my second question, I was curious about the standard of care for imaging for the sake of follow-up. So I mean, this seems like a lifelong thing, people are living with these and it's treated, so I'm curious, maybe for both open and a procedure with one of these devices, how often you would just typically use this. So this is a question to either you doctors who perform these procedures or maybe cardiologists who follow patients after such procedures.

DR. LANGE: So I'll follow up. The national data would suggest 80% of procedures are done with TAVR and 20% open.

Ben, is that your experience?

DR. STARNES: So I just looked at this for commentary at the Western Vascular, I looked at my own experience, and so we do about 350 aortic procedures a year at the University of Washington and last year I did 38% of my cases open and 62% endo. So we're a referral center for a large geographic distribution and we may be swayed more toward the open side.

DR. LANGE: And for the transcriptionist, that was Dr. Ben Starnes.

Dr. Woo, percentage of open versus TAVR or EVAR?

DR. WOO: I don't know the numbers exactly, but in my own experience it's probably 20% open or less.

DR. LANGE: Uh-huh.

DR. WOO: I think that Dr. Starnes's experience is a little bit out of the ordinary, as he

alluded to.

DR. LANGE: Um-hum. Dr. Horvath.

DR. HORVATH: Don't do EVAR.

DR. LANGE: Okay, that makes it pretty simple.

Dr. Eagleton.

DR. EAGLETON: It would probably resemble -- Matt Eagleton. It might generally probably resemble a bit more like Ben Starnes's program, we're about 50% endo and about 40% open.

DR. LANGE: Okay. I'm not going to ask Dr. Khaja because if he's doing open procedures, there's a problem. He's just an interventional radiologist.

Al, I didn't ask you. Dr. Hakaim.

DR. HAKAIM: Yeah. About 70/30 endo/open.

DR. LANGE: Okay. So Jason, that gives you kind of an idea, 20 to 40% open.

DR. CONNOR: Yes. Yeah, and then I had a question about imaging, if I can ask that, in terms of how you sort of track patients after.

DR. LANGE: So the recommendation is annual imaging after EVAR. Are there any of the surgeons that deviate from that? And I'm not going to describe the imaging technique.

DR. CONNOR: Sure.

DR. LANGE: Is there anybody that does anything other than annual imaging and regular follow-up?

Khaja, Dr. Khaja.

DR. KHAJA: So I would say 1 month after initial intervention followed by evaluation at that time and if there are no -- if there's an endoleak at that point, then you would consider following it up at 6 months to determine whether to treat it or not. And if not, then you would wait for a year and then yearly thereafter until there's a problem that

presents itself.

DR. LANGE: You're on mute, Jason, I'm sorry.

DR. CONNOR: Sorry, thanks. And I guess my question was more long term and how many patients actually come back once a year or after a year or two is good. You know, I'm not a very compliant patient on occasion when I need to be one. So you know, do people actually come back once a year, given a lot of our discussion is will we even know if there are leaks? I'm trying to understand how often those images are even done.

DR. KHAJA: I would say, as Dr. White earlier mentioned, education of the patient before the procedure is very important and I show all my patients an image of what an endoleak looks like and that it can happen in a large number of patients. That's just my opinion.

DR. CONNOR: Okay, thank you.

DR. LANGE: Jens, you had your hand up. Jens and then Dr. Shepard.

DR. ELDRUP-JORGENSEN: Yeah, thank you. I used to think I got annual imaging on all my patients. When I participated in VQI, I found out it was closer to 60 or 65%. So one of the values of participating in a registry like this is you get feedback on how you're doing and you get comparison to regional and national benchmarks. Participation in the registry improves the quality of care that we provide.

DR. LANGE: Dr. Shepard.

DR. SHEPARD: Yeah, Alex Shepard. I would concur with what the others have said, but I would have to say, in our experience here, imaging follow-up has been extremely hard and we have a lot of patients from Northern Michigan, from the Upper Peninsula, who just will not come back and sometimes you get them sending in a poor-quality CT scan that you just can't make heads or tails of. I am shocked at how hard it has been to get people to come back. We have been participants in the VQI since the very beginning and I don't think

we've ever gotten our long-term follow-up imaging above 60 or 65% despite working very, very diligently on it.

DR. LANGE: Great. Dr. Starling.

DR. STARLING: Yes, Starling. So I have a question related to VQI. Do any payers, for example, take into consideration information if a center is a participating in VQI? Number one. And number two, is the bench-marking information made available solely to the center? So in other cardiac areas with registry data there's lots of discussion about bench-marking and how payers may use that information.

DR. ELDRUP-JORGENSEN: Jens Jorgensen, VQI. We've had a number of discussions with different insurance companies to try to encourage them to get their participants to join VQI and this would allow them to show the reason for the intervention, the follow-up on the intervention, compliance with guidelines and so on. The initial response from most of the insurance companies is they have to treat all their providers equally, which they don't really do because they do have preferred provider panels and so on.

We have had ongoing discussions, especially with varicose veins, how maybe participating in VQI could replace second opinions, that's generated some interest. Second opinion panels are painful for the physicians, for the patients, and they're expensive for the insurance companies. So the bottom line is we've had a lot of discussion with the insurance companies but really have not made any headway.

DR. LANGE: Great. I've got Dr. Khaja, Dr. Shepard, and then Dr. Starling again. Do you want to follow up, Dr. Starling, because you had the floor?

DR. STARLING: Yeah.

DR. LANGE: Then Dr. Khaja and Dr. Shepard.

DR. STARLING: My follow-up was do centers of excellence, per se, exist within aortic surgery or EVAR that insurance companies designate?

DR. ELDRUP-JORGENSEN: Oh, I'm sorry, I didn't address that. We do not allow public reporting, that's part of our being a Patient Safety Organization and one of our rules is that you cannot use your data for --

(Audio feedback.)

DR. LANGE: I'm sorry, Jens, when you said you can't use your data and then it just garbled, so you can't use your data for what?

DR. ELDRUP-JORGENSEN: Okay.

DR. LANGE: I'm sorry, Jens.

(Audio feedback.)

DR. LANGE: So Jens, I'm going to come back to you, you're --

DR. GOODNEY: I can --

DR. LANGE: Go ahead, Phil, go ahead.

DR. GOODNEY: I was going to say I can pick up for Jens. The rules are that the data can't be used for competitive marketing. However, we have used integration with payers in projects designed to either improve overall efficiency for vascular care, as he alluded to around varicose veins, or even investigate appropriateness for vascular care, as we've done for low extremity vascular procedures and carotid revascularization.

DR. DALMAN: This is Ron Dalman, I can add to that a little bit, too. We have talked about, like SPAS does, providing one-, two-, three-star outcome for participating centers based on -- and that would, of course, not be possible under the current guidelines, but that is one of the issues that some stakeholders like U.S. News and World Report is asking us to do, to make our VQI data more transparent to the public. So there is the tension between transparency and competiveness and marketing leverage and that kind of thing and that's an area of active discussion.

DR. LANGE: All right. Dr. Khaja and Dr. Shepard.

DR. KHAJA: I was actually going to ask Dr. Shepard. Prior to being at UVA, I was at the University of Michigan and we were neighbors and so we did use that data, at least for peripheral arterial disease, for certain markers within the state and had some reimbursement that was tied to that.

Dr. Shepard, does that sound correct?

DR. SHEPARD: Yes. Alex Shepard from Henry Ford in Detroit. That's exactly what I was going to bring up, we have a unique situation here in Michigan where Blue Cross/Blue Shield of Michigan is the dominant payer, about 80% of patients in the state are covered by that type of insurance, and they formed, as Dr. Khaja alluded to, a Michigan Cardiovascular Consortium several years ago which is a collaborative consortium of a number of healthcare providers throughout Michigan and they have basically used a number of quality improvement projects across the state to provide rewards to participating centers, sort of a pay-for-performance in a limited number of cardiovascular outcomes.

Right now it's basically prescription of statins and antiplatelet agents at the time of discharge, but they have recently included follow-up of aneurysms at 1 year and it would seem to me that it's a short jump from that to requiring or rewarding for the obtaining of follow-up imaging at 1 year. So it's a unique situation here in Michigan, but I do think we should consider trying to leverage some of our payers as opposed to just government and industry in this initiative. Thank you.

DR. KHAJA: And that data was not used to compare different institutions.

DR. SHEPARD: No.

DR. KHAJA: It was bench-marking yourself to your peers to do better, correct?

DR. SHEPARD: Correct.

DR. LANGE: And in full disclosure, Blue Cross/Blue Shield and Blue Bell are completely separate, they're not the same, different organizations completely.

Other questions to ask that would -- Jacqueline, I'm so sorry, I've got you written down and I skipped right over you. Jacqueline, forgive me. Go ahead. You're on mute. Thank you.

MS. ALIKHAANI: Okay, Jacqueline Alikhaani. I wanted to know, do you -- for that organization -- oh, his picture disappeared. The organization, it starts with a Q. Where is it? Okay, anyway, so what I wanted to know is do you need to inform patients that you're using their data and how it's going to be used, and how do you get consent for this type of thing? Like, for example, when you get data through big organizations like CMS, Medicare, how is the patient involved in that? I mean, the data is just flying around, going everywhere. Do patients need to know, because I feel like we do, and give permission for their data to be used like this? How does Medicare do that?

DR. LANGE: So Eric -- yeah, Eric, I'm going to have you address that for your studies and then I'll have Phil address that for VQI. Eric.

DR. SECEMSKY: Eric Secemsky. Thank you, Jacqueline, for that great question. You know, we struggle with this a lot, this comes up a lot with linking studies and also in extending randomized trials so people, you know, sign up to participate for a certain amount of follow-up and then do a quest to find more data, which is what's happening in the paclitaxel debate. You know, in the CMS data standpoint, and I can't speak to the full nuances of how this agreement was made, but it's very challenging to be able to get a data use agreement to use that data and you have to go through a number of safeguards to protect that data.

