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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

+ + +

July 20, 2011
 8:00 a.m.

Hilton Washington DC North
 620 Perry Parkway
 Gaithersburg, Maryland

PANEL MEMBERS:

RICHARD L. PAGE, M.D.	Temporary Panel Chair
VALLUVAN JEEVANANDAM, M.D.	Voting Member
DAVID SLOTWINER, M.D.	Voting Member
DAVID NAFTEL, Ph.D.	Voting Member
JOHN C. SOMBERG, M.D.	Voting Member
JEFFREY S. BORER, M.D.	Temporary Voting Member
DAVID C. GOOD, M.D.	Temporary Voting Member
MICHAEL A. FERGUSON, M.D., CAPT, USN, MC	Temporary Voting Member
RALPH BRINDIS, M.D.	Temporary Voting Member
NORMAN KATO, M.D.	Temporary Voting Member
RICHARD A. LANGE, M.D.	Temporary Voting Member
ELIZABETH B. PATRICK-LAKE, M.S.	Patient Representative
BURKE T. BARRETT, B.A., B.S., M.B.A.	Industry Representative
ROBERT DUBBS, J.D., M.B.A.	Consumer Representative
JAMES P. SWINK	Designated Federal Officer

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FDA REPRESENTATIVES:

BRAM D. ZUCKERMAN, M.D.
Director, Division of Cardiovascular Devices

AMANDA SENA
Press Contact

FDA PRESENTERS:

LISA KENNEL
Division of Cardiovascular Devices, Office of Device Evaluation

CHENGUANG WANG, Ph.D.
Cardiovascular and Ophthalmic Devices Branch
Division of Biostatistics, Office of Surveillance and Biometrics

JULIE A. SWAIN, M.D.
Circulatory Support & Prosthetics Branch
Division of Cardiovascular Devices, Office of Device Evaluation

MARY BETH RITCHEY, RN, M.S.P.H., Ph.D.
Division of Epidemiology, Office of Surveillance and Biometrics

MATTHEW HILLEBRENNER, M.S.E.
Circulatory Support & Prosthetics Branch
Division of Cardiovascular Devices, Office of Device Evaluation

SPONSOR PRESENTERS:

JODI J. AKIN, M.S.N.
Vice President, Global Clinical Affairs
Edwards Lifesciences, LLC

CRAIG R. SMITH, M.D.
Chairman, Department of Surgery
Columbia University Medical Center

MARTIN B. LEON, M.D.
Director, Center for Interventional Vascular Therapy
Columbia University Medical Center

LARRY WOOD
Corporate Vice President, Transcatheter Valve Replacement
Edwards Lifesciences, LLC

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REBECCA TUNG HAHN, M.D.
WILLIAM N. ANDERSON, Ph.D.

OPEN PUBLIC HEARING SPEAKERS:

MARVIN WARD
HAROLD SCHOENDORF
TIFFANY CHARLESON, RN, B.S.N.
MARIAN C. HAWKEY, RN
STEVEN E. GREER, M.D.
AUGUSTO D. PICHARD, M.D. (SCAI)
DAVID R. HOLMES, JR., M.D. (ACC)
MICHAEL J. MACK, M.D. (STS)

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MEETING

(8:00 a.m.)

DR. PAGE: Good morning. I'd like to call this meeting of the Circulatory System Devices Panel to order.

I'm Richard Page. I'm Chair of this Panel. I'm a cardiologist, electrophysiologist, and Chair of the Department of Medicine at the University of Wisconsin in Madison.

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

For today's agenda, the Panel will discuss, make recommendations, and vote on information related to the premarket approval application for Edwards SAPIEN Transcatheter Heart Valve. The Edwards SAPIEN Transcatheter Heart Valve, model 9000TFX, sizes 23 millimeter and 26 millimeter and accessories, are indicated for use in patients with severe aortic stenosis who have excessively high operative risk.

If you have not done so already, please sign the attendance sheets that are on the tables at the doors.

We're going to do introductions in a few minutes, but first I'm going to turn things over to James Swink, the Designated Federal Officer for the Circulatory System Devices Panel, who will make introductory remarks.

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I'll also comment that the room is already warm and we can break with formality and remove jackets if we care to. Please feel free to do so.

And with that, let me pass things on to James Swink.

MR. SWINK: Good morning. I will now read the Conflict of Interest Statement.

The Food and Drug Administration 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 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's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act are being provided to participants in today's meeting and to the public.

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. Section 208, Congress has authorized FDA to grant waivers to special Government employees who have potential financial conflicts when it

is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special Government employees and regular Government employees with potential financial conflicts when necessary to afford the Committee essential expertise.

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

For today's agenda, the Panel will discuss, make recommendations, and vote on information related to the premarket approval application for the Edwards SAPIEN Transcatheter Heart Valve, sponsored by Edwards Lifesciences. The Edwards SAPIEN Transcatheter Heart Valve, model 9000TFX, sizes 23 millimeter and 26 millimeter and accessories, are indicated for use in patients with severe aortic stenosis who have excessively high operative risk.

Based on the agenda for today's meeting and all financial

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interests reported by the Panel members and consultants, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Section 208(b)(3) to Dr. Jeffrey Borer. Because Dr. Borer has an adjunct position at an institution identified as a study site for the PMA, the waiver addresses his affiliated institution's interest in the Sponsor's study. In the upcoming year, this institution will receive payments over \$300,000 for patient follow-up and as allocated for visits completed and potential travel reimbursement.

This waiver allows Dr. Borer to participate fully in the Panel deliberations. FDA's reasons for issuing this waiver are described in waiver documents which are posted on FDA's website at fda.gov. Copies of this waiver may also be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 6-30 of the Parklawn Building. A copy of the statement will be available for review at the registration table during this meeting and will be included as a part of the official transcript.

Mr. Burke T. Barrett is serving as the Industry Representative, acting on behalf of all related industry, and is employed by CardioFocus, Incorporated.

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

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to advise the Panel of any financial relationships that they may have with any firms at issue.

I'll now read the Temporary Voting Status Memorandum.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27, 1990, and as amended August 18, 2006, I appoint the following individuals as voting members of the Circulatory System Devices Panel for the duration of this meeting on July 20th, 2011:

Dr. Richard Lange, Dr. Michael Ferguson, Dr. Ralph Brindis, Dr. Richard Page, Dr. Norman Kato, Dr. David Good, Dr. Jeffrey Borer.

For the record, these individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

In addition, I appoint Richard L. Page, M.D., to act as a Temporary Chairperson for the duration of this meeting.

This has been signed by Jeff Shuren, M.D., J.D., Director, Center for Devices and Radiological Health, on July 8th, 2011.

Before I turn the meeting back over to Dr. Page, I'll make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated. Their telephone number is (410) 974-0947. Information on purchasing videos of today's meeting can be found on the

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table outside the meeting room.

The press contact for today's meeting is Amanda Sena. There she is. Thank you. She's over here to the left.

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

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

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

And, finally, please silence your cell phones and any other electronic devices at this time. Thank you very much.

DR. PAGE: Thank you, Mr. Swink.

We have our full complement of Panelists here, and before we begin, I would like to ask Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. And let's start with you, Dr. Zuckerman.

DR. ZUCKERMAN: Good morning. Bram Zuckerman, Director, FDA Division of Cardiovascular Devices.

DR. FERGUSON: Mike Ferguson. I'm an interventional cardiologist and the head of the cath lab at the Military Medical Center in Bethesda.

DR. GOOD: Good morning, I'm David Good. I'm Professor and Chair of Neurology at Penn State College of Medicine in Hershey, Pennsylvania. I'm a stroke neurologist and also interested in recovery from stroke as my research interest.

DR. BORER: I'm Jeff Borer. I'm a cardiologist. I'm a Professor and Chairman of the Department of Medicine and Chief of Cardiovascular Medicine at the State University of New York Downstate Medical Center in New York City, and the President of the Heart Valve Society of America. I'm also a member of the United States Valve Experts Committee of the ISO, the International Organization for Standardization of Biomedical Equipment.

DR. BRINDIS: I'm Ralph Brindis. I'm the senior cardiovascular advisor at Northern California Kaiser Permanente, immediate past president of the American College of Cardiology. I am trained as an interventional cardiologist. My areas of interest are in cardiovascular outcomes and in cardiovascular registries.

DR. LANGE: My name is Rick Lange. I am Vice Chairman of Medicine at the University of Texas, San Antonio, and a recovering interventional cardiologist.

(Laughter.)

DR. SLOTWINER: I'm David Slotwiner, an electrophysiologist at North Shore-Long Island Jewish Hospital School of Medicine.

MR. SWINK: James Swink, Designated Federal Officer for CDRH.

DR. PAGE: Richard Page. I'm acting as Chair today. I'm a cardiologist, electrophysiologist, and Chair of the Department of Medicine at the University of Wisconsin in Madison.

DR. NAFTEL: I'm David Naftel. I'm Professor of Surgery and Professor of Biostatistics in the Division of Cardiothoracic Surgery at the University of Alabama at Birmingham, and I'm the statistician on the Panel.

DR. SOMBERG: I'm John Somberg. I'm Professor of Medicine and Pharmacology at Rush University in Chicago.

DR. JEEVANANDAM: Val Jeevanandam. I'm a Professor of Surgery and Chief of Cardiac and Thoracic Surgery at the University of Chicago.

DR. KATO: Norman Kato, cardiothoracic surgery, in private practice, Los Angeles, California.

MS. PATRICK-LAKE: I'm Bray Patrick-Lake. I'm the President of the PFO Research Foundation, and I'm serving as the Patient Representative.

MR. BARRETT: Good morning, I'm Burke Barrett. I'm the Vice President of Regulatory and Clinical Affairs at CardioFocus, and I'm the Industry Rep on this Panel.

MR. DUBBS: Bob Dubbs, Consumer Rep, retired.

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DR. PAGE: Thank you very much.

It's now time to proceed to the Sponsor presentation from Edwards. I'd like to remind public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

The Sponsor will introduce the speakers. You have 75 minutes. We're going to be carefully watching the clock, and we've extended the time period for presentations, so we'll hold you to 75 minutes. Will the Sponsor step forward?

MS. AKIN: Mr. Chairman, members of the Committee, members of the Food and Drug Administration, good morning. My name is Jodi Akin. I'm the Vice President of Global Clinical Affairs for Edwards Lifesciences.

We're here today to discuss the risk/benefit of the Edwards SAPIEN Transcatheter Aortic Heart Valve for the treatment of patients with severe calcific aortic stenosis who are not candidates for conventional open heart valve replacement surgery. The specific indication seen here is identical to that proposed by the FDA and is supported by the results of the PARTNER trial, which we will discuss today.

In accordance to the American College of Cardiology and the American Heart Association guidelines for the diagnosis and treatment of valvular heart disease, aortic valve replacement surgery is a Class I indication

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for patients with symptomatic severe aortic stenosis, or AS. In the vast majority of adults with this disease, AVR is the only effective treatment.

There is no clear standard therapy for the inoperable patient. The guidelines outline non-definitive therapeutic options for patients who are inoperable due to severe co-morbid conditions or other technical reasons.

Balloon aortic valvuloplasty, or BAV, is a Class IIa indication as a bridge to surgery in hemodynamically compromised patients, a Class IIb indication for palliation of symptoms, or a Class III indication as an alternative to AVR. Limited medical therapies are available to control symptoms.

Despite wide acceptance that AVR is the gold standard for severe AS, studies show that in clinical practice at least 30 percent of patients with severe aortic stenosis do not undergo surgery for reasons including advanced age, left ventricular dysfunction, presence of prohibitive co-morbidities, or a patient's declining intervention.

The natural history of aortic stenosis before operative treatment was available was first depicted by Ross and Braunwald in 1968. In fact, survival analyses have demonstrated that the interval from the onset of symptoms to the time of death is approximately two years in patients with heart failure.

In the current era, with increased life expectancy and a more elderly population, still, in the absence of valve-restoring therapy options, the natural history for these patients remains unchanged. Importantly, a

consequence of this more elderly population is increased co-morbidities, rendering more of these patients at excessive risk for surgery.

Until the advent of transcatheter aortic valve replacement, or THV, patients who do not undergo surgical valve replacement have no effective long-term treatment option to prevent or delay their disease progression. A relatively high prevalence of the disease that exists today can be treated. So let's look at the estimates of inoperable patients.

Based on data from the 2009 healthcare utilization project, the estimated prevalence for severe aortic stenosis overall in the United States is approximately 360,000 procedures, and by echo criteria, 120,000 cases. Seventy-five thousand cases meeting the ACC/AHA Class I indication were performed in the year of the study, 40,000 of which were isolated surgical aortic valve procedures. The inoperable cohort is estimated to be approximately 20,000 cases per year, of which a smaller subset would benefit from restoration of aortic valve function. A subset of this cohort will be candidates for TAVR.

Because aortic valve replacement surgery is the gold standard and because there is poor long-term survival of BAV and standalone medical management, there has been interest in a nonsurgical option for these inoperable patients for many decades.

Edwards Lifesciences has been innovating valve therapy for more than 50 years. Our transcatheter program began in 1999, and we

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acquired the Cribier valve after its first successful implantation, which occurred in 2002.

Challenges in early experience with the antegrade approach led to technique refinement by Webb and colleagues in 2006, resulting in a retrograde approach employed today.

In the five-year period from 2006 to 2011, Edwards tested SAPIEN in more than 5500 patients in both open-label and randomized controlled trials. Based on these data, SAPIEN was first approved in Europe in 2007. Since 2007, SAPIEN has been approved in 40 countries within Europe, Asia, the Middle East, South America, and Canada. In 2010, the next generation SAPIEN XT was also approved in the European Union and subsequently in other regions.

U.S. regulatory requirements necessitate a non-inferiority trial between SAPIEN XT and SAPIEN prior to submission for approval of SAPIEN XT. We began enrolling patients in the PARTNER II non-inferiority trial earlier this year and plan to have sufficient data for U.S. approval by 2013.

To date, more than 15,000 implants worldwide have occurred, including 6,000 patients who have participated in phased clinical trials. Today we'll spend most of our time discussing the randomized clinical data from the PARTNER trial for the Edwards SAPIEN valve and delivery system. This trial studied the Edwards balloon-expandable valve, which consists of a stainless steel stent frame and three precisely matched bovine pericardial tissue

leaflets treated with the Edwards ThermaFix anti-calcification treatment and is available in sizes 23 and 26 millimeters.

The data from this study demonstrates a significant difference in favor of TAVR, including measures of all-cause mortality, repeat hospitalizations, valve performance, and quality of life.

While there was an increased risk for stroke and procedure-related adverse events such as bleeding and vascular complications, patients who received the SAPIEN valve had a substantial increase in survival compared to the standard of care.

With this information in mind, I would like to review our agenda and introduce our speakers for today's presentation.

Dr. Craig Smith, Chairman, Department of Surgery at Columbia University Medical Center, will review the PARTNER trial study design and conduct. Dr. Martin Leon, the Director of the Center for Interventional Vascular Therapy at Columbia University Medical Center, will present the PARTNER data. I'll return to present additional details on our global clinical experience and to discuss our U.S. postapproval study. And, finally, Larry Wood, Vice President of Transcatheter Valve Replacement, will review our experience with commercialization outside the United States and our plan for a disciplined U.S. commercial rollout, including site selection and training.

Drs. Smith and Leon were the co-principal investigators in the

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PARTNER trial. Neither own stock in Edwards Lifesciences, and neither have received financial remuneration for any aspect of their participation in the PARTNER trial or for their participation in today's meeting. Edwards has reimbursed them for out-of-pocket travel expenses.

At this time I would like to invite Dr. Smith to the lectern.

DR. SMITH: Thank you. Just as a bit of background in the design of the trial, at the top of this table you see several series summarizing the expected one-year survival for the series focused on high-risk surgery for aortic valve replacement. That will be the focus of a future Panel presentation, but it's there for your reference. At the bottom is a summary of several series exploring standard therapy, where you'll see that the range is from a high of 67 percent to a low of 44 percent lower in the series focusing on BAV.

So based on this information, if you'll look at TAVR from the feasibility trial revival in the middle, with a one-year survival of 76 percent, we might've expected a 10 to 30-percent gap between the two therapies. So that was the basis of our planning.

This trial had two individually powered cohorts. On the left, the high-risk surgical cohort -- as I said, you'll hear about that later -- which had two arms employing transfemoral and transapical techniques, separately randomized. You will only hear about transfemoral today, and you'll only hear about the right side of the slide, which is the 358 inoperable patients

randomized who received TAVR versus standard therapy, with a primary endpoint of all-cause mortality over the length of the trial, designed to demonstrate superiority.

These are the sites, 21 sites, where the trial was carried out. The large yellow circles are those who had experience with more than 20 patients.

And the next slide, if you subtract sites that had prior experience, you'll note that 14 of the sites in the trial had no prior experience with this device before entering the trial.

How do these sites become sites in this trial? Site selection was based on the presence of a heart team, first and foremost, consisting of representatives of cardiac surgery, clinical cardiology, interventional cardiology, echocardiography and anesthesiology, and more than just presence, it required the presence of a surgeon with substantial experience performing high-risk aortic valve surgery. The institution had to demonstrate infrastructure that was suitable for the procedure and the presence of a clinical research team capable of managing the data.

Training began with a didactic course followed by training in the preparation of the device and use of the device, hands-on simulation training. The clinical phase involved two proctored cases and two roll-in cases were permitted and were not included in the analysis.

Screening involved a clinical evaluation including echo, cath

with coronary angiography, and an assessment of vascular access by CTA. Each case was reviewed on a webcast done twice weekly, at which time the cohort was assigned and treatment strategies were discussed. Inoperability was determined by two surgeons, and every case had to be confirmed as inoperable by case review and the biweekly conference calls. Treatment was designed to occur within two weeks of randomization.

For the procedure itself, it was carried out in a sterile, hybrid operating environment with general anesthesia available and fixed imaging systems, transeptal echo. In the room itself, just prior to commencement of the procedure, the valve size and the delivery system appropriate to that size were confirmed by prespecified criteria, and the team roles and procedures were run through for consistency and efficiency.

This animation shows a guide wire passing up the femoral arterial system retrograde, around the aortic arch and across the valve. This will be followed by the balloon valvuloplasty, a balloon traveling up over the guide wire, around the arch and across the valve, and during a brief period of rapid ventricular pacing shown there, the balloon is inflated to pre-dilate the valve.

Now the device, the RetroFlex 3 device, is passed up over the guide wire, around the arch, positioning the balloon at the level of the valve. Again, a brief period of ventricular pacing. The valve is inflated in place. Once it appears satisfactory, the entire system is withdrawn. And the next

picture will show you a top view of the valve with the leaflets opening and closing.

A very important feature of this trial, of course, is how do we define what is an inoperable patient? And we acknowledge and we were faced with the fact that there is no validated instrument for the definition of inoperable. There are surgical risk scores, notably STS and EuroSCORE and others, that provide what we're calling a biomarker that relate procedural morbidity and mortality in sort of an analogous way to a patient who is inoperable. The risk scores, of course, were developed in operable patients.

So we anticipated and found that the STS scores would be somewhat bimodal. There would be a group with very high STS scores because of the presence of one or more common-enough risk elements that are in the algorithm and would produce a high score in aggregate. The other part of the distribution would be patients with a low STS score because of low prevalence, usually technical factors that are not part of the risk model, a good example being a severely calcified or porcelain aorta.

The risk model itself, just for your background, was developed from 67,000 patients over a four-year period, updated in 2007, employs 29 variables in the algorithm that calculate operative risk. The risk figure estimates 30-day mortality. So an STS risk of 10 predicts 10 percent perioperative mortality, 30-day mortality.

One example. Here is one with a low STS score, a 61-year-old

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male, severe aortic stenosis, radiation treatment for Hodgkin's lymphoma at age 19, which, as it often does, produces a severely calcified aorta. You can see the bright ring of calcium in the CT scan slices, a completely calcified aorta, technically inoperable, although the STS score was only 1.5 percent.

A second example, a 91-year-old male with hypertension, a previous coronary bypass, PCI, atrial fibrillation, renal insufficiency, COPD, diabetes, and so forth, all of the risk factors, parts of the algorithm, adding up to a risk score of 29 percent.

At the end of it all, the governing definition of inoperable was based on the judgment of experienced cardiac surgeons. Specifically, they had to feel that the risk of death or serious irreversible morbidity exceeded the probability of meaningful improvement. A surgeon had to ask himself before a TAVR, would I operate on this patient? And the answer had to be no.

We talk about ascertainment of endpoints and how they were adjudicated. In general, clinical assessments took place at seven days or at discharge, 30 days, 6 and 12 months, and then annually for five years. A sweep analysis by phone follow-up was carried out after the last patient enrolled reached one year.

Clinical endpoint adjudication was accomplished by a CEC composed of physicians with relevant expertise: two cardiac surgeons, a vascular surgeon, two clinical cardiologists, an interventional cardiologist, a

neurologist, using FDA and the Valve Academic Research Consortium, or VARC, consensus definitions primarily.

Eligibility criteria, first and foremost, meeting the definition of inoperable; also had to have severe aortic stenosis defined as an area of less than .8; a mean gradient greater than 40 or velocity greater than 4 m/s; had to be significantly symptomatic with an NYHA functional Class II or greater.

There were certain anatomic exclusion criteria, notably bicuspid or non-calcified valve; annulus too large or too small; iliofemoral anatomy precluding safe sheath insertion; severe LV dysfunction; untreated coronary disease that would require revascularization.

Also a list of anatomic features that would result in exclusion: a recent MI; a CVA or TIA within six months; certain cardiac procedures such as BAV or a bare metal stent within one month or a drug-eluting stent within six months; severe renal insufficiency defined as creatinine and defined as a creatinine greater than 3, or dialysis dependence or upper GI bleed within three months.

The study was prospective. Patients were consecutively enrolled. There was no opportunity for compassion or emergency use. There was a blinded randomization scheme that was essentially administered. There were random, undisclosed variable block sizes by site with no mechanism to reassign. The goal was to have 100 percent of the data monitored.

There are several endpoints and we'll start with the primary endpoint, which was freedom from death over the course of the trial, which was a superiority test, two-sided, 85 percent power to detect difference, with an alpha of .05.

There was a co-primary composite endpoint added early in the trial. This is a hierarchical composite of all-cause mortality and repeat hospitalization. A non-parametric method was employed, which has been described by Finkelstein and Schoenfeld. It uses multiple pair-wise comparisons, has 95 percent power -- greater than 95 percent power to detect a difference, an alpha of .05. The Hochberg method was used to adjust for multiple comparisons.

There were four prespecified secondary endpoints. First the composite endpoint, based on time from randomization to the first occurrence of a major event, and those four elements of the composite were death, all stroke, myocardial infarction, and renal failure. The second, third, and fourth were total hospital days through one year, the NYHA functional class at one year, and the six-minute walk test at one year. So those are the four prespecified secondary endpoints.

Next, I will go through several important protocol definitions that we want to -- to help you understand: rehospitalization, stroke, bleeding, and vascular complications.