So although the agreement is not made necessarily with the patient, it's more an agreement to ensure that the insurance has, before they use that data, the ability to research that data is strictly enforced by Medicare. And you saw some of the protective habits that come out of this, including how Dr. Goodney demonstrated that there's a certain

limit of number, so less than 11 or 12 patients that you can't show those numbers, just because then there's the potential that a patient could see that maybe they were one of those 12 people. So there are a number of safeguards that are in place, in particular, the type of center that can access these data, link these data and can input this data, but I'm sure that there are many opportunities to be more transparent with the patient and I think that's been a continuous theme between yesterday and today.

DR. LANGE: Dr. Goodney.

DR. GOODNEY: Phil Goodney, VQI-VISION. Ms. Alikhaani, thanks very much for your question. I'll pick up where Dr. Secemsky sort of left off. Our Patient Safety Organization structure does not require explicit permission but it does require us, as the guardians of that data, to make sure that we use that data for the improvement of any assessment of the quality of care we provide to patients with vascular disease.

We had a project with PCORI a couple years ago where we were actually funded to generate a cohort of what we call patient advisors, so they're patients who had vascular disease and they've undergone vascular treatments and we actually flew that cohort of patients out to one of our meetings, which was held in San Francisco, and this was just before COVID, and we had the patient advisors join us and asked them almost the same question that you brought up, how do you feel about the fact that your data would be used, and patients -- and we actually had a few family members join us, too, and it was interesting, they almost invariably didn't worry so much about identification.

You know, they did worry about making sure that it wasn't shared inappropriately and they wanted to know who was going to be the guardian of that. And similarly, they also wanted to know the purpose of using their information and how it would benefit future patients. So I think that project helped us understand, because we studied patients directly and use their opinion, really helped us formulate our strategies going forward. So now

when we talk about this and you say well, gosh, we've got all of this valuable information, I often will bring up at those discussions, well, gosh, should we reimburse the patients for the information they give us as part of our registry? If we have extra money left over at the end of the year, is that something that we should think about doing? So I appreciate it, I think you brought up a great point. Thank you.

MS. ALIKHAANI: Thank you.

DR. LANGE: All right, we're soon about to head into the FDA questions and when we do that, it will only be panelists, there will be nobody else from industry, so this is your last chance to ask any questions that would help inform your answers.

MS. ALIKHAANI: I have one other question.

DR. LANGE: Go ahead, Ms. Alikhaani.

MS. ALIKHAANI: To Phil, I meant to ask you about are you outreaching, networking with community health centers to collect data from them? Because they're often left out of various research efforts and the safety net network.

DR. GOODNEY: You know, another great -- Phil Goodney, VQI-VISION. Another great question, Ms. Alikhaani. We are fortunate, you know, in VISION -- I've helped, I've collaborated with a group called Vascular Cures that just secured a PCORI grant to basically use broad stakeholder engagement to try to understand the entry into and the maintenance of vascular care. So just what you talked about, that gosh, maybe patients can come once and get their endovascular aneurysm repair and that's a one-time treatment.

But then, for them to come back year over year, travel to -- you know, to the center where they had their operation often can be quite burdensome and one of the things that we've heard, that we've seen very clearly in our failure to surveil patients over time is that we need to do a better job of understanding the input of primary care providers, community -- you know, community clinics where it's easy for these patients to receive

their care.

And one of the main focuses of this PCORI project that Vascular Cures is heading up is to better understand how we can integrate our vascular care with community health centers, with primary care providers, with patients and their families. So again, it definitely is a weak point in the current way that we provide vascular care, but something that we're trying to study and do a better job at.

MS. ALIKHAANI: Yes, the FQHCs are federally funded, so the government should already have a listing of all of those and it's a great resource to tap into.

DR. GOODNEY: Yeah, absolutely. Thanks for your information.

DR. LANGE: At this particular time I'm going to ask for a 15-minute break, we're going to come back for FDA questions. Jim, if you'll set the timer. Bram and Joaquin, if you'll stay on for just a second, and we'll see everybody back in 15 minutes. Thank you.

(Off the record at 3:15 p.m.)

(On the record at 3:31 p.m.)

DR. LANGE: Welcome back to the Panel. At this time let's focus our discussion on the FDA questions. Panel members, copies of the questions were sent via e-mail, you should have them at your disposal. I would ask that each Panel member identify herself or himself each time she or he speaks to facilitate transcription. So at this time I'll ask the FDA to please show the first question. So I'll read it for the Panel and then I'll ask -- I'd particularly like the input of our vascular surgeons.

Please discuss the safety and effectiveness of endovascular stent grafts in the treatment of abdominal aortic aneurysms stratified by near-term and long-term outcomes.

And I said our vascular surgeons, not to exclude Dr. Khaja, as well. So who'd like to start off?

Dr. Starnes.

DR. STARNES: Ben Starnes from Seattle. I would say that we have safer and more effective devices to treat abdominal aortic aneurysms than we did 10 to 20 years ago and that all depends on the adherence to the labeling and the compliance with the instructions for use for any given device. There are limitations in the long term with higher rates of secondary intervention, but newer devices and newer technologies are leading to better outcomes, in my opinion.

DR. LANGE: And to pose those two comments, Ben, better outcomes but still long-term limitations that require long-term follow-up, I'm assuming you said that?

DR. STARNES: Yes.

DR. LANGE: Okay. Dr. Hakaim.

DR. HAKAIM: Yeah, Al Hakaim. Yeah, I second Dr. Starnes and point to the roughly 30% reintervention rate in the long term and would specify long term as meaning out to 10 years.

DR. LANGE: Okay. Thank you, Dr. Hakaim. And I pronounced your last name six different ways.

DR. HAKAIM: That's all right.

DR. LANGE: Thank you.

DR. HAKAIM: I've heard worse. Just don't say Hack-em (ph.).

(Laughter.)

DR. LANGE: Any other comments? I think that there was general consensus from industry, from the FDA, from all Panel members and I don't want to beat this, we've got other stuff that I'd like to spend more time on.

Alex, Dr. Shepard.

DR. SHEPARD: Well, I think over the short term there's no question that EVAR is the way to go. Long term, I think devices are getting better and safer and we can hope for

better outcomes, but given the current data, I think there's still a question long term about the safety of EVAR compared to open surgical repair. But there's no going back to open surgical repair, we're not NHS. There's a whole generation of vascular surgeons now who are not comfortable or experienced with open surgical repair and I think in addition, we disenfranchise all non-surgical specialists who are currently treating EVAR.

DR. LANGE: Okay, thank you. I wrote those comments down.

Ed, I see your hand up and then Dr. Brindis.

DR. GRAVEREAUX: I just again concur with the --

DR. LANGE: I'm sorry, this is Dr. Gravereaux, I'm sorry. Okay. I'm sorry, just for the transcriptionist, this is --

DR. GRAVEREAUX: Sorry.

DR. LANGE: -- Dr. Ed Gravereaux.

DR. GRAVEREAUX: Ed Gravereaux, correct. We've again discussed this and I think that the longer-term outcome is less we can grasp specifics sometimes with the better technology, but it's more what's happening to the anatomy, which we don't have answers to as there are extensive or extension of the aneurysm changes that are, you know, irrespective of the technology that we're using and I think that's like yesterday, separating -- whereas Dr. Oderich's visual aid today brought up about patient factors, surgeon factors, and device factors, I think we don't have an answer to sometimes what the aorta will do. Even in an IFU-compliant patient 10 years out, it's not that common to know what's going to happen. So I think a good long-term result is important to know.

DR. LANGE: Great. Thank you, Ed.

Dr. Brindis.

DR. BRINDIS: Ralph Brindis, who is not a vascular surgeon, but I wanted to just add the point that there's also device-specific concerns in addition to the class of endovascular

stents that we are concerned about.

DR. LANGE: Okay. So Dr. Zuckerman, what you've heard is that EVAR is here to stay and has a role, it has short-term benefits. Long-term benefits are -- I don't want to say questionable, but the longer-term benefits aren't quite as good as the short-term benefits. Everybody acknowledges a reintervention rate of about 30% plus or minus 10%, and it may be related -- it may be device specific, indication specific, whether it was placed for the appropriate indications and anatomic considerations, as Dr. Gravereaux mentioned, as well. The last two obviously won't be overcome with any changes in the device.

DR. ZUCKERMAN: Okay, that's very helpful, Dr. Lange, but a follow-up question to Dr. Starnes. The general discussion had centered on on-label use. With so-called off-label use, what is your gestalt as to how much worse the 10-year results are and does that change your benefit-risk thinking for longer-term use of these devices?

DR. STARNES: Well, I would say that when you start to get into the arena of off-label use, treating shorter necks with infrarenal devices and not devices that are purpose built, the outcomes are clearly going to be worse. But I'll also kind of refocus us back to the fact that if you look at all of the pivotal trials that have ever been done on EVAR, the average age is between 74 and 76. And so we're only asking the device to outlive the patient and most of the time up to 50% of these patients are dead within 5 years, not related to their aortic aneurysm, but because of other causes of morbidity, lung cancer, heart attacks, strokes. And so I think that we -- I agree with the 10-year time frame, but to answer your question directly, I think that the long-term outcomes would be worse with off-label use. That's my gestalt.

DR. LANGE: Dr. Khaja, Dr. Shepard.

DR. KHAJA: So Minhaj Khaja. I would just say, you know, tomorrow morning we have an aortic conference with our vascular surgeons and cardiothoracic surgeons where

we are looking to push the envelope on endovascular repair of patients that have significant comorbidities, like I'm sure many of my colleagues here are. So I agree that when we push the envelope and we do this, we are going to have poorer outcomes, but that is sort of the world that we live in and we are sort of trying to mitigate that risk.

DR. LANGE: Dr. Shepard, your comments.

DR. SHEPARD: Alex Shepard, Detroit. Dr. Zuckerman, I think that your question you asked was basically answered by the data that Dr. Fairman presented this morning with his own institution having a 7.8% rate of secondary interventions at 8 years versus the Medicare data at 10 years being 33%. And again, I can't blame all of that or we can't blame all of that on staying outside of the IFU, but I'm willing to bet that that's a large part of the difference between those two secondary reintervention rates.