Rehospitalization criteria required that rehospitalization

depend on symptoms of aortic stenosis, such as heart failure, angina, syncope, or rehospitalization for procedure-related complications.

Stroke was defined as a focal neurologic deficit lasting 24 hours or, if less than 24 hours, with imaging findings of acute infarction or hemorrhage. These events were further classified as ischemic or hemorrhagic.

Stroke ascertainment depended on an NIH Stroke Scale exam performed by a certified examiner at the times listed: baseline, 7 days, 30 days, 6 months, and so forth, and annually to 5 years. Imaging was used in the event of any positive findings, and the CEC adjudicated and classified these events based on source documents.

Major vascular complications included any thoracic aortic dissection, access-related vascular injury leading to either death or need for a significant transfusion defined as greater than three units, unplanned percutaneous or surgical intervention or irreversible end-organ damage. Also included is any non-cerebral distal embolization from a vascular source, requiring surgery or resulting in amputation or irreversible end-organ damage.

Major bleeding events were those causing death, prolonged hospitalization, meaning greater than 24 hours, or those requiring pericardiocentesis or open and/or endovascular procedures for repair and achievement of homeostasis, and those resulting in permanent disability or a

need for transfusion, more than three units within 24 hours.

In summary, I think there are several things that are important about this trial from a design perspective. Surgeons have enjoyed for many years complaining about watching interventional cardiologists act as the gatekeepers in the definition of treatment plans, and this trial and, I believe, going forward, there is a very disciplined surgeon-driven definition of inoperable employed. So if there's shift in that line, the surgeons here will be wearing it.

This also initiated, and I think will sustain, a unique collaboration between specialties that have expertise in the treatment of valve disease. This may be one of the principal contributions of this trial.

This was also a fairly nimble trial. A very thoughtful addition of secondary endpoints and refinement of definitions took place as necessary to help refine the data.

And I think, importantly, the endpoint here is not something soft and subject to manipulation like pain or perhaps NYHA class, and it's not something nebulous and debatable like patient prosthesis mismatch or something of that sort. This is mortality, the hardest endpoint we have. And I think that the results speak for themselves. And you will hear about the results from Dr. Leon.

So next is my colleague Dr. Martin Leon.

DR. LEON: Well, I must say that I've had a very interesting

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experience working with my surgical gatekeeper colleagues on this clinical trial, and I want to reiterate that this really has been a collaborative effort. And on behalf of Craig, the co-principal investigator, the executive committee of the PARTNER trial, and the many very dedicated investigators, it's really a privilege to present the results of the PARTNER trial in the inoperable patient cohort.

First, I need to get you to understand the kinds of patients that were enrolled in this study, so we'll begin with baseline patient characteristics. From the standpoint of demographics, the mean age of these patients was 83 years. Twenty percent were over the age of 90 at the point of enrollment. Unusual for clinical trials that I have participated in, the majority of these patients were actually women, close to 54 percent. The mean STS score was between 11.2 and 11.9.

To put this in some perspective, the upper decile of risk within the STS database would be an STS score of eight or above, so this is somewhere above the top five percent of the risk strata in the STS database.

These were severely symptomatic patients, New York Heart Association Class III or IV in 92 and 94 percent of patients, respectively, treated with either TAVR or standard therapy.

The baseline characteristics were generally balanced, but recognize that this is a somewhat small randomized trial and there were some differences in baseline characteristics. When those differences were

statistically significant, we denoted that by highlighting the characteristic in yellow.

First let me speak about vasculopathy. This was a highly vasculopathic group of patients with a high frequency of coronary, cerebrovascular, and peripheral vascular disease. As can be shown here, most of the patients had coronary disease, a significant minority previous myocardial infarction, previous bypass surgery, or previous PCI. Approximately 20 percent of patients had previous balloon aortic valvuloplasty before entering the study, and about 30 percent had both cerebrovascular and peripheral vascular disease.

There were multiple other co-morbidities, including any evidence of chronic obstructive pulmonary disease in 41 and 53 percent of patients treated with either TAVR or standard therapy; elevated creatinine; atrial fibrillation was especially common in 33 and 49 percent of patients, respectively, in patients treated with TAVR or standard therapy; almost 20 percent had permanent pacemakers prior to enrollment; and over 40 percent had pulmonary hypertension.

In addition, there were many other inoperable features that are generally not well captured in a conventional STS risk algorithm, such as oxygen-dependent COPD in more than 20 percent of patients; the subjective determination of frailty in about 20 percent of patients; as was shown in Craig's example, severely calcified or porcelain aorta in 19 percent of patients

treated with TAVR, and 11 percent with standard therapy; not infrequent, patients with either chest wall radiation or chest wall deformity; and a minority of patients with severe liver disease. So this was a highly co-morbid population of patients that were categorized as inoperable.

The baseline echocardiographic characteristics are shown here. The mean aortic valve area was 0.6 in both groups, the mean aortic valve gradient 45 and 43 millimeters of mercury, and the mean ejection fraction was above 50 percent in both groups. About 20 percent of patients had either moderate or severe mitral regurgitation prior to study entry.

Before we discuss the results and discuss the primary and secondary endpoints, we should spend a few moments reviewing what treatments were received by these two cohorts. Let's begin with the standard therapy patients.

As indicated earlier by Jodi Akin and the recent guidelines, there really is no standard homogeneous therapy for so-called inoperable patients with aortic stenosis. The guidelines indicate that medical management can be appropriate in many patients, and balloon aortic valvuloplasty, either for symptom palliation or as a bridge to AVR, would be reasonable in other patients. And I think this study did reflect that heterogeneity of treatments in the standard therapy group.

In the first 30 days, medical management only was provided in 31 percent of patients, 65 percent had balloon aortic valvuloplasty, an

additional three patients had BAV, then felt better and were bridged to AVR, and there were three additional patients, even though they were considered inoperable, that somehow received either AVR or an LV to Ao conduit.

After 30 days, there were an additional 21 patients, or 11.7 percent, that got a first-time BAV, 37 patients had repeat BAV, and several patients had three and even four BAVs during the course of the trial. There were four patients that received TAVR outside the United States, outside of this study. All of these patients had previous BAV. And an additional 12 patients who received either AVR or LV to Ao conduits, and 9 of those 12 had prior BAV.

So to summarize, sole medical management only was received in 17.9 percent of patients, the total number of patients who received BAV at any point in time during the study was 79 percent, and as a subset there were additional patients who received either surgical or TAVR intervention, 12.3 percent, usually after a prior BAV with sufficient clinical improvement to bridge to a more definitive procedure.

The treatments in the TAVR patients are listed here. Of 179 patients, 170 received an implanted valve, or 95 percent. In the nine patients in which a valve was not implanted, two had died prior to TAVR after randomization. The median time to treatment after randomization was six days. In two patients the transesophageal echo during the procedure indicated an annulus size too large for the 23 and 26-millimeter valves

available, and in five patients there was intra-procedure access failure for the five. The large sheaths could not be advanced through the iliofemoral system, and in one the device could not cross the aortic valve. Of the seven patients who were alive without an implant, six received BAV and in one medical management was applied.

As Craig said, the primary endpoint was a hard endpoint of all-cause mortality during the course of the trial. The primary endpoint of all-cause mortality is shown on this slide. I'd like to first focus on the standard therapy patients in yellow.

I think you can see clearly that over the course of this trial, there was an extremely high, higher than anticipated, mortality in the standard therapy patients, with more than half the patients dying in the first year, despite best efforts with either medical therapy or balloon aortic valvuloplasty to palliate and treat these patients. And it's important to note that there was not significant differences in the outcomes in the subsets of patients that had either BAV or medical therapy, other than a slight early improvement in mortality in the BAV subset.

When we look at TAVR you see, after the first month, that this actuarial event curve begins to diverge and continuously diverges during the course of the clinical trial, such that there is an overall 49-percent improvement in all-cause mortality during the course of the trial, with a log rank p-value of less than .001.

Another way to look at this is to look at the Kaplan-Meier estimates of 12-month mortality shown here, 50.7 percent for standard therapy versus 30.7 percent for TAVR; that delta is 20 percent at one year, which translates into a number needed to treat to save a life in the PARTNER trial of five patients during the first year.

I'd like to focus on the early outcomes and to telescope in on the early portion of this actuarial event curve. The procedural mortality is perhaps best denoted by the 30-day outcomes, and when we look at the 30-day outcomes of all-cause mortality for TAVR, 5 percent versus standard therapy, 2.8 percent, a non-significant but a numerical difference. These results of a five-percent 30-day mortality were certainly as good as and probably better than most reported results in the TAVR literature and, I think, are a testament to both the training and the quality of sites participating in the study.

These curves converge at day 39 and then begin to diverge, as we had previously discussed. So the initial morbidity of the procedure was now overwhelmed by the mortality benefit soon after the procedure, shortly after a month.

The co-primary endpoint, as Craig mentioned, was a hierarchical analysis of a composite of mortality or repeat hospitalization. This was a non-parametric methodology using a multiple pair-wise comparison but is sufficiently complex, that I won't bore you with the details,

sufficient to say that the p-value of this analysis was less than .001.

The more traditional or familiar way to represent composite endpoints are shown here on the Kaplan-Meier event curves, and you can again see that there is a dramatic divergence of these two curves, suggesting a 54-percent reduction in the composite endpoint of mortality or repeat hospitalization in this non-hierarchical analysis; highly statistically significant. Now, the delta is greater than 29 percent at one year, with the number needed to treat to prevent either death or repeat hospitalization of 3.4 patients.

We recognize that there were some numeric and even statistically significant differences in baseline characteristics. Therefore, we did a post hoc effect analysis for baseline imbalances, looking at the primary endpoint, calculating risk ratios and looking at interactions.

You'll see in the next two slides eight subgroups of patients where there were small and sometimes significant differences in baseline characteristics, but there were no significant differences in the effect on all-cause mortality, and the p interaction values did not approach significance in the subgroups of patients with atrial fibrillation, COPD, calcified aortas, the presence of coronary disease or prior bypass surgery, elevated creatinine, prior MI, or frailty.

As Craig indicated, there were four prespecified protocol-defined secondary endpoints: time from randomization to first occurrence of

death, all stroke, MI, or renal failure; total hospital days through the first year; New York Heart Association functional class at one year; and six-minute walk tests.

This is the time to first occurrence of death, stroke, MI, or renal failure. It takes a little bit longer for these curves to diverge, but there's still a 39-percent difference favoring TAVR, highly statistically significant, with a one-year Kaplan-Meier estimate delta of 15.5 percent.

Interestingly and paradoxically, the total hospital days were actually higher in the TAVR patients than in the standard therapy patients, clearly related to the fact that these patients had an initial procedure with a hospitalization that usually lasted anywhere from a week to 10 days.

Perhaps a more relevant analysis of therapy benefit is to look at days alive out of hospital during the first year, and in this analysis there was a highly statistically significant difference favoring TAVR, with 64 additional days in the first year the patients were alive and out of hospital.

In addition, looking at repeat hospitalization is also meaningful, and there was a twofold higher frequency of CEC-adjudicated repeat hospitalization in the standard therapy patients.

Although NYHA class may be a relatively crude estimate of therapy benefit, we've already indicated that these were severely symptomatic patients, with more than 90 percent in Functional Class III or IV.

It's important to recognize that in the first 30 days there's

already a dramatic difference in the TAVR patients by 30 days. The frequency of Class III or IV symptoms is now reduced to 32 percent. It's still 72 percent in the standard therapy patients, perhaps somewhat affected by the high frequency of early balloon aortic valvuloplasty, but this difference was highly significant. It improves even further by a year with only 25 percent of patients having severe symptoms, and 63 percent in the standard therapy arm.

We attempted to do six-minute walk tests in all patients, but this analysis is limited. It's limited by two factors. The first, because of the disparate survival, we have unequal numbers of patients in each group, and second, this is an elderly, frail, severely symptomatic population, so to perform the six-minute walk tests was not simple and there was much missing data.

So we felt the best way to represent this data is to show you the paired data available in all patients. So in this paired analysis there is approximately a 40-meter improvement in the six-minute walk tests in the TAVR patients when you look at baseline compared to one-year data, which was highly significant, and no change in the standard therapy patients, despite the fact that, as noted, almost 80 percent had received balloon aortic valvuloplasty.

Another way to look at these data is to look at the change from baseline at 30 days and one year. Again looking at paired data, you see highly

significant differences favoring TAVR, which are present very early, in the first 30 days, and increased slightly by one year, but no change in the standard therapy patients.

We were fortunate to have an independent subanalysis looking at quality of life by a dedicated laboratory that was directed by David Cohn and Matt Reynolds. This quality of life evaluation, we felt, was very important to capture the clinical therapy benefit associated with a new therapy.

The instruments used were the KCCQ questionnaire, which is the Kansas City Cardiomyopathy Questionnaire, which is more heart failure specific; the SF-12, looking at physical and mental health changes, and the EuroQoL instrument, which is more generic instrument for assessment of utilities for calculation of quality of life years.

For those not familiar with the KCCQ instrument, it involves 23 items that measure four clinically relevant domains of health status, including symptoms, quality of life, physical or social limitation. The individual scales are combined. Then a global summary scale is derived, the so-called summary score from 0 to 100, with higher being better; a minimally clinically important difference is five points.

We're showing you the overall summary score in all survivors out to one year. Again, by 30 days, there is a very significant difference with a delta of 13.9. It's interesting that in the standard therapy patients there's

also an improvement probably related to the balloon aortic valvuloplasties in many of these patients early. But the standard therapy patients flatten and decline. There's a further increase in the TAVR patients, such that the delta at one year is 24.5, a highly statistically significant difference in this independent and validated tool of quality of life.

If you look at all of the KCCQ subscales, we see consistency in the benefit, looking at social limitation, the overall quality of life, symptom score, and physical limitations.

Another way to look at this is a binary analysis incorporating survival and the quality of life, looking at patients who are both alive and have a KCCQ score which improved greater than 20 points, which is a dramatic improvement versus baseline. You see already, at 30 days, there's more than a twofold higher frequency of both alive and greatly improved patients, and that widens even further at a year, with more than a fourfold greater frequency of patients being alive and clinically benefited. These differences again were highly significant.

We were also fortunate to have an excellent echocardiographic core laboratory at Duke University that was led by Pam Douglas. We did careful echo assessments at baseline, post-discharge, at one month, six months, one year, and we'll do them annually for at least the first five years after enrollment.

This is a summary of the valve hemodynamic data looking at

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mean gradients at 30 days, 1 year, and even have now 50 patients that are out to two years that have been studied in the core laboratory. As you can see, there's a slight reduction in gradients in the standard therapy patients, again, likely associated with the balloon aortic valvuloplasty, but a rapid return to baseline, whereas in the TAVR patients there's a dramatic immediate reduction in gradients to slightly more than 10, and that persists over the course of the study. These differences, of course, were highly statistically significant.

And the reverse of this, which is the effect of orifice area calculations, again show an increase from baseline of 0.6 to 1.5, 1.6, which persists during the course of the two-year evaluation period shown on these slides.

From previous experiences in the feasibility study and from the worldwide literature, we were prepared to understand that there would be some degree of paravalvular regurgitation with this device. As you can understand, the transcatheter implantation of a valve with a support frame to achieve circumferential flush apposition with a heavily calcified and deformed aortic annulus is difficult, so we expected to see some paravalvular regurgitation. On this slide we've summarized the PVL, or the paravalvular leak, categorized as none or trace, mild, moderate or severe.

Another way to look at this is zero, one, two, three, and four plus by other conventional ways to look at severity of AR. You can see that

mild paravalvular leak is common. Moderate and severe paravalvular leak is uncommon, 13 percent and 12 percent at 30 days and 1 year.

We did a shift analysis to see if patients changed from the standpoint of paravalvular leak or progressed during the course of the study, looking at all patients who had received TAVR with both 30-day and 1-year data. As you can see on this slide, 66 percent of the patients were unchanged. This is echo core lab data. There were a total of 12 patients where there was a one-grade progression, and a total of 17 patients where there was a one-grade improvement, which was 20 percent.

To further put this in perspective, severe aortic stenosis is really mixed valvular heart disease. Most of these patients have some degree of central aortic regurgitation, and probably most relevant is the total volume burden or the total aortic regurgitation in these patients.

As you can see, at baseline, between 15 and 20 percent of patients in both groups have moderate or severe aortic regurgitation, usually moderate, but very infrequently severe. By 30 days, in the TAVR patients, most of the aortic regurgitation is paravalvular, but you see a persistence of the central aortic regurgitation in the standard therapy patients. This continues at one year. So the total aortic regurgitation in these two groups are about the same, the difference being, in the TAVR patients, it is paravalvular; in the standard therapy patients it is central or transvalvular.

We also looked at ventricular hemodynamics. Perhaps the

most important index was to look at left ventricular mass regression. In this slide we show a percent change from baseline at 30 days, 6 months, and 1 year, comparing the two therapies. And I think you can see clearly that there is a progressive and a dramatic reduction in LV mass index over time, suggesting favorable ventricular hemodynamics and remodeling.

It's very important to discuss outcomes of special interests, which is a euphemism for complications. And the four that I want to focus on are neurologic events, vascular complications, bleeding events, and arrhythmias.

Many times when we talk about complications, we present as-treated analyses feeling that it's most relevant to really reflect on the complications associated with the treatment. That was difficult in this trial because the as-treated and intend-to-treat populations were quite different for the following reason.

Clearly, it's easy to define intention to treat from the point of randomization, but as treated was defined differently for each group. In the TAVR patients it was from the point of beginning the procedure, which means the patient entering the hybrid OR or catheterization suite. But in the standard therapy, since they did not receive a designated procedure, as treated was from the time of randomization. This imbalance or phenomenon made it difficult to present the as-treated patients, so we're showing you the analysis for intention to treat, but of course the as-treated data are available

upon request.

Let's begin with strokes, which has been an area of focus, I know, in the FDA briefing documents and elsewhere. Great pains were made to make accurate diagnosis of neurologic events and their etiology. The CEC classified neurologic events as either TIAs or strokes. Causes were assessed as either ischemic hemorrhagic or unknown. We tried to conform to the new VARC and FDA consensus definitions.

But during the trial we realized we need greater sensitivity and greater refinement of the stroke analysis, so efforts were made within the CEC and with the neurologic consultants, the neurology consultants participating within the CEC, to do post hoc severity ranking of stroke between minor or major, based upon a modified Rankin score of two or greater.

This is modified Rankin scale, and major stroke was really defined as a modified Rankin scale of two or more. And if you read through, two is a slight disability, able to look after your own affairs without assistance but unable to carry out all previous activities. In the overall stroke literature, this is a very conservative definition of major stroke, and in all patients where post hoc analysis could not be applied, the patients were assumed to have a major stroke.

These are the data of all neurologic events at 30 days and 1 year. As you can see, regardless of what subgroup you look at, stroke or

TIA, all events, stroke, major or minor, there is a higher frequency at 30 days and 1 year in the TAVR than the standard therapy patients, which was statistically significant. If we look at all neurologic events at 30 days, 7.3 percent versus 1.7 percent. If we look at 1 year, 11.2 versus 4.5 percent. The increment from 30 days to 1 year is about the same, so the major difference is in the first 30 days.

If we look at the post hoc analysis of stroke severity, we can see that about 75 percent of these events were classified as major stroke, with the same differences persisting.

The timing of neurologic events in the ITT analysis is shown here, showing the disparity of a higher stroke frequency occurring in the first 30 days. But it's more interesting if you actually look at the as-treated population, where you don't have the time offset from randomization to treatment, which gives you a realistic picture as to timing, and clearly the vast majority of the difference is in the first five days, with very little difference after five days, in stroke frequency.

It's also interesting to look at the kinds of strokes. In the 20 TAVR patients with neurologic events in the first year, 19 strokes and 1 TIA, and those patients with events less than 30 days, 12 of 13 were ischemic, presumably embolic. After 30 days, however, four of six were hemorrhagic. The standard therapy patients, of the eight neurologic events, seven of eight were ischemic.

However, if we add major stroke to the mortality endpoint and we look at the actuarial event curve, you can see that these curves now diverge a little bit later, at around six months, accounting for the early neurologic events, but still continuously diverge over the course of the trial, with a 44-percent improvement, highly significant, and the delta falls to 17.8, with a number needed to treat of 5.6 at a year.

Let's take worst-case scenario, all neurologic events. We see the same phenomenon, highly significant, a 39-percent difference. The delta now falls to 15.5 percent over the first year.

Other important complications include major vascular complications, 16.8 percent in the first 30 days, with not much change between 30 days and a year; in TAVR much more obviously than standard therapy. We believe that the large sheath size and case selection factors and training may have had an impact on this. We think there are things that could be done to improve this, but it's important to note.

There was a higher frequency of bleeding events as well, usually in accordance with vascular complications, certainly in the first 30 days. But interestingly, an increment beyond 30 days, it was even higher in the standard therapy patients, and in looking at the individual case reports and narratives, a high frequency of out-of-hospital GI bleeds, particularly in the standard therapy patients.

We're very sensitive to these complications. On this table

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we've outlined major stroke, major vascular and major bleeding complications to show you how these patients did from the standpoint of mortality at 30 days and 1 year. Clearly, if you had a major stroke, there was a fourfold higher frequency in mortality at 30 days; about a twofold higher frequency if you had either major vascular or a major bleeding event.

By one year again you can see the mortality is almost 50 percent in those patients who had a major stroke, a little bit higher than the control population, with either a major vascular or a bleeding event, but the greatest impact certainly is early for the vascular and bleeding event complications.

Arrhythmias were infrequent. New atrial fibrillation occurred infrequently in both cohorts. Interestingly, new pacemakers were also infrequent, 3.4 percent in the first 30 days with TAVR versus 5 percent with standard therapy, a non-significant difference and that non-significant difference persists out to one year. There were two episodes of endocarditis in the TAVR patients and one in the standard therapy patients.

So to summarize, and I'd like to summarize by recapitulating, by showing again four result slides. First, this slide, I think, needs to be savored because in the history of cardiovascular medicine, it is rare to find a randomized trial comparing an existing therapy for an important disease versus a new therapy that demonstrates this magnitude of clinical benefit: an all-cause mortality difference of 20 percent in the first year, with only five

patients needing to be treated to save a life.

Second, we are very sensitive to the complications, and we're certainly sensitive to the concerns about stroke, vascular and bleeding events. But even if we add these complications to mortality, as shown on this slide, that one-year delta only drops from 20 percent to 18 percent. Clearly the benefits outweigh the risks.

Third, this device performs as we had expected from the standpoint of valve hemodynamics: an immediate, dramatic, and persistent improvement in valve areas and reduction in mean gradients, thus far, out to two years.

And, finally, you have to ask the patients, how do you feel? It's not just a matter of living longer. This slide clearly shows an almost immediate, dramatic, and persistent improvement in quality of life by an independent core laboratory. When one of my colleagues, a clinical trialist from Harvard, looked at these data, he said it's clear to him that TAVR not only adds years to life but adds life to years.