DR. ZUCKERMAN: Right, but just a general comment. Pushing the envelope is part of medicine and innovation, for sure, but the organized collection of data when one pushes the envelope seems to be lacking here, so we just have these general comments and in looking at Question 3, I'll be posing this question again as to how we can get some better data here. Thank you.

DR. LANGE: Bram, are there other nuances with -- Dr. Eagleton.

DR. EAGLETON: I guess I just want to ask Dr. Khaja a question so we can clarify some vocabulary. When you say we're pushing the envelope, are you saying we're going to go off label? Do those two go hand in hand?

DR. KHAJA: This is Minhaj Khaja. I was saying I think a hybrid approach is fenestrated grafts, snorkels, different types of -- different other types of techniques, much like you guys do, as well.

DR. EAGLETON: I guess that's different, though, than treating an infrarenal aneurysm with an EVAR and I guess, Dr. Zuckerman, what direction are we going here, are

we going to start talking about outcomes for EVAR when they're used for physician-modified endografting, snorkeling, chimneys, etc., or is that another topic for another day?

DR. ZUCKERMAN: That's for another day, but what the Agency is concerned about as a public health agency, and I hope all stakeholders are, is that there's significant off-label use for treatment of AAAs. We've talked about it. Can we get better organized data collection to see what the benefit-risk ratio is such that patients and physicians can be better informed? There may be subsets where it's perfectly acceptable while in others, just having that data would make everyone improve the practice of medicine.

DR. LANGE: Bram, any other nuances regarding this question that you'd like for the Panel to address?

DR. ZUCKERMAN: No, the Panel has done a great job.

DR. LANGE: Okay, all right. Then moving to Question 2a. And would the FDA like to read this or would they like me to read it?

(Off microphone response.)

DR. LANGE: All right. Question 2a: Available long-term data demonstrate that adverse events continue to accrue post-EVAR. Please discuss which of the following real-world clinical outcomes should be assessed in a long-term EVAR surveillance system. They include:

- All-cause mortality
- Aneurysm-related mortality
- Aortic rupture
- Aortic reinterventions
- Others

DR. LANGE: Bram, would it be -- if you'd like, I can just do a show of hands of the ones that are up there.

DR. ZUCKERMAN: Sure.

DR. LANGE: And that may stimulate some discussion. Everybody that feels all-cause mortality should be one of the adverse events. Show of hands.

(Show of hands.)

DR. LANGE: Okay, it looks unanimous. Not much discussion there.

The second one is aneurysm-related mortality. Show of hands.

(Show of hands.)

DR. LANGE: Okay, it looked like all but one voted for that, perhaps.

Aortic rupture.

(Show of hands.)

DR. LANGE: All voted for that.

Aortic reinterventions.

(Show of hands.)

DR. LANGE: All for that. Okay. Dr. Starling, I'm going to put you on the spot for a second. You did not vote for aneurysm-related mortality and I'll let you explain why and then we're going to talk about other adverse events that we should monitor.

DR. STARLING: Could you repeat that, please?

DR. LANGE: When I asked about aneurysm-related mortality, you did not raise your hand.

DR. STARLING: Yeah, that was strictly being parsimonious. In a perfect world, I would vote for it.

DR. LANGE: Okay.

DR. STARLING: If I had no restrictions on data collection.

DR. LANGE: Got it, got it.

Dr. Starnes.

DR. STARNES: This is Ben Starnes from Seattle. We had a nice presentation from our industry representative this morning, Scott Williams, and he conveniently divided the outcome measures into three buckets and that was vital status, aortic rupture and aortic reinterventions and we kept hearing that theme over and over again, especially from Phil Goodney, that those are the three data points that he looked at long term, as well. So I think those are adequate for long-term outcomes, in my opinion.

DR. LANGE: Okay.

DR. STARNES: And I'm not referring to the next question, which refers to anatomic data.

DR. LANGE: Okay. Other discussion regarding events?

Dr. Starling and then Mr. Conway.

DR. STARLING: Yeah, Starling. And just to add to that, I also questioned in my mind, and other panelists could elaborate, that to me appears to be a softer endpoint and how that adjudication would take place, that the mortality was related to the aneurysm was a question in mind.

DR. LANGE: Well put. Thank you, Dr. Starling.

Mr. Conway.

MR. CONWAY: Yeah, just a brief point, I think Dr. Starnes hit on it perfectly here. In the presentation this morning, Dr. Williams went through the three buckets, but what he said immediately after that was also of interest to me, which was patient survey information and he had two studies on that particular slide that were of interest. And so I would just put that out there, what matters to patients may fall within these, but FDA ought to take a look at that for "others", as well.

DR. LANGE: Thank you for that comment. Thank you, Paul.

Ms. Alikhaani.

MS. ALIKHAANI: Let's see. Jacqueline Alikhaani, Los Angeles. Just to add to what Paul is saying about the surveys, I have here that just to make sure that we get some kind of patient self-reported PROs about side effects, potential side effects that might be underreported, quality of life issues and lifestyle-related issues. And the other thing is if it's possible to get more outcomes from ethnically diverse trials and studies.

DR. LANGE: Thank you. Thank you for that comment. Other adverse events that are not listed that people feel should be followed?

Dr. Zuckerman.

DR. ZUCKERMAN: Yeah. Certainly, the industry presentation was very interesting this morning, but we had interesting case examples yesterday. So I would like to ask someone like Dr. Woo or Dr. Cigarroa, just having those three buckets, would that have been adequate or do we need more granularity? Maybe we can start with Dr. Woo.

DR. WOO: So is the proposal to only have those three and then have -- like have them categorized into those three? Like have the things that we just talked about? So I would prefer the granularity of the outcomes that we just discussed. That's what I think is necessary.

DR. ZUCKERMAN: Personally, I got the impression that it was just a high-level three buckets, but other people -- that the industry proposal would not have that granularity, but other people should speak.

DR. CIGARROA: So this is Joaquin Cigarroa. I think that the three high-level categories will be insufficient over the long term to detect signals of potential safety/harm and therefore would believe strongly that increased granularity is important. In our discussions throughout yesterday we had seen that several of the devices appear to function in similar ways over time, whereas another has not. And I think that as we continue to move forward and see further device iterations, it's essential that these

observed complications that will continue to occur, given the interactions between the disease, the anatomy, the operator, and the device design will result in. And I don't think the very high level alone will be sufficient for societies, FDA, and industry to identify and respond appropriately.

DR. LANGE: Dr. Yeh and then Dr. Khaja.

DR. YEH: I agree with Dr. Cigarroa, I think it's important to remember -- you know, vascular surgeons and interventionalists can respond on this, is that aortic reintervention is a composite endpoint of many different things. And so understanding the components which drive any signals for that endpoint in particular to show up would be important, whether it's relining or endograft extension, whatever those things are, I think I would think that it would want to be known which are the components that are driving an increase in that endpoint should that signal show up.

DR. KHAJA: This is Minhaj Khaja. I agree that aortic reinterventions should be a single output but should also be stratified into endovascular interventions or what type of endovascular intervention versus surgical explantation or surgical interventions, I think that would be useful, but I'd defer to my surgical colleagues.

DR. LANGE: Dr. Gravereaux.

DR. GRAVEREAUX: Ed Gravereaux from Boston. Ultimately, I think that waiting for clinical endpoints means that you've missed the opportunity to survey and intervene at a safer, potentially safer time if you're waiting for an eventuality like rupture or limb occlusion or something. So I think we should consider doubling back whether there's a way to increase the yearly surveillance imaging and tap into that or reports of a change in the size of the aneurysm sac or an endoleak potential, if possible. I mean, it sounds more daunting than waiting for a clinical endpoint that would trigger a CPT code, I mean that's -- or if you can wait for the trigger and dial back and look in retrospect about what happened,

but again, that's not helping someone in prograde fashion.

DR. STARNES: Just upon my comment, this is Ben Starnes. So you know, death is an all or none phenomenon, rupture is all or none phenomenon, and I agree that reintervention comes in many different shades, but I think what you're describing is actually Question 2b, which are the anatomic characteristics that we should be evaluating. But for overarching data collection that can be linked to registries and obtained easily and is realistic, I think those three buckets are good, they're good measures. Obviously, we need the granularity of the reinterventions.

DR. LANGE: Bram, what I think you're hearing is, in terms of vital status, people want to know whether their patients are alive or deceased and if deceased, whether it was aortic related.

In terms of reinterventions, again another great big bucket, but they want granularity about what that means, what kind of intervention that was. And then finally, aneurysm.

So the four major categories and the granularity to dig down and again, I think that's going to be tied with 2b, what was it that led to each of these and how can we prevent it either by correct indications, different patient selection, different operators, different devices or a different procedure.

DR. ZUCKERMAN: Great discussion, we're ready for 2b.

DR. LANGE: Okay, let's move on.

MR. BRYSON: Question 2b: Although imaging outcomes are collected in premarket and FDA-required postmarket studies, these studies have a modest sample size, and it is challenging to collect serial imaging data in real-world surveillance. Please discuss the importance and feasibility of capturing the following imaging outcomes in real-world surveillance:

- Endoleaks
- Loss of device integrity
- Aortic enlargement
- Device migration
- Device patency

DR. LANGE: Great. And let's leave that slide up while we talk about it.

Dr. Eagleton has his hand up first. Take it, Matt.

DR. EAGLETON: Yeah, I guess the way I look at this, some of these are easy for us to identify in the real world and some of these are probably missed a lot. I think endoleaks, provided the CT imaging is done correctly with the three phases, most people will identify an endoleak, as a provider, and be able to report on that. And I think aortic enlargement falls into that and probably the one that's probably missed the least is when we measure the -- everybody measures their aortic diameters when they follow-up patients. The thing with device patency, you have a limb occluder and the aorta occludes, you're going to know that because it's an acute process. I think where we're going to run into trouble is identifying loss of device integrity and potentially, device migration.

We see these pictures of everybody with the angular stress collapsed in the bottom on the aneurysm sac, but it didn't happen there overnight and they probably missed the migration along the way on some of their follow-up imaging or if the patient didn't come back for imaging for years. And then identifying things such as stent fractures are even harder for the practicing vascular surgeon or vascular specialist to identify on imaging postoperatively. That will be a tough one to capture, in my opinion, and I think we're seeing that miss at sites during trials and then picked up by core labs, I think that's pretty well documented.

DR. LANGE: Dr. Khaja, you're an imager and you had your hand up.

DR. KHAJA: Yeah, so I agree with Dr. Eagleton that endoleaks, enlargement, patency are something that any of the clinicians can capture. Part of the reason I was harping on having cardiovascular imaging people involved as well is for specific things like loss of device integrity and device migration where you can perform center-line measurements and look at angles that have changed or look at pre-op imaging, the immediate post-op and 1-year, 3-year and you look and see what's happened to the device and, as Dr. Eagleton has mentioned, we see that in a lot of trials.

DR. LANGE: Dr. Eagleton, back to you.

DR. EAGLETON: I guess the only question -- Matt Eagleton, Boston. The only question I'll give you on that is you'd probably see that with your cardiovascular imaging because you're at an academic medical center with an interest in it. If you take this to a small community hospital where there's a single radiologist doing all the aspects of radiology, that may not be picked up as readily.

DR. LANGE: Dr. Starnes and Dr. Horvath.

Ben, you're muted.

DR. STARNES: Sorry. Ben Starnes from Seattle. I agree with Matt that these -- what we collect, the data that we collect has to be generalizable and one quick comment about aortic enlargement. The biggest surrogate for clinical success has been shown to be failure of -- actually, it's been sac regression. And so I think we should be measuring not aortic enlargement but failure of the aortic -- the residual aortic sac to regress, because that's clinical failure.

DR. LANGE: Great, thank you.

I've got Dr. Horvath and then Dr. Woo and then Dr. Khaja.

DR. HORVATH: Keith Horvath. While I understand the importance of imaging, we've also heard how difficult it is to get the additional burden it puts on the patient, the lack of

consistency with regard to the type of imaging that is done, there's never going to be a central core lab to adjudicate all of this. To me it just ends up being problematic. What we will have is peri-procedure imaging when the operation or procedure is done to begin with and then we will have four things likely just identified for the other outcomes that we talked about, aortic reinterventions, you're going to get another set of imaging then. So you will have some imaging that's part of the standard of care or part of the clinical progress. I think it's going to be hard to mandate any type of regular imaging and I think if that's done, it's going to be very problematic to have it standardized.

DR. LANGE: So Keith, let me come back to you, isn't it already mandated as part of the recommendations?

DR. HORVATH: It is, but again I think that we've already heard that it's not done to -- it's done barely over 50% and I think that it's fine to leave those in as guidelines, but I think if the results of this Panel are to then reinforce that or reiterate it or make it even somehow more mandatory is going to be even more problematic.

DR. LANGE: Okay. The reason I said that, it will require cultural change, but the fact that every organization has recommended it would suggest that it is important and we suggest, as well.

DR. HORVATH: I'm not denying it's important, but I think there's a difference between what the expectation is going to be and how much you're going to lean on the imaging as opposed to those other outcomes that we've just covered.

DR. LANGE: Point well taken.

I've got Dr. Woo and then Dr. Khaja.

DR. WOO: Actually, Dr. Horvath just said exactly what I was going to say. To Dr. Starnes's point about looking at sac shrinkage as an outcome, you'd think that that's straightforward, but oftentimes at our institution we get patients like flown in, helicoptered

in, who end up with an EVAR and they don't come back. But if we get their CT scan at an outside hospital or wherever they live and we can get the report, you know, you get this crazy report that has a measurement that makes no sense. Sometimes people measure the length of the aneurysm versus the transverse diameter of the aneurysm and report that as the maximum diameter, and so I just wanted to bring that up as a challenge in terms of this question asking us the feasibility of capturing imaging outcomes.

DR. ZUCKERMAN: Okay. So Dr. Woo, let's pause here a moment. You're absolutely right, we're starting at a situation which is not optimal. But again, I would ask you to consider the case study that we had yesterday, where we do need imaging data to really better define the uncertainty with that case study and given that these devices exist in a harsh biological and physical environment, it is not the only device that will have problems. So we all need to do better here and help us think about a way where we can improve the current ecosystem here. This is what Question 2b is really designed to challenge all of us.

DR. LANGE: So to that end, I've got Dr. Khaja, Dr. Shepard, and Dr. Yeh. Let's refocus. Everybody agrees it's important, everybody agrees it's not being done well enough, so how do you move the needle? So Dr. Khaja, Dr. Shepard, and Dr. Yeh.

DR. KHAJA: So Minhaj Khaja. So that is what I am trying to get at, is that at least for the period of time that we need to evaluate this for the FDA for the stent grafts, I believe that it would be useful for the VQI type of registry or for the FDA or some other core lab to be doing these things in center-line methodology at certain time points. I'm looking at the SVS guidelines where many of you are co-authors, the ACR guidelines as well as the STS guidelines, and they all have very distinct ways of describing how to measure this. I think if we're going to make a recommendation, it would be to have consistency.

DR. LANGE: Okay. Dr. Shepard, De. Yeh, and Dr. Cigarroa.

DR. SHEPARD: Alex Shepard from Detroit. I was basically going to just reinforce

what Dr. Woo said, how important or how difficult it is to get these images on patients who aren't in our catchment area and the difficulty of interpreting outside CT scan reports. This absolutely will require having the images in hand and the use of some sort of core lab, maybe centralized in different regions around the country to do this. So I don't have any good ideas of how to do it and perhaps something along the lines of the VRC that Dr. Jorgensen presented this morning, where certain VQI centers on steroids, I think he described it as, could be tasked with following a sample of these patients. But trying to get us to do it on a larger scale, I mean, it's proven impossible over the last decade.

DR. LANGE: Dr. Shepard.

(Off microphone response.)

DR. LANGE: Thank you. Dr. Yeh.

DR. YEH: Robert Yeh from Beth Israel. You know, similar comments with some additions. I think it sounds really completely infeasible to do this in a systematic way in the real world to collect imaging outcomes for the reasons stated. So what it starts sounding like to me is moving less toward "real-world surveillance" and more toward more robust conditions of approval postmarketing studies. I mean, I'm making a fine separation there, but what I'm thinking of is in order to do this with a central lab for adjudication, etc., comprehensive follow-up, the type of data you really need to make inferences that are important here, is you need there to be a dedicated research study.

This is not something that can be done with limited resources in the background of a real-world kind of passive system, this is an active study that needs to be supported presumably by industry as part of their condition of approval or requirements. So this is a stick to get this to happen because the patients probably need to get reimbursed, the sites definitely need to be reimbursed for this to happen, and it gets back to who is -- you know, the questions that Dr. Starnes and others raised earlier, who is ultimately responsible for

this, generating this, and this type of important information, we all agree, needs to be generated, I think, by the manufacturers who are bringing the devices out there.

DR. LANGE: Okay. Dr. Cigarroa, Dr. Horvath.

DR. CIGARROA: So clearly the current state is not acceptable relative to the surveillance imaging, which we know is essential to prevent catastrophic events in patients with aortic aneurysms who have been treated with endovascular techniques. I think there are potential lessons to be learned from systems of care that have been developed around primary PCI versus fibrinolytic therapy.

I remember the saying of an interventionalist, "Well, I did everything I could once the patient got to me. The fact that they presented late and were in another facility for 4 hours and in essence completed their infarct wasn't my responsibility." And obviously, AHA with the guidelines and working with systems to provide metropolitan and state-wide approaches have overcome many of the barriers and that's impacted mortality.

So I think this comes back to what Dr. Zuckerman had mentioned, we have to change the ecosystem and industry and health systems, and providers have to collaborate and identify what are the seven things that we can do to improve imaging and reporting of imaging and how do we facilitate the transfer of that information. I maintain it's doable and it may be that one pilots it in some of these super sites and identifies the different tactics that can allow us to consistently obtain imaging in greater than 90% of patients, that results in actual -- but it is a change in the ecosystem and culture, and I think if we look back at the primary PCI experiences, there are lessons that can be applied to changing the culture and the ecosystem here.

DR. LANGE: So I'm going to summarize what we've heard to date and then I'm open for other discussions. It is considered important. There are two times to get the follow-up imaging: one is, as recommended by the societies, on annual basis, and at the very

minimum every time there's a reintervention. All of that data is there and available and it should be analyzed to give insight about why the reintervention occurred. There are some challenges with interpretation that need to be addressed.

For new trials for new devices, Ben recommended that a condition for approval be that they have regular imaging follow-up and adequate imaging follow-up, as Dr. Yeh suggested.

Then as Dr. Cigarroa suggested is addressing this at a system level much as we did during the balloon time, or it involves the healthcare systems, the provider, and industry and that's going to involve regular reporting and regular follow-up of the data to find out how a health system or a hospital or a practice is doing with regard to the follow-up.

Any other comments?

Dr. Starling.

DR. STARLING: Yeah, I have a question for Dr. Zuckerman. Maybe I missed this, so I apologize, but does the labeling on all of these EVAR devices stipulate metrics with respect to follow-up imaging at specific time points and provide any detailed description as to what the minimum imaging should include?

DR. ZUCKERMAN: Yes. And Dr. Shepard, I think, knows it pretty well, better than me. He can comment, also. And so the real question again, Randy, is how do we get patients, physicians, and hospitals to buy into a better way of doing things?

Dr. Shepard, did you want to comment also?

DR. SHEPARD: Alex Shepard from Detroit. No, you're absolutely right. As we discussed yesterday, all of the major stent graft manufacturers recommend follow-up at least annually with a CT scan. Now, whether that's necessary or not versus duplex scanning could be argued, I'd suspect, but they all recommend annual surveillance.

DR. LANGE: So Bram, I would add that as a part of the shared decision making, when

we do informed consent about what the long-term and short-term "benefits" are, one of the things when the patient decides whether "I'm going to have open procedure or an EVAR" is that if you have EVAR you acknowledge that the recommendation, the expectation is that you will have annual imaging follow-up. Obviously, if you live near Detroit they may not come, okay, and I get that. I'm only kidding, Alex, but it ought to just be a part of the routine information.