So, in summary, we've tried to demonstrate that with this new procedure, that there are benefits that outweigh the risk, and we're hopeful that during the course of the many presentations today and the many questions that will fill this day, that at the end of all of this, that on behalf of our patients and the PARTNER investigators, that we in this country might have access with regulatory approval of this technology for these inoperable

patients with severe aortic stenosis. Thank you.

MS. AKIN: Thank you, Dr. Leon.

Now, I'd like to take the opportunity to review our key data from our global SAPIEN experience and then I'll review our U.S. postapproval study plan.

Over the past decade, Edwards SAPIEN THV has undergone comprehensive clinical evaluation from first in man through postmarket surveillance. Of these studies, REVIVE, REVIVAL, PARTNER Europe, TRAVERCE, and the PARTNER trial incorporated core labs for echocardiography, comprehensive data monitoring, and independent endpoint adjudication. These trials are in various stages of protocolized, prespecified five-year follow-up. One trial has now consented to 10 years.

All studies, including the postmarket SOURCE registry, employed the heart team approach, from patient selection through procedure management. Excluding the transapical approach evaluated in some studies, more than 2800 patients with the transfemoral approach alone have been formally evaluated.

Additionally, three independent national registry initiatives have been endeavored and widely reported, totaling nearly 1800 cases. Some of these cases are represented in the Edwards studies; however, the outcomes were independently analyzed.

Looking at 30-day mortality over the time course of the phased

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studies, a trend of improvement suggests that learnings from the early experiences have informed the next, particularly from the critical perspectives of patient selection, procedure, and complications management, and the development of best practices.

Contemporary learnings from the European studies, including the SOURCE registry, have been passed forward into the PARTNER trial, which may have contributed to the efficient learning curve observed in PARTNER.

The SAPIEN THV global clinical experience is a mix of high-risk surgical and inoperable patients, treated both transfemorally and transapically, as calculated by a surgical risk model known as the logistic EuroSCORE. This risk model uses co-morbidities similar to the STS predictive risk model. The label for use outside the United States indicates for a minimum EuroSCORE of 20.

This table demonstrates remarkably similar patient risk factors such as age, predicted risk, New York Heart symptom Class III or greater, valve hemodynamics, and incidence of cardiovascular disease. Across studies and in independent country registries, we see that the 30-day survival is consistent.

Stroke outcomes have consistently been reported within a range of three to five percent outside of the PARTNER trial. The higher reported rate in PARTNER may be accounted for due to the strict definitions, ascertainment and adjudication.

Vascular complications significantly improved after the early period, and it remained an outcome of concern leading to delivery system improvements and focus on procedure management.

Permanent pacemaker rates range from 1.8 to 8.5, with noted variability based on site practices where both self-expandable and balloon-expandable TAVR devices are available.

Results of the feasibility studies led to postapproval best practices globally and were validated by the SOURCE registry results, which confirmed the effectiveness of training.

In the Edwards studies we see that one-year survival in the preapproval period is relatively consistent, and in fact, the postapproval SOURCE registry has reported a higher survival rate of 80.1 percent at one year. This suggests disciplined commercialization and generalizability of learnings.

Two-year echocardiographic follow-up in REVIVE, REVIVAL, and PARTNER Europe indicate good valve performance with sustained hemodynamic function with stable post-TAVR effective orifice areas and mean gradients.

As previously mentioned, REVIVE, REVIVAL, and PARTNER Europe are well into their planned five-year follow-up, with a significant number of patients followed to three years. The continuous hazard after one year is largely reflective of age and co-morbidities rather than valve-related

cardiovascular deaths.

The next generation SAPIEN XT with NovaFlex and Ascendra 2 delivery systems are approved outside the United States, following two feasibility studies, PREVAIL TF and PREVAIL TA, each with more than 150 patients.

Additionally, Edwards initiated a voluntary postmarket registry, SOURCE XT, currently enrolling in nearly 100 participating centers in Europe and Canada, and more than 1300 patients enrolled to date. SOURCE XT has the added feature of endpoint adjudication in accordance with the new valve academic consortium and is monitored.

The PARTNER II trial was initiated in the United States in March of this year. The PARTNER II trial design is of similar nature to the PARTNER trial, with two individually powered cohorts evaluating SAPIEN XT for both operable and inoperable, symptomatic, severe aortic stenosis patients. The inoperable cohort is a non-inferiority trial comparing SAPIEN to SAPIEN XT, with a sample size of 500 patients.

Approval for an amendment to include the operable cohort in intermediate-risk patients, as well as a registry for the transapical approach in the inoperable patient without femoral access, is anticipated soon.

In summary, the Edwards global clinical program demonstrates responsible commitment to evaluation of our technology evolution from first in man through each generation. The effectiveness, safety, and durability of

SAPIEN has been demonstrated in more than 5500 patients in Edwards studies, as well as from independent registries tracking more than 1700 patients. Three-year effectiveness, safety, and performance data also support the PARTNER trial results. Outcomes continue to improve with experience and U.S. commercialization will incorporate lessons from these large data series.

I would now like to briefly review our U.S. postapproval proposal.

As previously mentioned, longer-term results from U.S. and global clinical studies are emerging. Postapproval studies should take into consideration the amount of prior clinical experience with the device, the age and risk profile of the patient population, the existing commitment to long-term follow-up, and the requested indication.

The aim of our postapproval study is to confirm the long-term safety, effectiveness, durability, adherence to indication, and the effectiveness of the SAPIEN valve training program. In TAVR setting, we also have the opportunity to partner with professional societies to develop and implement a longitudinal national registry to evaluate aortic valve therapies.

The FDA has requested that we extend the scope of the PARTNER trial to include five-year quality of life measurements. In addition, FDA's requested a prospective, consecutive enrollment in a random, representative sample of sites who did not participate in the PARTNER trial,

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based on hypothesis-driven endpoints with both short and long-term outcomes, which I will review in more detail in a few minutes.

Edwards has already agreed to continue the PARTNER study for a total of five years. We will follow both the 179 randomized patients and all inoperable continued access patients, bringing the total to 425 patients. We will perform annual clinical and echo follow-up for five years, with a continuation of the echo core lab, DSMB and CEC.

Given the dramatic benefit at one year, we do not believe that tracking QOL measures for an additional four years will provide important incremental value.

The second study requested by the FDA is a hypothesis-driven, non-inferiority design with prespecified individually powered endpoints, including all neurologic events, major vascular events, major bleeding events, learning curve assessment, valve durability to five years, and again quality of life to five years in the postapproval population.

This trial design would necessitate an infrastructure similar to the PARTNER trial, which we estimate would require enrolling more than another 1,000 patients, considering the vast database on the SAPIEN valve and the fact that we are already enrolling patients to a trial with our new SAPIEN XT valve and a proposed design that would study neural events in both inoperable and operable patient populations. As such, the postapproval study would be duplicative of both the PARTNER pivotal and the PARTNER II

trial.

We have proposed continuing the PARTNER I study, as previously mentioned, and having a second postapproval study which would be prospective, consecutive enrollment in a random, representative sample of commercial sites who did not participate in the PARTNER trial. We would enroll up to 750 patients and monitor procedure 30 days and annual outcomes to five years. Our plan would be to transition this study to a national aortic stenosis outcome registry conducted by the professional society.

In selecting sites for a postapproval study, Edwards will ensure that sites are capable and committed to collect data and report clinical outcomes by participating in a national registry or other comprehensive cardiovascular databases for all TAVR patients.

In closing, Edwards has demonstrated leadership and partnership with professional societies to conduct clinical trials that drive evidence-based training, product and procedure development, and responsible commercialization in TAVR. We are committed to maintaining this standard as we launch TAVR for the inoperable patient in the United States. Thank you for your time and attention.

Larry Wood will now review our commercialization and training plans.

DR. PAGE: Thank you very much. I do want to remind you of

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the time check. You have about seven minutes left out of your 75.

MR. WOOD: I'll do my best to be right on time.

DR. PAGE: Thank you.

MR. WOOD: My name is Larry Wood, and I'm the corporate vice president responsible for the transcatheter valve program for Edwards Lifesciences.

The Edwards SAPIEN valve was first commercialized in late 2007. Globally, there are about 400 heart centers that have implanted more than 15,000 Edwards transcatheter valves. Each of the 400 heart centers has completed our Edwards training program and our focus has and continues to be on ensuring excellent patient outcomes.

The key to our commercialization effort is our commitment to training. In every center that we have trained, we have focused on a heart team comprised of both interventional cardiologists as well as cardiac surgeons. We declined to commercialize in centers where cardiac surgery support was not available.

The Edwards THV training program is multifaceted. It includes didactic, simulation, proctoring, and ongoing support.

Prior to training, once a site is selected, we have an initial meeting at the center to review the heart team requirements. They are then provided with the training manual, along with specific radiologic and echo training videos. Lastly, the site begins the patient screening process and an

eLearning test.

After pretraining, the site attends a formal two-day training at one of our training centers. The first day of the training focuses on the heart team, patient screening and operative assessment, along with echo and vascular screening. The site is also expected to present two screening cases for review. The cases brought by the site to training are important, as it transfers the learning of screening to real-life examples. We also cover step-by-step case management and the decision-making process.

Day two focuses on potential complications. We spend extensive time on complications, as early detection and proper management are critical to a successful TAVR program. We then move to a hands-on session with device demonstrations where we explain not only the function but the design intent of the system. Device preparation and the handling are also explained. Lastly, the team proceeds to simulation training.

Following training there's a case library available, a complications refresher course, and training updates are also provided.

Case simulation is a key part of our program. The simulators are custom for the Edwards SAPIEN program and allow the operator to practice the procedural steps. The system is very sophisticated and captures critical metrics such as contrast usage and trains the site on terminology specific to the procedure.

On the next slide I will show a short video clip of the SAPIEN

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valve being deployed on the simulator.

(Video played.)

On the next slide we'll actually show an actual SAPIEN deployment in a person.

(Video played.)

You can see the similarities of the two videos, and it shows the attention to detail and the sophistication of the simulators.

After the two-day training course, the heart team is ready to perform their first cases and moves to what we call the proctor phase. We proctor a site until the proctor and the Edwards field clinical specialist determine the site is ready to be proctor-independent. A site is proctored for a minimum of two cases, but the average number of cases has been five.

After the proctoring phase is complete, the heart team is still supported by the Edwards field clinical specialist. The clinical specialist is available and can arrange a proctor if needed, and they are there until deemed ready for complete independence, but not less than 20 cases after the proctoring phase.

The Edwards field clinical specialists are primarily trained cath lab technicians or certified physician assistants. They provide device preparation, training, and support, training updates, and they arrange proctor assistance or screening support for complex cases, and they ultimately decide when the site is ready for full independence. Many of our field clinical

specialists were hired from our clinical group that supported the PARTNER trial, as well as trained personnel from the PARTNER sites themselves, and they bring welcomed extensive experience with the Edwards SAPIEN valve.

After a site is fully independent, the field clinical specialist will still attend cases periodically. Additionally, we have 24/7 tech support and provide continuing education and training through a web portal.

The training program has been defined and developed over the last four years. We have trained over 1600 physicians on patient selection and device use worldwide. We have hosted over 1500 proctored cases and we've supported over 8,000 clinical cases. Procedure outcomes have been maintained and tracked in our SOURCE registry.

Sites are vetted and selected through a detailed process. Factors include having a dedicated heart team, proper infrastructure, and support of administration to start a TAVR program.

We have developed an application so that during each site visit, all of the key elements are captured for the site. This includes high-level issues such as the presence of a heart team, but we also look at more specific examples such as PCI volume, AVR volume, dedicated staff, presence of a valve clinic and facilities. Based on our experience in both the PARTNER trial and commercial sites in Europe, we've been able to refine site selection and better predict what sites will develop a successful TAVR program.

Edwards plans for a very disciplined roll-out of this technology.

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While there are over 2,000 interventional centers and 1200 cardiac surgery programs, we expect to train between 150 and 250 centers in the first year of commercialization. The pace will be dictated based on maintaining high procedural outcomes. Additionally, the heart teams will be trained to document the patient's inoperable status in the patient record.

In closing, the Edwards SAPIEN valve has been shown to have a significant mortality benefit compared to best medical therapy. It's also been shown to significantly improve quality of life, and even when considering major complications, the benefit of TAVR clearly outweighs the risks.

Thank you for your time and attention, and we look forward to a meaningful conversation with the Panel. Thank you.

DR. PAGE: Thank you very much. I want to compliment the Sponsor and its representatives for putting together a very complete presentation and perfectly on time.

At this point I can ask the Panel for any brief clarifying questions of the Sponsor. Please remember that we will have opportunities to ask the Sponsor questions during Panel deliberations in the afternoon as well.

Any questions from the Panel now? Dr. Good.

DR. GOOD: Thank you very much. Thank you for a thorough presentation.

I have a question for Dr. Smith. He had indicated that the NIH

Stroke Scale was performed on patients with stroke, but I didn't see any of that information presented in your presentation. Would you comment on that?

UNIDENTIFIED SPEAKER: Turn on your microphone, please.

DR. SMITH: While it was performed, I don't think we summarized all the baseline stroke scale recordings. But do we know? Is there someone that has that? One of the neuro slides?

MS. AKIN: We can clarify that for you.

DR. PAGE: If you have data you could put together after the lunch break.

DR. SMITH: Sure.

DR. PAGE: Shall we plan on that?

MS. AKIN: Yes.

DR. PAGE: Thanks.

DR. GOOD: And one follow-up question to that. So the only measure of stroke severity was the post hoc modified Rankin Scale; is that correct?

DR. SMITH: Correct.

DR. GOOD: Uh-huh, okay.

DR. ZUCKERMAN: So, Dr. Good, they'll be working during lunch. Can you be a little bit more specific as to what data you would like to see?

DR. GOOD: Well, you know, first of all, it's quite possible that a number of minor strokes were missed because you're having some studies of neuroimaging pre and post this valve, which have suggested that subclinical strokes can occur as well, which, of course, you wouldn't be able to pick up, which is of some concern but not a direct question to you.

But I'm concerned about the severity of the strokes and whether you have any other measure other than a post hoc analysis of the modified Rankin, and I wonder if you could comment on the validity of a post hoc modified Rankin as well, as a valid measure of severity. And if there is any information on other standard stroke severity scores like the NIH Stroke Scale, that'd be great if you could present them.

DR. LEON: Let me just clarify. I did not want to give the impression that the only assessment of these patients was a post hoc Rankin score. Anyone who had any evidence of neurologic change in NIH Stroke Scale, that jettisoned the phenomenon of neurology consultation, neuroimaging, and close follow-up. That close follow-up included repetitive subsequent NIH Stroke Scales. But the assessment of the clinical significance of these strokes was used, not based on that early assessment, but the post hoc from SOURCE narratives and from SOURCE documents, as adjudicated by the CEC, imputing a modified Rankin score.

MS. AKIN: A couple of quick comments. We do have the NIH, so we can show that after the lunch break. We also looked at potential

impact on quality of life, again, crude measures. But we analyzed -- we can also show after the lunch break -- the KCCQ scale, for example, pre and then post with patients with stroke, and there are some interesting data to share with that.

Additionally, as this endpoint became of interest, we do want to share that in the PARTNER II trial we will go into very deep detail. We've invited of Dr. Brott to be the PI of the neuro investigation in the PARTNER II trial, and already a much more sophisticated approach.

DR. PAGE: Okay, next, Dr. Somberg had a question.

DR. SOMBERG: My question also relates to stroke. You said there's extensive experience OUS with the device. I wonder if you can tell us the stroke incidence there and also the difference in the course of experience from early run-in to they have much more experience in follow-up. Does that diminish? Does that change? And the severity, major, minor, as well?

MS. AKIN: Again, most of our trials were observational in Europe, and I did report about a three to five-percent stroke rate across all trials, including the independent country registries.

I'd also like to invite our colleagues, Dr. Martyn Thomas and Olaf Wendler, who are principal investigators in Europe and very experienced with the device. Perhaps they can comment on their experience with stroke and neurologic events.

DR. THOMAS: Thank you. My name is Martyn Thomas, from

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London.

The stroke rates, as Jodi reported, are around four or five percent and are probably slightly underreported in all of these registries. I'm not aware that there's been any change over time, and it's clearly an area that there is work to be done on. I don't think we're entirely clear as to the causality, and I think it may be multifactorial.

I mean, when we're doing the procedure, we do a number of things to try and limit it. I think we try and limit the number of rapid pacing runs. I think we try and keep the hemodynamics stable with the anesthetist. We are in the process of starting to evaluate deflectors and debris catchers, and then finally, clearly, we have to optimize the pharmacology of the procedure.

So I think there are a number of areas that we need to work on, and I think we all acknowledge it's something that can be improved.

DR. ZUCKERMAN: Dr. Thomas, can I ask you one more question? For the purpose of educating this Panel, when we're referring to the European data, what is your gestalt for what percentage of patients actually are similar to the PARTNER Cohort B, (a)? And (b), even if you're giving us a gestalt, given that you are using a logistic EuroSCORE in your evaluation, how can we compare apples with apples and see, as a result of that, how do we best appreciate the European experience?

DR. THOMAS: So I think the European experience is based on a

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heart team approach; I can assure of that. In our own institution, the gatekeeper remains the surgeon. If you look across all of the European registries, the mean logistic EuroSCORE is in the region of 25 to 26.

Now, we all accept that that is not an ideal measure of risk, but it is some measure of risk, and given that our indication for use is a logistic EuroSCORE of greater than 20, then I think this is broadly indicative that we are sticking to that indication.

Finally, in the SOURCE registry, clearly what is a potential worry is there's some degree of change in the risk of the patient when the device is commercially available. We were able to look at two groups of patients over the first year and the second year of the commercialization of the device, of over 1,000 patients, and there was really very little change in the demographics of those patients. In the first year, as you'll see on this slide, in the first year it was 27 for the EuroSCORE, in the second it was 25. But in fact, that is only one measure of risk. And another measurement, actually the left ventricular function was worse in the second year. The degree of mitral regurgitation was actually higher. So I have not seen, in our own experience in the SOURCE registry and in my own institution, a major change.

The one thing I would say is, clearly, in the European field, our patients do not have to be absolutely turned down for surgery. The decision is made by a group of six or seven people; in my own institution, two surgeons, two interventional cardiologists, an imager and an anesthetist, who

decide, on balance, what they feel is the best treatment for that individual patient.

DR. PAGE: Could you clarify the indication in Europe for placement of this valve?

DR. THOMAS: So the general indication is that it's for high-risk patients with symptomatic severe aortic stenosis. The general view is that it's measured by a logistic EuroSCORE of greater than 20. But the truth is that I think the decision is made by a heart team. And just as you've already seen demonstrated, a patient with a logistic EuroSCORE of, say, 6 might have a porcelain aorta, and a porcelain aorta is clearly a contraindication to surgery, but it's not captured in the various risk scores that we measure.

DR. PAGE: Thank you. I saw Dr. Borer raised his hand, and then Dr. Naftel.

DR. BORER: Thank you. This section is for clarification, and it's sort of a difficult boundary between what's clarifying and what's not. I'll limit my questions therefore to two. I hope they're clarifying rather than other kind of discussion questions.

The first has to do with the indication. Dr. Thomas, you just said something that I thought was very important. In Europe, the indication is severe, symptomatic aortic stenosis. The population studied in PARTNER was severe, was a population of severe, symptomatic aortic stenosis. In fact, most of them were in Functional Class III or IV, very symptomatic. And yet

the requested indication is for severe aortic stenosis and the word symptomatic is left out. I'd sort of like some idea why that happened.

The next thing is with regard to the quality of life. I personally think that that is extraordinarily important. It's impacted, importantly, by stroke. But quality of life, I think, in the population that you studied, may be more important than the mortality, so its measurement is very important.

And I only want to ask, what led to the selection of the KCCQ? It's a wonderful tool, I think. Marty Leon said it was validated. Well, it is; it's validated for heart failure. It's not validated for surgery for valve disease. In fact, to my knowledge, only one instrument is so validated, and that's the Minnesota Living With Heart Failure score, and I know that because my own group did it.

So the question I would have -- I mean, I like the questions on the KCCQ. I think they get to, no pun intended, the heart of the matter. But I would like to know what led to the selection of that tool. There were other tools available.

MS. AKIN: I'd like to invite Matt Reynolds to respond to that question.

DR. REYNOLDS: Hi. Matt Reynolds, Harvard Clinical Research Institute. Thanks for your question.

I agree with you in part about the Minnesota Living With Heart Failure Questionnaire. The truth is there is no originally developed

questionnaire specific for aortic stenosis and specific for aortic valve surgery.

When the KCCQ was developed and very well validated, you are correct, it was not in a specific AS population, but it was compared directly with the Minnesota survey and found it to compare quite favorably; in some technical aspects, maybe even slightly better. That was viewed as an either/or decision. It was felt that it would be redundant to use both, so the decision was made to the KCCQ.

DR. BORER: May I just follow that up? I mean, I'm not in any way disputing that. I wouldn't suggest KCCQ is no good for this. When I said that it wasn't validated, I meant that it wasn't formally, statistically validated with the internal consistency types of testing that statisticians do to do that. And it's perfectly fine for you to have selected that. I just wanted to know why, that's all.

DR. PAGE: Okay, thank you. Dr. Naftel.

DR. BORER: Can they answer the question about the symptoms, though?

DR. PAGE: Oh, I'm sorry. Please go ahead.

DR. BORER: I mean, why was symptomatic left out of the indication?

MS. AKIN: It wasn't intentionally left out. This was the indication that FDA provided for us. We use symptomatic in our European label, so it's not a problem.

DR. PAGE: Thank you. Dr. Naftel.

DR. NAFTEL: So the presentation was extremely easy to understand and, I think, statistically well presented. I will just politely remind the statisticians that confidence limits and standard error bars are a nice thing to show measures of uncertainty, so that would've been okay. But let me get to my real question.

(Laughter.)

DR. NAFTEL: When we look at all of the Kaplan-Meier curves that you presented, they all stop at two years, and the mind extrapolates beyond that and they all look like they're sort of leveling out and things are looking good. But I know these are elderly patients and survival is not good in elderly patients. And I'm sure we're going to be discussing that more so.

So here's my question. Let's just start with mortality. Can you tell me how many deaths were in each group during the first two years, and then tell me how many deaths you know about totally, the deaths that are beyond two years.

And if you could do that for all of your major events, for death, how many patients had death or rehospitalization in the first two years and beyond, and then your other combined measures, because I feel like we're going to focus later today on results after two years. So you can do this after lunch, but we're real interested in knowing everything you know for the data. Thank you.

DR. LEON: I mean, clearly, we respect the use of error bars and would be glad to show the backup set of slides with the error bars.

The median follow-up was 1.6 years. All patients were followed for at least one year. There is precious few data out beyond two years in most of these patients. We truncated the Kaplan-Meier curves at two years because the number at risk had fallen to less than 10 percent of the total patient population and felt that it would be confusing to extend those curves further, but we'll certainly try to accumulate all of the very late follow-up data that we can.

Recognize, this is such a co-morbid patient population that there is a natural attrition in terms of mortality in these patients, even beyond two years, as shown in some of the longer European and Canadian registries, but do not bespeak structural valve deterioration but simply the age, frailty, and co-morbid condition of the patients.