Dr. Eagleton and Dr. Shepard.

DR. EAGLETON: You know, as a vascular surgeon, we have to take some credit, though, for the loss of follow-up, so I don't know that we are, as a group, a hundred percent effective at convincing our patients that they need to come back for follow-up and so it's not just the responsibility of the patient, it's also our responsibility as the treating physician.

DR. LANGE: Thank you.

Dr. Shepard.

DR. SHEPARD: Well, I was just going to say it's sometimes probably no harder to get follow-up in Detroit than it is in Walla Walla. So it is amazing to me, despite -- and I think the interventionists on the Panel will all agree, it's amazing to me that you have these discussions with patients preoperatively and they come back to you at a year and you remind them that they need to come back every year and they all look at you, not all, but many of them look at you kind of cross-eyed like well, what are you trying to do here, Doc, you're just trying to biopsy my wallet? You operated on me and now you want me to come back every year, and they seem to have forgotten that discussion that we had preoperatively about the importance of this annual follow-up and it's really tough sometimes to convince them to continue to follow-up for these surveillance studies.

DR. LANGE: Mr. Conway.

MR. CONWAY: I think one of the current themes here is along the lines of patient

burden and as Dr. Shepard just talked about, patients remembering. But there's a very simple rule in communications in politics, which is say it once, say it twice, say it multiple times through multiple people that are credible and it's not simply the doctor sitting in front of them, so patient stakeholder organizations, other organizations that they're involved in. So you have multiple opportunities and FDA knows this quite well because they convene workshops where you can pull together the major stakeholder organizations, the major organizations that people are involved with, they have communication channels with these groups to reinforce exactly what the standard of care is for those who opt to get this type of procedure and start communicating it early.

You know, if you have patients that are inclined and you have a target population that's at risk, you can talk to them long before they're diagnosed on something like this so that they're aware of it. It's what we do in the kidney community. Long before somebody's looking at transplant or a collapse into dialysis in an emergency room, we're trying to get them at the front end. I'll just put that out there because it's pretty powerful as a communications system to use the stakeholder organizations and it adds a different dimension other than just medical professionals and industry and FDA. Thanks.

DR. LANGE: So Bram, what I hope you get a sense of is how important everybody feels that it is and how disappointed in how things are going, and I actually think the suggestion, it can be attacked in different ways depending upon the patient population and why they're not coming or why you're not getting good scans, is to use some of the VQI super sites as pilots to see what we could do to improve imaging compliance.

DR. ZUCKERMAN: This has been a very helpful discussion, Dr. Lange, thank you.

DR. LANGE: Great. Do you want to continue this or move on to the next question, Bram?

DR. ZUCKERMAN: I think we're ready to move on.

DR. LANGE: Okay. Question 2c, please.

MR. BRYSON: Question 3.

DR. LANGE: Oh.

MR. BRYSON: Please discuss whether strengthening existing real-world surveillance is needed to evaluate long-term real-world EVAR performance.

DR. LANGE: Dr. Eagleton, I see you smiling, do you want to go for this first?

DR. EAGLETON: I kind of felt like it's that first part we were just talking about.

DR. LANGE: All right.

DR. EAGLETON: To answer the question, yes.

DR. LANGE: Yes. If there's anybody that would disagree, now is the time to do it because we're going to go to 3a and 3b and 3c. Okay, let's go to 3a.

MR. BRYSON: Question 3a: If so, please discuss the key attributes that should be included in a real-world surveillance infrastructure to assure high-quality and clinically useful long-term EVAR device evaluation (e.g., enrollment strategies to address potential selection bias, data monitoring and auditing, event adjudication, core labs, major endpoints, and statistical analysis plans).

DR. LANGE: Bobby and Jason, I'm going to ask you guys to think about this and comment, if not first, fairly soon.

DR. YEH: I'll let Jason go first on this.

DR. LANGE: Okay, so Dr. Eagleton raised his hand. You guys, Jason and Bobby, think about it.

Dr. Eagleton.

DR. EAGLETON: I guess briefly I'll just a question. If we're setting up a whole new infrastructure that will be only given to selected sites, is that really real world anymore?

DR. CONNOR: Yes, this is Jason Connor here. So I'll comment on that point and then

maybe say my bit. So I think the key there is getting the right sites. So I mean if we only have academic medical centers, obviously that's not the right site, but at the same time non-academic medical centers probably aren't great, assuming some folks -- I shouldn't say aren't great, they're not used to it and they're not set up for it. So I guess thought would have to be provided to really get the right sites that are representative and even if academic centers or centers used to doing clinical research are predominant, incorporate, say, the appropriate weight so that those other centers are maybe upgraded with the non-academic sites. And that goes to one of the other things that I was going to say, that I think in terms of enrollment strategies, it sounds like VISION is great because they try to capture a hundred percent.

They have audits to ensure that patients who get these devices are included to do that. So I think looking at that and then looking at the major endpoints, the imaging, to understand what data is there and isn't there, and there's a chance to be proactive to do that. I mean, it sounds like patients just don't come back, you know, you can't force people to come back, but at the same time the patients are going to make sure that that data is captured because the obvious issue with these observational databases is bias and to the extent that we can understand the bias, that helps us to understand the data that we have.

So I mean, I'll let the docs speak to what we need to measure, which we've been doing, but I think that the key is obtaining the right sites, weighting the right sites is necessary, and then understanding what data that we're not having, to try to understand the bias in what we're measuring.

DR. LANGE: Okay. Dr. Yeh.

DR. YEH: So maybe just taking a step back, I agree with everything Jason just said. The guiding principles that I'm thinking of are that ideally we're striving for completeness of data and that means completeness of baselines or like a really thorough or at least a

random, a non-biased study sample, so that's a generalizable patient population. We'd like to have complete follow-up. We'd like to have endpoints that are captured that are important to patients. We'd like to be able to make valid inferences which speaks to both the study population bias as well as just the treatment selection, potential treatment selection bias in a non-traditional study. And ideally, we'd like to catch signals as earlier as possible, prior to some catastrophic event happening.

And then taking a step back on feasibility, we'd like that system to be not too onerous for the participating sites, for it to be not expensive, for it to be not dependent on extensive volunteerism at the participating centers or contributing data, which I think has been a burden for sites that are commonly participating in registries, at least in the cardiovascular space. It needs to be transparent. And I do think that it should not hinge or rely on a single organization or a single system. This was a comment that Dr. Starling had made earlier, which was data sharing, etc., it should have a system that I think at least is not reliant on a single entity to do such. And with all of that in mind, I really don't think that there is one real-world surveillance infrastructure that can accomplish all of those goals. And so the question becomes which are the ones that we need and how can we collectively accomplish each of those goals and what are the ones that make up for certain limitations of one versus the other?

And with that in mind, I think that it's -- well, it's important to focus on, I think, the predominant -- and I think it's -- and I can talk more deeply about it like later, which is the VQI linkage proposal, which I think is a terrific proposal. I think that Dr. Goodney and Dr. Sedrakyan are absolutely world-class investigators to be able to pull that off and to do it well. I don't have concerns about the linkage. What I do have concerns about are just some of the key things about the generalizability of what would be obtained as well as potential limitations of it being -- and I'm learning from our experience, and Ralph can comment

more about TVT linkage, which TVT linkage, as a postmarket entity, I think, has been a success but it has not been easy and it has not been, I think, the sort of -- you know, I'm just a little bit concerned about some of the descriptions of that strategy being a little too optimistic for what is still a very difficult process and Ralph can comment more about the challenges of CMS data use agreements, etc., with ACC and how the current system has actually gone through multiple iterations and actually, there's a new version of it just coming out now based on difficult data use agreements for exactly -- which is essentially exactly this approach that has been proposed.

DR. LANGE: I'm going to turn to Dr. Brindis, then go to Dr. Shepard.

DR. BRINDIS: Yeah, Ralph Brindis. It's been an interesting past 2 years, Dr. Yeh, in terms of CMS's desire or need to change our previous relationship and contracts related to their own concerns. But it was done, it took 18 months, but its complex. New data agreements were set up between ACC, STS, and CMS. New data agreements had to be set up between industry and us. New data agreements had to be set up between industry and CMS and we moved from a deterministic matching to probabilistic matching and it has to be the data is uploaded by industry and CMS then puts its data on the virtual site in ResDAC and then industry does the analysis, CMS checks it, and then it gets allowed to be used.

There may be some other -- the way Phil had described it, being a PSO may have short-tracked some of those issues that we had to deal with and took a lot to surmount. The other issue that we have is the delay in data in terms of the follow-up linkage but again, Phil described mechanisms where that data delay is even going to be shorter.

DR. LANGE: Dr. Shepard and then Ms. Alikhaani.

DR. SHEPARD: Alex Shepard, Detroit. I think that the infrastructure we're looking for already exists in the VQI and I'm particularly impressed with the presentation we heard from Dr. Jorgensen with regard to the vascular research collaborative. Not only will this

give us the data in a much faster timeline than what we can get from the administrative datasets, but it will be much more granular data. And to Dr. Yeh's comment about relying on volunteerism, I can understand that concern but again, I think one of the things that this group is addressing is who's going to pay for this surveillance and I don't know whether it's going to be industry support of something like the VRC, or government support or even support, but I think it's critical that we all join together in terms of paying for this sort of a surveillance program. And again, I think -- I don't mean to sound like a shill for the VQI, but I think the VRC plan that was discussed this morning sounds like an excellent one to me going forward.

DR. LANGE: Okay, I've got Jacqueline Alikhaani, Dr. Connor, and Dr. Brindis.

Jacqueline.

MS. ALIKHAANI: Jacqueline Alikhaani from Los Angeles. Regarding enrollment strategies, I think it's really important to make sure that we have diverse representation there, ethnic diversity, for traditionally underserved communities and I just hope that there's a way to reach out and collaborate with federally funded community health centers, FQHCs, I think that would be helpful.

And also in terms of getting more people getting more participation with enrollment, maybe we should think about making that part of the mandated guidelines, maybe working with organizations like the National Quality Forum to make that enrollment part of the required guidelines, or organizations like the American Heart Association that has a program called Get With The Guidelines, and you get organizations and hospitals and providers who participate with that. They get points for that. So I think we need to just really mandate it as part of the required guidelines.

DR. LANGE: Okay. Dr. Connor and Dr. Brindis.

DR. CONNOR: Yes, Jason Connor. So I agree with almost everything Dr. Yeh said, I

think it's -- and I agree that having multiple sites or multiple programs that collect data is a good idea. I worry about how pragmatic that is. I mean, this is really hard to do once and it's hard to find the funding and get all the right databases and organizations talking and it seems like doing that in parallel with multiple is a challenge. So I mean, it's possible and that's fine, but I would work on getting one right first. And the other point I was going to make, and maybe this is obvious, but the question refers to long-term EVAR device evaluation.

But I would also want to make sure that we have open surgery long-term evaluation, too, just because that seems like the control group, and if all the EVARs are similar to one another and it seems like they may be with the exception of yesterday and hopefully yesterday's is getting in line with everyone else, but it seems like the question is, is it even worth doing? And so having good long-term data on the open procedures that are done seems like a very important thing and though I get it, that comes with its own challenges, too.

DR. LANGE: Okay. Dr. Burgess, Dr. Khaja.

DR. BRINDIS: Brindis.

DR. LANGE: Brindis. I'm sorry, Dr. Brindis.

DR. BRINDIS: As long as you give me Blue Bell, I'll answer.

(Laughter.)

DR. BRINDIS: So again, I have to acknowledge my serving on the executive committee of the VQI PSO and also being involved in MDEpiNet. But just for context, if somebody wanted to start a new registry with the NCDR, basically it costs 2 to $3 million to launch a registry. We already have a registry here through SVS called VQI. It takes a long time to start a registry. We talked about the data use agreements, it takes years for you to have something up and running and working. Jens described very well an incredible

mechanism to be able to identify enrollment strategies that address potential selection bias, whether it be hospital, academics, rural, whatever, making sure that underrepresented minorities can be enrolled. So they already -- VQI has set that up. The data monitoring and auditing strategies have been talked about and I think auditing over time is going to be improved at VQI. Phil described very nicely their mechanisms for event adjudication and looking at data and they have a pretty good research network with which to do such.

And one of the concerns in terms of the data being available to the public or other interested parties, VQI, in all honesty, has been very forthright in sharing data even more than the NCDR has to date, and the NCDR has things to learn from VQI in that mechanism. So not only does the VQI and VISION process have a lot of the key attributes, it's up and running, you don't have to start from scratch.

And then the last point I'd like to make is we should always consider ourselves to have a Coordinated Registry Network process like MDEpiNet has. And there are other folks out there, Kaiser Permanente, with good data, we talked a little bit about the veteran association and stuff and so these sources should not be ignored and also be available, of course, to the FDA.

DR. LANGE: Thank you, Ralph.

Dr. Khaja and Dr. Woo.

DR. KHAJA: I agree that the VQI is already established and has many of these things going. I think we shouldn't limit ourselves and if we can, again, I mentioned earlier, we can -- the device manufacturers are -- they seem very much involved here. And so much like the IVC filter group was in PRESERVE where the seven manufacturers and the FDA put in the money for this, this may be something where we get robust data through the VQI but get more data through it and have the device manufacturers contribute, as well.

DR. LANGE: Great. Dr. Woo. Thank you, Minhaj.

DR. WOO: I just wanted to comment on Dr. Connor's comment -- Karen Woo -- about the outcomes of open surgery. I think that it's going to be very difficult to track or to compare the outcomes of open surgery nowadays because open aortic surgery done nowadays is for people who essentially have no endovascular option or for a very small percentage of people who opt for an open option, so it would be very difficult to compare the two. We know from historical experience that straightforward open infrarenal aneurysm repair is extremely durable and we know what the typical long-term outcomes are from historical data. So that's my one comment.

And then my second comment is about VQI and I agree that VQI is established and it would be the way to go because we don't have to do all the setup. My only concern is that it could be criticized for not being generalizable, which has been brought up a lot and people say that VQI is essentially preaching to the choir, it is voluntary, these are people who volunteered to do all of this work because they're committed to providing high-quality care. So we may not be capturing things like physician judgment that may be off label or things that affect device outcomes in the VQI population. So I would encourage FDA to try to work with VQI to try to find a way to make it more generalizable, to try to find a way to allow people to participate that may not be quite as onerous as the full participation.

DR. LANGE: And I would argue -- I'll get Dr. Hakaim, I'll get to you. I would argue that we already have that. Bobby Yeh and the group at Harvard has provided that complementary study that is not just the 457 people that have decided to join VQI, but 1200 sites and that again, those two studies not competing, I don't think we have to choose between because they offer complementary data and hopefully they corroborate one another, is that they confirm, what you see in one is confirmed and are more generalizable.

Dr. Yeh.

DR. YEH: Well, I'll just say that to be transparent about it, that was only possible

because there is a specific code for unibody devices for time and you saw the limitations of that analysis because we still didn't know which unibody device was being used, it was based on time cutoffs. So going forward, I don't know that that approach would be able to tell you -- I know for sure it wouldn't be able to tell you between different manufacturer non-unibody devices, for example. So that approach, while I think when possible it is easy, certainly it's not expensive, as expensive and it can be done rapidly, may not be generalizable to this entire class discussion which is, I think, the rationale for Dr. Secemsky's proposal of creating a limited device file.

And the other attribute about the limited device file, I think -- and I agree, totally agree that complementary to VQI, I think -- let me just be clear, I think the VQI initiative should move forward. The question is, is there -- beyond trying to expand VQI and making it generalizable, is there also an additional, more generalizable, and even less burdensome approach that can be done and sort of as a complement, in a way also from an industry -- you know, just from an industry perspective, allows industry manufacturers maybe to be able analyze their own data.

The challenge with the VRDC, and I'll say that we have a project with an AHA registry linked to VRDC data, is that, as Dr. Goodney was explaining, the VRDC only is allowed to be analyzed by one person sitting in one seat at any one time and you're actually not allowed to export data off the VRDC, certainly not individual patient data, but you can't even export aggregate data off the VRDC, which is the system that's going to be able to give you more real-time data, without permission. And so that greatly creates a bottleneck for the system to be able to deliver analyses and it further limits the ability to share that data. Those data can't be shared. I know that VQI may have been very interested in sharing their data and their registry, but once you involve a linkage that involves a seamless data user agreement, those data can no longer be shared, certainly not in any individual patient form and

becomes difficult to share even in aggregate form.

So I just wanted to make sure that, again, I think that the proposal is excellent, it should move forward. I just want there to be full acknowledgement that it is not a perfect solution to all of the elements that are required, I think, for a complete surveillance system.

DR. LANGE: I've got Dr. Hakaim and then Dr. Shepard.

DR. HAKAIM: Yeah, just picking up on the VQI group and comments, we have, I guess, now 457 sites that are participating out of a possible 1600. If there's a way -- I guess the question is what is the barrier to being a member of VQI, is it financial, is it the data extraction, is that the spot that we need to hit and potentially have industry support, so potentially the subscription to be in VQI? I mean, we're basically making aneurysm disease a chronic disease and something that we used to treat once with an open repair we now are kind of committing to following patients and we wouldn't be doing it if industry wasn't involved with it. So I think a little more of the onus has to be on industry and probably financial.

DR. LANGE: Thank you. Thank you, Al.

Dr. Shepard.

DR. SHEPARD: Yeah, Alex Shepard from Detroit. I just wanted to move back to what Dr. Yeh was mentioning about the difficulties with data sharing and in terms of using these large administrative datasets, and I just am looking for some guidance as to what the legal and regulatory prohibitions are and if there's anything the FDA can do to impact these. Is this a national legislation that would be required to change some of these prohibitions or regulations? Is there any way the FDA could impact these prohibitions that are obviously keeping us from doing what we want to do?

DR. ZUCKERMAN: The answer is no, Dr. Shepard. Dr. Yeh has told it like it is. CMS is a separate sister agency of HHS, but they have their own criteria and right now we need to

work within those criteria. It would need congressional legislation to really change the system, so that we have to all be cognizant of the practical realities that Dr. Yeh and others were mentioning during this discussion. So if I might summarize, Dr. Lange, I think this has been a great discussion in that the key attributes have been mentioned and discussed. I would, though, underline Dr. Khaja's comment that the FDA ultimately will be able to set parameters for what we're looking for to develop a better national infrastructure as part of this discussion. However, I can tell you, based on a decade's worth of experience with registry development, it's very important for all these competing organizations to really understand that industry is an important stakeholder here and they need a seat at the table in planning, because ultimately FDA is going to require timeliness of data reporting and high-quality data and for industry to put some of those major responsibilities into other people's hands, it's really important for these organizations to understand really what the objectives are and strategic goals of industry.

DR. LANGE: And to that end, having VQI and their steering committee having all of the industry heads at the table as a part of that, I think, speaks to what you're talking about, Bram.

DR. ZUCKERMAN: Yes.

DR. LANGE: And to a large extent, VQI has mitigated some of these things to address any selection bias by enrolling a hundred percent of the people, data monitoring and auditing, and they have event adjudication and they do major endpoints, statistical analysis and having industry and the major organizations at the table working together on this.

DR. ZUCKERMAN: It takes a team, absolutely.

DR. LANGE: Great. And I think their next move is to move to faster data acquisition from CMS, it will benefit the consumers and industry as well, towards developing the answers we want with more timely data. Great. Should we move on to Question 3b, Bram?

DR. ZUCKERMAN: Yes.

MR. BRYSON: Question 3b: Please discuss the frequency and duration of surveillance for patients post-EVAR that would be clinically meaningful and feasible to capture through a real-world surveillance infrastructure, including recommendations for patients who undergo aortic reintervention.

DR. LANGE: The figure I heard proposed by FDA, supported by industry and several thumbs up in the Panel was 10 years. Is there any dissenting opinion?

Dr. Starnes.

DR. STARNES: Just with the caveat that appropriate 30-day imaging followed by an interval of either 6 months if the patient has an endoleak and then annually thereafter out to 10 years.