DR. PAGE: So shall we expect a report after lunch, the ability that you can provide?

MS. AKIN: We're happy to provide the extended Kaplan-Meiers after lunch, for sure. That's no problem.

DR. PAGE: Great, thank you.

MS. AKIN: Also just on the confidence. We felt we provided the data in the briefing document, but again, not an issue to present it with confidence.

DR. PAGE: Thank you. Dr. Good, I've got a couple other people who have raised their hands who have specific follow-up. I'm going to go in the order that I recognized them.

Dr. Slotwiner.

DR. SLOTWINER: Thank you. I just wanted to ask for a clarification, if there was a formal mechanism by which patients were deemed to be -- their co-morbidities were too severe for them to benefit from a TAVR.

MS. AKIN: It's a great question. One thing that was mentioned in Dr. Smith's presentation is the scrutiny that went on not only at the site level, but every case was presented each week on a case review call that still occurs today. And there were challenges about, you know, the multiple co-morbidities, and the question was asked, if valve restoration occurred, would the patient still have a survival, potentially?

So yes, it's a consideration, something we talk about a lot today. We call it the cohort C patient, and we're thinking carefully about defining some parameters around an inoperable but shouldn't be treated patient. Yeah.

DR. SLOTWINER: I anticipate that that'll be discussed extensively, and I would be interested in hearing suggestions from the Sponsor on the criteria.

MS. AKIN: We'll have the physicians respond to that.

DR. SLOTWINER: Thank you.

MS. AKIN: Sure.

DR. PAGE: Thank you. Ms. Patrick-Lake.

MS. PATRICK-LAKE: My question is for Dr. Leon.

Hi. I was hoping that you could help me get a better understanding of how standard the standard of care was for the control group. I notice that 79 percent of the patients underwent balloon valvuloplasty, and I was wondering, in the management of inoperable patients, is that a real-world -- does it reflect the real-world clinical practice?

DR. LEON: That's an excellent question, and it's really difficult to answer because there is no single homogeneous standard therapy for so-called inoperable patients. In fact, if you scour the literature, you'll find precious little data in this subgroup of patients. So it's difficult to say what truly is standard of care and it certainly is not homogeneous. And, in fact, if you look site by site with regard to the use of balloon aortic valvuloplasty, it varied based upon the site's impression as to whether or not that therapy was valuable in these patients.

So I think we have to accept the fact that there simply is no single homogeneous standard therapy for inoperable AS patients, recognizing their high morbid situation and the high likelihood of early mortality.

We were surprised with the frequency of BAV use. I'm sure we'll share with you later that those patients actually did a little bit better.

They had a reduction in early mortality compared to those standard therapy patients who did not get BAV, but that rapidly dissipated. Sometimes it was used to bridge to another procedure. Some of those patients ended up getting AVR. They felt well enough and improved enough where they could have valve therapy restoration by more conventional means. But there is some dirtiness, if you will, in the standard therapy arm because I think that does bespeak what happens in the real world with these patients.

DR. PAGE: And that's the real world in the centers that have the capability to perform the interventions we've described.

Dr. Ferguson had his hand raised.

DR. FERGUSON: Yes. In your global clinical data, you showed us information on mortality out to three years, but you only showed us valve performance data out to two years. Do you have any longer-term valve performance data including EOA and the incidence of AI?

MS. AKIN: Yes, I'd like to invite Dr. Josep Rodes to the podium, who has done the study in longer-term follow-up with an excellent echocardiographic core lab.

DR. RODES-CABAU: Hello, I am Josep Rodes-Cabau from the Quebec Heart and Lung Institute in Quebec.

In among the 30 -- more than 300 patients that we included in the Canadian experience series, we are now analyzing all echos from around Canada in a central echo core lab at the Quebec Heart and Lung Institute.

And this is the data that shows that the three-year follow-up -- they don't see that -- a three-year follow-up. These are data from 30 patients with Edwards SAPIEN valve, with -- echos at discharge and then at one, two and three-year follow-up. As I said, all of these echos were analyzed in the central echo core lab, and we didn't see any significant deterioration of the valve in terms of valve performance and hemodynamics, as you can see in the slide, with the valve areas and the mean gradients.

And when we look at the aortic insufficiency in this cohort of 30 patients, none of these 30 patients had moderate aortic regurgitation. Most of them had mild aortic regurgitation. But we did not observe nadir in any significant increase in either paravalvular or central aortic regurgitation over time in these patients. And we divided also this group of patients among those who had aortic regurgitation fraction in between 16 and 29 percent and those with mild regurgitation, but regurgitation in between 1 and 50 percent regurgitation fraction.

And we analyzed the ventricular diameters and we analyzed 11 -- fraction in these groups. I don't know if this is the next slide. Next slide, please. I don't see the slide, but we analyzed these parameters for this subgroup of patients, and we didn't observe nadir, any significant hemodynamic impact of the central paravalvular or aortic regurgitation at the three-year follow-up.

DR. PAGE: Thank you.

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DR. ZUCKERMAN: Can I just remind the speaker and Edwards' other consultants that, before they begin in response to a question, can they initially just indicate what their relationship is to Edwards and any associated payments that they've received from the company?

DR. RODES-CABAU: I am a consultant for Edwards Lifesciences, and I've been proctoring in many centers with this valve.

DR. ZUCKERMAN: Thank you.

DR. PAGE: Thank you. I've seen Dr. Brindis, then Dr. Lange, and Dr. Good had raised their hands.

DR. BRINDIS: My clarifying question relates to the issue of stroke, particularly late stroke. I appreciate, looking through the data that was presented, that we may not have standard protocols related to anticoagulation. I was wondering if you'd like to comment a little bit on what was actually present in the PARTNER's B. And also, appreciating that there was a marked difference in atrial fibrillation between the treatment group and the control group, was their difference related to antithrombotic therapy in those groups?

DR. LEON: Thank you, Ralph. The recommended anticoagulation regimen was dual antiplatelet therapy for six months after the procedure. Given the elderly nature of these patients, their frailty and other factors, many of the centers, based upon individual clinical considerations, made decisions about whether or not to continue for that

period of time or if they truncated earlier, and I would submit that the majority did not have dual antiplatelet therapy for as long as six months.

As you noted, there was a high frequency of atrial fibrillation in both groups, higher in the standard therapy patients. Overall, about half of those patients were on chronic antithrombin therapies, warfarin being usually used. Again, that decision was made by the individual caring physician, taking into account the morbidity of chronic anticoagulation in these patients. There were attempts to try to generalize that, but it was difficult during the course of the early stages of this trial.

In the future, we have developed -- now, that is, it's been launched in PARTNER II, a much more rigorous antiplatelet/anticoagulation regimen that we hope will be applied more uniformly in these patients, and with that, more rigorous adjunctive pharmacotherapy. We're hopeful that that may have some influence on strokes.

I think, recognize, this is a very stroke-prone patient population. If you look at CHADS2 scores, they're off the wall. They all have heart failure, they're elderly, they're diabetic, they've a 30-percent previous cerebrovascular event, so that two and a half to four percent frequency of stroke in the 30-day to 1-year period is not unexpected in this kind of patient population.

DR. SOMBERG: Can I just ask one, a clarification? Most of the strokes I thought you presented earlier were in the first five days or so, or a

large majority of them. The standard therapy, pharmacologic therapy of heparin --

DR. LEON: Yes.

DR. SOMBERG: -- transfer to Coumadin and then --

DR. LEON: Yes.

DR. SOMBERG: -- antiplatelet therapy within that five days or is that up to the investigator?

DR. LEON: It's recommended, but there was some variation from site to site and from investigator to investigator. But yes, during the procedure, intraprocedural heparin is always used. But many times, in patients with atrial fibrillation, the Coumadin was stopped, then restarted, and that stop/restart period of time in the first several days was not uniformly applied.

DR. SOMBERG: So there's no prespecified to clarify a transitional program from heparin to Coumadin because we all know heparin has a short half-life; Coumadin has a very long half-life. There's going to be a dichotomy between stopping one and starting another.

DR. LEON: Since that's such a common phenomenon in clinical practice, it was left up to the best decisions of the caring physicians.

DR. PAGE: Okay, Dr. Lange.

DR. LANGE: Several questions and in no particular order. The first is, after the study was completed, was there a continued access to the

device, and if so, can we talk about -- show those results?

A couple other things. Dr. Leon had mentioned frailty. I wondered if there was a consistent definition or an evaluation to identify those patients. And tying in to Dr. Slotwiner's question, and that is regarding application of this procedure to individuals whose lifespan will be otherwise limited, that is, for example, have some co-morbid condition that their expected lifespan will be less than a year, and whether that was addressed or not.

And then finally the last two things. Did the vascular complication rate decrease with center experience? That is, as centers became more experienced, did their complication rate go down? And the last thing is I've not seen any of the data with respect to ejection fraction, and that is, stratified by the 80 percent who had a normal ejection fraction and the 20 percent that had a lower ejection fraction.

DR. PAGE: Thank you, Dr. Lange. We'll probably have to take those one at a time. We might need you to repeat them. Why don't you go ahead and --

MS. AKIN: Can I work backwards because I remember the last, the ejection fraction. We have done an analysis of that and we can provide that and I'll --

DR. PAGE: Great. After lunch.

MS. AKIN: -- invite one of my colleagues. I'll answer the easy

one, the continued access patients. We've actually enrolled more than 1600 continued access patients, out of which a smaller set are Cohort B. We provided the available data to date in the PMA and also in the PMA update, but there's not a complete set, you know, to a specific endpoint. We anticipate ending continued access as soon as the amendment for PARTNER II is completed, at which point we'll be able to do some wonderful analyses and larger datasets.

The vascular complications, we looked at that across sites. If you recall, there's 179 patients enrolled across a fair amount of sites, and only about five sites enrolled more than 20 patients. So it's a little bit hard to tease that out. What we do see is that we had a very high major vascular complication in our feasibility study, REVIVE and REVIVAL, REVIVAL being the precursor to PARTNER. And we were able to reduce that down into the high teens. And that seems to stay the same across all of our studies globally with the SAPIEN device, which is why we introduced SAPIEN XT, which is a 40-percent reduction in the size.

DR. LANGE: Can we present that --

MS. AKIN: Do you want us to address the ejection fraction?

DR. LANGE: Can we present that continued access data after lunch? Just the available stuff.

MS. AKIN: Sure. And Dr. Smith can address the frailty. This is a subject of great interest.

DR. SMITH: Again working backwards, there was an exclusion for anyone who was unlikely to survive a year, so that shouldn't come up, although that issue is what helps us draw the line between operable -- or, I should say, inoperable and cohort C, who should have nothing done. So just as there is no validated instrument for defining the line between operable and inoperable, there is no validated instrument for drawing the line between what we think of as utility and futility. In fact, that was the subject of a half-hour debate at AATS this year, on exactly that question in this patient population. So it's something we're working toward. But the short answer to the 12 months is that if they were unlikely to survive 12 months, they were excluded.

Frailty is also, in the same sense, not a definition for which there is a validated instrument in this population. We got very interested in this question when we started the trial, and there are a number of reasonably validated instruments that have been used and developed in geriatric populations. Recently there was one surgical series published of a frailty index applied in a surgical population with only a few cardiac patients. So that's a work in progress.

We have developed an index that's a combination of CATs, ADL, dynamometer, hand strength, hand grip, serum albumin, and a few things that are taken from the more commonly applied scores, and we are in the process of validating. Those elements are used in the discussion each week

of inoperability. The case conference calls are used by centers to varying degrees, but it is not yet validated. I think something that may come out of this is such an index.