DR. LANGE: Thank you. Thank you for that verification or clarification. I was just going to do one study at 10 years, Ben.

Dr. Khaja and Dr. Shepard.

DR. KHAJA: I agree exactly with what Dr. Starnes says, because that's what the SVS and ACR guidelines say.

DR. LANGE: Great. Dr. Shepard, then Dr. Horvath.

DR. SHEPARD: I agree completely, but I would ask Dr. Zuckerman how that fits into the FDA's guidelines of burdensome, their definition of burdensome. I personally don't think it's burdensome, but I guarantee you some of the graft manufacturers and others will.

DR. ZUCKERMAN: Okay, the discussion today is really where we, we meaning the FDA is trying to get the best clinical input as to what is a realistic and practical structure for post-approval surveillance and if I hear you correct, Dr. Shepard and your vascular surgery colleagues, this is a doable structure, it would be clinically meaningful and would provide a lot of value for a better postmarket surveillance system. That's what FDA needs to hear

today, am I correct, Dr. Shepard?

DR. SHEPARD: I would agree with all that you said except for the doable part, I'm skeptical about how doable it is. I could not agree more that it's critical to do this, but I'm just skeptical that we are going to be able to do it.

DR. ZUCKERMAN: Well, we're going to make an optimist out of you, there's been a lot of work in the postmarket sphere over the last decade. Off line, Dr. Brindis and others can recount some of it and I think the time is now in this particular area, so let's go forward.

DR. LANGE: Dr. Horvath.

DR. SHEPARD: Thank you.

DR. LANGE: Yeah, Dr. Horvath.

DR. HORVATH: Sure. I just wanted to add a question, does the clock then restart with an aortic reintervention, another 10 years annually?

DR. STARNES: This is Ben Starnes from Seattle. I think we would all agree that lifelong surveillance is paramount, so I think that annual imaging is part of the process. The statement that I made earlier, that the average age of any of these patients that undergo EVAR is between 74 and 76 and if you're following them out to 10 years, they're going to be in their mid-eighties or dead by that point and I just think diligence is key here.

DR. LANGE: Great. There are several things that I do annually, I pay my taxes, I register my car, I used to have birthdays annually, it's every other year now, so not terribly burdensome. Painful, but not burdensome. So 10 years I think is what you hear, Bram.

DR. ZUCKERMAN: Thank you.

DR. LANGE: Great, 3c.

MR. BRYSON: Question 3c: Please discuss strategies that can incentivize relevant stakeholders to participate in real-world data collection on a routine basis.

DR. LANGE: Dr. Eagleton, what's your thoughts? As a stakeholder, what would

incentivize your colleagues to participate in real-world data collection?

DR. EAGLETON: You know, I think the rate-limiting step for a lot of us to participate in programs like VQI is just data entry and data identification, and if there was some support in that fashion, that would be extraordinarily helpful to people participating.

DR. LANGE: Okay.

(Cross-talk.)

DR. LANGE: Okay, data entry support.

Dr. Shepard.

DR. SHEPARD: I think this is not something that's going to be easily done voluntarily and either the FDA or the government mandates this, either the government requires it or industry pays for it, but again I think to expect that the physicians are going to do this voluntarily is a pipe dream.

DR. LANGE: Okay. Dr. Woo, what are your thoughts? What would incentivize stakeholders? And then Dr. Brindis.

DR. WOO: I agree with Dr. Eagleton, but it's not just the data collection or the data entry. So VQI requires you to enter the data in this web-based mechanism, it's following up the patients and tracking them down and getting their imaging results. So I think there has to be some -- I don't know how we would incentivize providers without a stick.

DR. LANGE: Okay.

DR. WOO: Not a carrot or a stick. Something financial.

DR. LANGE: Okay. I've got Dr. Brindis, Dr. Starnes, and Dr. Yeh.

Ralph.

DR. BRINDIS: Well, this is a very important question, but it has multiple components and one of the key things that registries such as the NCDR, in this case VQI does, it has to make sure it has value to the clinicians and hospitals of the data that it's giving back in

bench-marking, improving quality, measuring performance. And so to date, it obviously has shown value to the VQI participants despite the efforts related to data entry. So continued work, first of all, from a registry perspective to show value to its participants is going to breed continued enrollment. The challenge is the longitudinal follow-up and data entry and that's why I'm particularly -- I think a number of us have been particularly engaged with this tiered approach that Jens talked about, where you can have data from the registry that can be very helpful for up to 1 year for all its participants, but then choosing the so-called VQI steroid approach of a network where there is some reimbursement, some carrot for the longitudinal follow-up necessary to be able to capture the elements that we would want.

The last comment I would want to make is yesterday we spent a whole day talking about a device that we were concerned in particular that it was an outlier to comparators. So again, I'm not the FDA, but one could state that maybe that company stakeholder might have some sort of extra incentive or a so-called ask from the FDA that all their devices be entered into the registry and followed so that we can assure the safety and efficacy of their most recent iteration.

DR. LANGE: Dr. Starnes, Dr. Yeh, and Dr. Starling.

DR. STARNES: Yeah, as a stakeholder, it's hard for me to believe that this would happen without some sort of incentive, but my biggest incentive is an easy button. I'm a busy clinician and I just want this to be easy. When I do an IDE patient now, I have to enter three separate operative notes, I have to go separately into my own EMR and I have to go into M2S to enter the data and that's just cumbersome, and I think we should be able to leverage the technology of the electronic medical record to merge with some of these other data collection systems and registries so that all of the data can just be shared with an easy button. That would be worth it all, to me.

DR. LANGE: Thank you, Ben.

Dr. Yeh, Dr. Starling, and Dr. Blankenship.

DR. YEH: I really like both Dr. Brindis's comments and Starnes's comments because they were sort of the amalgamation of what I was thinking. One is that I do think that incentivizing long-term follow-up is probably not feasible and that the tiered approach that Dr. Brindis mentions, which at least as a fallback option has systematic follow-up in claims data for a linked population, is the right one. Those hospitals that want to participate more intensively can. But I also think there should not only be VQI on steroids but there ought to be VQI Lite and maybe that's what Dr. Starnes is sort of thinking of here and maybe this is really the merger of the two proposals that you heard from Dr. Secemsky and Dr. Goodney, which is I don't see why this limited device file that Dr. Secemsky proposed couldn't also just be part of the VQI.

I mean, that could also be the VQI Lite, it's the bare minimum, the bare bones, not the hundreds of data elements that I think are informative for some analyses but are just not necessary and actually preclude the participation of some busy interventionalists and many busy physicians who aren't going to take the time to enter those data.

You probably want to provide some option that collects just a very minimal amount of information that allows you to link, tells you the device, tells you maybe just a couple of key attributes that are going to be the real important stratification variables but will allow much broader participation in what I think is and that will -- you know, than was currently -- the registry currently has.

DR. LANGE: Okay. Dr. Starling and -- thank you very much, Bobby.

Dr. Starling, Dr. Blankenship, Dr. Cigarroa.

Randy, you're on mute.

DR. STARLING: Sorry. Starling. So perhaps idealistically I think the incentive here is quality and you know, physicians want to have excellent outcomes. So I think the role of

professional societies as well as almost all of us work for an enterprise now, so I think these metrics have to work their way both from the societies but also into the culture of the health systems have to be behind these things. And you know, you have to acquire the data before you can collect the data, so this has to be driven. And just to give you an example, so I work in a world of heart transplantation. We have publicly reported data. We're not given an option, we have to submit the data, we are held accountable to payers, to patients, it's publicly reported and it comes down to us in surprise. So I think EVAR falls into this category, everyone that is providing this therapy should have the incentive to support whatever needs to be done to ensure the highest quality. Thank you.

DR. LANGE: Thank you, Randy.

I've got Dr. Blankenship, Dr. Cigarroa, and then Mr. Conway. Then I'll try to summarize.

DR. BLANKENSHIP: Okay, Jim Blankenship. I agree that physicians need incentives to do this. One strategy could be to try to create a CPT code that's reimbursable, CPT 96XXX, patient visit with data entry for purposes of registry and get CMS to pay for it since they're one of the major beneficiaries of this. The second point is that making it easy for the doc, as has been mentioned, is critical. I went from a system where, for instance, the information for the CathPCI registry went automatically from the cath reporting system into the registry.

I'm now in a system where you have to -- every time I do a coronary intervention, I have to fill out a form and it takes 20 minutes and somebody else enters that into the system and it gets reported and you have to really want to do it to go through filling out a form for every time you do a procedure or for that matter, for every subsequent visit. So making it easy, if you can get templates in the dominant electronic medical record systems where you could simply go into Epic or Cerner and access a template and that automatically

files, that would be much easier for physicians.

DR. LANGE: Thank you, Jim.

Dr. Cigarroa, Mr. Conway.

DR. CIGARROA: So the environments in which we practice have radically changed over the last 5 to 10 years, from physicians being independent to being part of specialty groups, multi-specialty groups employed by hospitals and now employed by health systems. So I think that I would -- I think it would be safe to say that physicians would like to participate in this. We now have to convince not only hospitals but health systems to allocate the resources and the personnel to support this, and hospitals are now involved in ambulatory care.

So strategically we must engage hospital and health system representatives to make certain they understand that not only is there a benefit to the patient, but there is a benefit to quality and therefore, what they're in now, it's not just catastrophic care, it's ongoing monitoring of care. So strategically, societies must be involved; we, as clinicians must be involved and experts, but we must bring in individuals who are parts of health systems, which are often integrated delivery systems which will provide, I think, advantages to enabling us, potentially.

DR. LANGE: Thank you, Joaquin.

Mr. Conway.

MR. CONWAY: Thanks, Doc. I actually think an answer to this question is kind of tied to some of the elements in 3a, which are attributes, and I like what Dr. Starling said and I also very much like what Dr. Cigarroa mentioned here. You know, the transplant world is an interesting kind of place and so if you're trying to change a culture, which has been said several different times, a little bit of sunlight is sometimes pretty helpful. And so in terms of some of the key elements that have been talked about today, you heard transparent,

diverse, trackable by device, off-label use, these are all elements that are important and should be seen and they create incentives, they create incentives if there's a public-facing view to this and because of that, I'd say that it's primetime for comparative measures. You want your patient/consumers to be able to see this and you also want competing health systems to be able to see this as an element of quality because it's a highly competitive environment in a lot of places in the country. Some places, not so much. But if you actually elevate this into the domain of quality and then have it as part of the competitive basis, I think you'd get a lot of people incentivized to embrace it a little bit further. And again, final point, everyone at the table as stakeholders, including patient organizations. Thanks.

DR. LANGE: So I'm just going to summarize what's been said so far:

Ease, whatever can make this system easy to use.

Second is to show value to the organization, both for quality, measures of performance, the value may be public-facing and you want to be the best organization, as Mr. Conway mentioned, and sometimes the value in Michigan is actually increased reimbursement based upon the quality and maybe others, but to show value.

Third is to have a tiered approach so everybody can participate, some to a lesser degree, some to a larger degree, but everybody can if it's a tiered approach.

And then finally have a systems involvement where it's everybody across the organization, hospital MV, societies, and patient organizations are integrated to make this happen.

So I think I've tried to capture everybody's comments.

Bram, do you need any further clarification or further discussion from the Panel?

DR. ZUCKERMAN: No, I think this has been an excellent discussion, we all agree it's going to be very challenging but it can be done and that's why I want to underline the concept of the tiered approach. It's one that FDA has been pushing for the last decade, I

think it could work here with the appropriate structure and I would really encourage the industry and the organizations thinking about developing a new national infrastructure to consider that pathway. Thank you.

DR. LANGE: Thanks. Question 4.

MR. BRYSON: Question 3d.

DR. LANGE: I'm sorry, 3d.

MR. BRYSON: Please comment on how device manufacturers, healthcare systems, professional societies, individual providers, and other stakeholders should collaborate to maximize long-term follow-up compliance and data quality on EVAR device performance.

DR. LANGE: Okay, so this is the last one. The previous question was on incentive, this is about collaboration.

Dr. Starnes, your hand shot up.

DR. STARNES: Well, I think it's the same discussion, we had so many different discussion points about how to incentivize different stakeholders that I think it's essentially the same discussion. Maybe I'm missing some nuances.

DR. LANGE: Dr. Cigarroa.

DR. CIGARROA: I think it's an extension of 3c, but ultimately somebody has to serve as the convener to keep all of these different entities aligned with reasonable priorities and action steps. So the question is, is who would that body be?

DR. LANGE: Dr. or Mr. Conway, I'm sorry.

MR. CONWAY: Not to add to FDA's workload, I actually think government has a lot of power. One of the most impactful powers that it has when exercised judiciously is the power to convene. And so I would actually suggest that FDA continue what they're doing, however, take a new approach to it if you want to change the culture, which is to convene it with all stakeholders. I would edit Question (d) to include patient stakeholder organizations

by name, using that term, not "other." And I do think you have the elements here to bring it together and that's kind of the key, is that it's brought underneath the rubric of the federal agency that probably has the largest stick to bring to bear if it so chose to, but instead it's choosing to bring people together and not necessarily dictate or proscribe but to try to bring all the best elements together.

The last thing that I would say is the patient stakeholder organizations, I've brought it up several times over the past several days, the communications capacities have become much more sophisticated over the past 10 years, to a degree that I think the American Heart Association and others probably don't get full credit for, but their reach is quite deep and the sophistication on data analysis, data collection, and the relationships they have with other federal agencies is pretty huge. So having them at the table at the front end often eases the way for data sharing and data collection. I brought up Tricare, as well. I don't think you can leave the Department of Defense out of this and definitely not the VA. So thank you.

DR. LANGE: Dr. Cigarroa.

DR. CIGARROA: I would agree with the suggestion for the FDA to consider being the convener.

DR. LANGE: I always find, for the person that's not able to vote on the Panel, to make them responsible for things, I always find it very useful.

So Ms. Alikhaani.

MS. ALIKHAANI: I want to reiterate the same thing, I think that the FDA, in collaboration with -- there's tons of patient advocacy groups, American Heart Association all the way down the line, there's so many of them, and this is a quality of care issue that patients and family members and caregivers care about. So I think you would have a lot of traction in reaching out and touching these organizations and forming a collaborative to

address this particular issue as a partnership. It's unique, it's new, I think it would be win-win.

DR. LANGE: So Bram, I'm not sure if you like how I'm going to summarize this, but there's two consensuses, one is among the groups that should be active participants and collaborators is to make sure we say patient stakeholder organizations, others, so we make sure they're an important part of it. Thank you for that comment, Paul and Jacqueline, as well, for drilling that home.

But everybody feels like the FDA has both the knowledge, the expertise, the gravitas and a little bit of the federal government behind them to help encourage and push and I'd say mostly just encourage this collaboration. I hope the FDA wasn't asking for somebody on this Panel to step up and be that convener, I don't see anybody raising their hands. Oh, Jason, it looked like he almost had his up.

DR. ZUCKERMAN: No, I think the FDA wants to put your tax dollars to good work, Richard and some others, we're more than happy to be the facilitator.

DR. LANGE: Great. Do you need any other input into this particular question, Bram? A lot of people thought that 3c also covered it, as well. Any other comments about this?

DR. ZUCKERMAN: No, I think we're all set.

DR. LANGE: Good. At this point I'd like to ask our non-voting members, Jacqueline Alikhaani, our Consumer Rep; Gary Jarvis, our Industry Rep; and Paul Conway, our Patient Rep, for any additional comments.

Jacqueline, I'll ask you to start, please.

MS. ALIKHAANI: Jacqueline Alikhaani. I think we've had a very productive discussion, I'm really pleased with the outcomes. It's really exciting because every time you talk about quality of care improvements, I mean that's just extra special. I mean, it really gets to the heart of all of the issues that we care about the most, especially patients who

are living with these chronic conditions that can be life threatening and devastating, you know, in so many ways, financially and other ways. And we already have enough to do with dealing with COVID and we need to get things moving along more and more on a lot of these ongoing chronic conditions issues. And to me, patient education, engagement, getting patients to understand more and more about all of the different variables and factors that affect our healthcare outcomes, all of the healthcare consumers including family members, caregivers, and patients, too, this is something that I think is just number one on the list, what we've been talking about all day. So I'm really excited about new ways to engage patients and help patients to be more proactive and working with the doctors and helping to improve their care.

DR. LANGE: Jacqueline, after your second full day of this Panel, I'd say you're really excited about what you're talking about, I really appreciate that. Thanks.

MS. ALIKHAANI: You're welcome.

DR. LANGE: Mr. Jarvis, despite the fact that you've dominated most of the conversation today, I'm going to let you have one last word.

MR. JARVIS: I appreciate that, Dr. Lange. Yeah, I think today has been actually a great discussion, there's been all kind of things discussed and I think it's all moving in the right direction. I agree with a lot of what people said, you know, for all the stakeholders we need to show the benefit for them and what this can do. Being involved in something like this like 25 years ago with cardiothoracic surgeons trying to get some change, we're talking about changing practice here and how they do things, a heavy lift.

It's going to take longer, it will be more expensive and probably a little bit more frustration than we all want, but I think we can get there. But I do think that the more we can get societies, the patient organizations, even the physicians yourselves here on the Panel, because we are asking you to potentially modify or change your standard of care as

we go out forward here. So it's everybody involved, but I think it can be done, but probably not as fast, unfortunately, as we'd all like to see. So thanks a lot, Dr. Lange, I appreciate the opportunity.

DR. LANGE: Thank you, Gary, great to serve with you.

Mr. Conway.

MR. CONWAY: Just a thank you to everybody and especially for what I would call a shared sense of urgency. I think it's an interesting time in America where you don't reach a lot of consensus, but on this one I think you have a couple of consensus points. I think everybody embraces innovation and they can see the promise that it has to help people that are quite sick and quite ill, especially the doctors that are on this Panel. But I also think there's a great deal of empathy for those folks who may initially benefit, but down the road we don't have the adequate assessments in a uniform way to actually work with patient/consumers to say hey, what's safe and what's not.

But I think the way that folks have gone about this for the past 2 days has been optimistic and hopeful. As a patient and a policymaker, it's good to hear. For FDA, I would say again, hats off to you, you have a long history in this space. You have the Kidney Health Initiative, which is an FDA-launched initiative with the kidney industry and the kidney professionals, you have the Clinical Trial Transformation Initiative out of Duke, which has changed clinical trials in the United States, and this sounds like another area to wade into and the best of luck to you, because I think it's necessary and I think you have consensus. Thanks.

DR. LANGE: Thank you very much. I would like to thank the Panel, the FDA, the presenters, the speakers at the Open Public Hearing, all of your contributions in today's meeting and yesterday's, as well.

For anybody on the Panel, if you make it to El Paso, I will share Blue Bell with you. I

don't do that with just anybody, but I'll make that offer.

Bram, do you have any final remarks?

DR. ZUCKERMAN: I really want to thank you for your leadership, Dr. Lange, you should go out now to the grocery store and buy three quarts of Blue Bell, you really deserve it. Seriously, it's been an outstanding 2 days and I want to thank all participants. The bottom line is that there is a lot of work to do. FDA is prepared to work with all relevant stakeholders, so please stay tuned and please continue to try to work with the Agency. Thank you.

DR. LANGE: Great. It's 5:10 Eastern Time and at this point I'll conclude the meeting of the Circulatory Panel. The meeting's adjourned. Thanks, everybody.

(Whereupon, at 5:10 p.m., the meeting was adjourned.)

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C E R T I F I C A T E

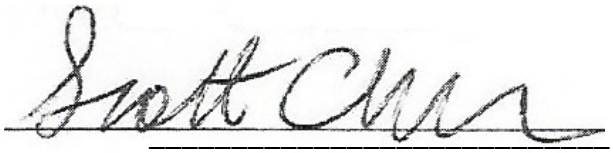
This is to certify that the attached proceedings in the matter of:

CIRCULATORY SYSTEM DEVICES PANEL

November 3, 2021

Via Zoom Videoconference

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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