DR. LEON: If it's okay with Dr. Page, some of the other questions about ventricular function and the detailed echo data, we might want to defer for the afternoon. We have all of those data. Unless you'd like to hear it now.

DR. PAGE: Yeah, we're nearing our break, and I would like to defer that until the afternoon.

DR. LEON: And we'd like to discuss further the issue of vascular complications, but that's a somewhat longer discussion, and if it's okay, I'd like to defer that as well.

DR. PAGE: That'd be fine, thank you.

I saw Dr. Good had his hand raised and let's -- if we need to continue beyond the break, we will. Otherwise, I will let us go another five minutes, and we'll have a 10-minute break at five minutes after the hour.

DR. GOOD: Thank you. One of my clarification questions has already been answered, and that's the rigor with which the recommended protocol for antiplatelet agents was applied pre- and post-procedure, and that's certainly an important issue, and it was already discussed.

The other question I had was related to quality of life. I agree with Dr. Borer that this is a very important point. And you presented the data

from the KCCQ, but you didn't really mention anything about the SF-12 and the EQ-5D, and I was wondering if you were going to present that.

MS. AKIN: We have all the detailed data we can present after lunch as well.

DR. PAGE: Thank you. Dr. Jeevanandam.

DR. JEEVANANDAM: I think you presented data looking at mortality benefit with a higher risk of stroke in this patient population, which is defined as an inoperable patient population. So clearly this device works in the inoperable patient population.

So, you know, the question is, how do you make that standardized going forward, right? Because you don't want to start having creep into people who are not -- who don't fit that definition.

So, you know, you are going to have a surgeon, supposedly, who's going to be in this group making a decision. Now, exactly, are they going to be using the STS or EuroSCORE or are they going to be using the frailty index? Or what parameters are they going to be using as objective measurements in determining inoperability? Or is this going to be more subjective inoperability determined by the surgeon?

I think that's important because in Europe you can see -- I think somebody said that the indications they deal with is dealing with high-risk AVR. The word inoperability is out. So at least for the short term, until the other cohort is presented, this device should be only for the inoperable

patient in the United States.

MS. AKIN: Yes, this is a subject of great discussion. I can speak from the Sponsor perspective, and then we can ask our surgical colleagues to address the rest.

Our intention is an excellent training and education program, number one. I'm sorry, I'll start with site selection. We're very serious about site selection and the heart team, and I think we've demonstrated that well in our European experience. At the end of the day, we have to rely on our physicians, especially the heart teams and the surgeons, to make the appropriate decisions.

More and more we can come out with guidelines and parameters around appropriate and inappropriate patients. But in the absence of a validated tool, the EuroSCORE or STS are not, by themselves, appropriate instruments.

Secondly, in the training, it's important for us to carry our data forward to be as informative as possible, and our continued collaboration with the physicians to educate the community from an academic perspective as well. But I can bring up Dr. Smith to --

DR. PAGE: I don't think we'll bring up Dr. Smith right now.

MS. AKIN: Yeah, okay.

DR. PAGE: We can perhaps do it after the break.

MS. AKIN: Okay.

DR. PAGE: Thank you.

MS. AKIN: Thank you.

DR. PAGE: Ms. Patrick-Lake had one brief question, and then I want to make sure our Consumer and Industry Reps don't have any questions for clarification before we break in two minutes.

MS. PATRICK-LAKE: I have a brief question, and I think actually Dr. Lange might've brought it up, but it didn't get addressed, and basically it relates to procedural risk based on operator experience. I was wondering if there was a separate reference. I've noticed that the reference that we were given was an article by John Webb that says procedural risk, actually, you can see, after 25 cases, outcomes are improved for patients in the 25 to 50 range, but yet, in the postmarket study, it shows that you're going to enroll 10 patients, perhaps up to 20, and I was wondering if there's a better reference you could provide us that supports that.

MS. AKIN: I guess the greatest reference of all -- and we can go deeply on this in the afternoon -- is to really look at the totality of our experience over a time course. Something that I think is demonstrated, and we'll try to depict this clearly, is the learnings that are going forward. So in other words, I don't believe -- and I think we can demonstrate that the learning curve per site, de novo, is it requires 20 to 25 patients.

When we launch new sites now, their complication rates are lower than when we launched sites years ago. So the learnings have

translated. We've shown an artery on a stick so many times that there's fearful respect of that. So I just think we're not starting de novo. We have a lot of shared learnings that are coming forward that are applied in our training.

DR. ZUCKERMAN: Okay, but Jodi, could you answer the question in a little bit more detail?

MS. AKIN: Um-hum.

DR. ZUCKERMAN: The way that you're looking at this is site training per site as opposed to site training per investigator, so that at a particular high-volume site, you think that there might be up to, say, five investigators who could do five cases --

MS. AKIN: Um-hum.

DR. ZUCKERMAN: -- get up to the 25 and still be trained as a site and as individual operators.

MS. AKIN: Well, I think a little bit of our approach is relying on the expertise of our proctors and our site support to ensure that the new physician that's trained is capable. They will not be declared to independence without demonstrating, you know, the appropriate skill metrics.

I think the question is, should we evaluate every single physician to 20 cases? That will happen. What we do do is we do collect procedure success in all of our cases. This is not the academic 30-day, but

every single case has a procedure success that we receive at Edwards, and we have looked at that very carefully. What we have seen is that if there is a high complication early, those sites get more and more proctoring.

So did I not answer that completely?

DR. PAGE: Thank you.

MS. AKIN: Yeah, okay.

DR. PAGE: I want to make sure Mr. Dubbs and Mr. Barrett don't have any specific clarification questions.

MR. DUBBS: In the operator selection process, I understand the training, but in the selection of who might go through training, what was your experience in terms of rejecting people, or how did you find these people? And what kinds of things would an operator doing this procedure, in terms of qualifications, have versus an operator who does an open procedure have? What makes them unique, if there is anything that makes them unique?

MS. AKIN: I'll bring up Larry Wood to discuss a bit of our site selection and physician selection, but I want to clarify that the open procedure, for example, surgery, that's applicable in our transapical procedure, and we do have strict criteria for that. But that's not the subject of today's discussion or indication. Regarding the rest, I'll have Larry address it.

MR. WOOD: Just a quick follow-up to Bram's question. Our

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goal is to train one heart team at each institution, not to train multiple teams at each institution, so we try to maximize our learning within one heart team.

In terms of the selection of the heart team, we typically work through the chiefs of the department at the hospitals and they designate who they feel the most appropriate people are, based on their skills and their experience, to participate. We focus a lot on the team dynamics. So we try to get very experienced surgeons and experienced interventional cardiologists, who are the lead operator, and they pick who the secondary operators are for those procedures as well. So we depend a lot on the institutions and the chiefs to designate who the most appropriate people are at their institution because once we designate that heart team, that heart team's going to stay together throughout the process and in performance of the procedures.

DR. PAGE: Did that answer your question? All right. In that case we'll now take a 10 -- I'm sorry. Did you have another -- please hold. Mr. Barrett, I'm sorry.

MR. BARRETT: Now I'm holding up the break --

(Laughter.)

MR. BARRETT: So just a couple really quick things. First of all, I want to compliment the Sponsor for preparing a very well organized and very cogent Panel pack and presentation. And I don't always say that. It was very well put together, as a number of the Panel members have already said.

I'd like to quickly clarify a couple of regulatory points, so Jodi, you may need to come back up. Can you tell me approximately what timeframe the protocol in the original IDE was approved? You know, just roughly, year-wise. And can you clarify for me if the primary efficacy endpoint has been stable throughout the course of the study and if it was always a one-year primary efficacy endpoint?

MS. AKIN: The protocol was initially approved in early 2008. I'm sorry, '7. The primary endpoint never changed, and it was always over the duration of the trial, not one year. Cohort A, the high-risk operable group, is a one-year endpoint. And we consider these over the course of the trial because of the consideration of the natural history of the control population.

DR. PAGE: Thank you. Before we break, I do want to remind the Panel members not to discuss the meeting topic during the break among yourselves or with any members of the audience. We will take exactly a 10-minute break and reconvene for the FDA presentation. Thank you.

(Off the record.)

(On the record.)

DR. PAGE: Welcome back to our meeting. We are reconvening now.

I have an announcement to make, and that is both the Sponsor and the FDA have agreed that the word symptomatic belongs in the

indications, and that being the case, unless I see any indication from our Panel that that shouldn't be there, we'd like to move forward and have that be part of our further consideration of this device.

Looking at my Panel, do I see any concern about that? So all further consideration will be in the setting of the word symptomatic being inserted into the indications.

It's now my pleasure to ask Lisa Kennell from the FDA to provide the FDA presentation, and you're provided 60 minutes. Thank you.

MS. KENNEL: Thank you. Good morning, members of the Panel. My name is Lisa Kennell, and I will be presenting the introductory information for the FDA for PMA P100041 for the Edwards SAPIEN Transcatheter Heart Valve. On behalf of the FDA, I would like to thank the Panel for their time today, and look forward to an active discussion of this PMA.

I want to introduce today's presenters from the FDA. First, I'll give the background. Next will be Dr. Chenguang Wang, who will summarize the statistical review. Then Dr. Julie Swain will go over the summary of the clinical data. Dr. Mary Beth Ritchey will discuss the proposed postapproval studies. And lastly, Matthew Hillebrenner will summarize the FDA's perspective of the submission.

This slide gives an outline of our presentation.

The investigational device exemption that was associated with

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this study began in 2003 with a single investigator. The feasibility studies, known as the REVIVAL I and II, began in 2005 and the pivotal PARTNER study began in 2007. The information presented to this Panel includes data up to November 1st, 2010.

After enrollment in the study was complete, FDA granted a continued access study, which allows sponsors to continue limited enrollment at the study sites that participate in the pivotal trial.

We worked with the Sponsor to develop the indication for use statement appearing on this slide ,and you'll see that the word symptomatic has been added to that.

We believe that it reflects the most important factor to be used in determining the patients who should receive the valve, that is, that the surgeon should determine that the patient is inoperable. And it also brings out an issue that surfaced after data analysis, that is, that there are some patients who are too sick to benefit from therapy.

This is a quick description of the valve and accessories, already given in enough detail by the manufacturer.

I wanted to give special recognition to the many members of my team who helped to review the substantial information in this multifaceted submission.

This slide summarizes the preclinical testing that was done. Testing included assessments of the stent and of the whole valve, typical of

the testing that is done for a surgical heart valve. There were also tests that were unique to transcatheter valves, that addressed the novel features of the transcatheter delivery of the valve and accessories. Testing is ongoing for valves that are deployed at a more severe elliptical angle, but most tests are complete and satisfactory.

We did want to point out, however, that the Sponsor has not performed any testing to simulate "valve-in-valve" deployment. FDA believes that this testing should be done. We believe additional testing is needed because it appears that this type of deployment will be used more frequently after commercialization of the valve.

Cases have been reported in literature for all valve positions, including not only the transcatheter valve in a transcatheter valve configuration but also a transcatheter in a surgical bioprosthetic valve configuration, and even transcatheter valve in an annular plastic ring configuration, which may lead to a decrease -- excuse me.

There are very little data on the potential risks associated with the valve-in-valve approach. We don't know, for example, if the valve will be a good fit such that it doesn't migrate, embolize, or cause compromised hemodynamic performance. There's also the possibility of corrosion resulting from placing the valves in other valves, which may lead to a decrease in durability. There have been reports of inability to access the coronary ostia, resulting in death.

Switching gears now, we turn to an overview of the pivotal PARTNER trial. This graphic depicts the overall study design. There were two cohorts, A and B, with A focusing on patients who were operable and could be randomized to surgery, and Cohort B focusing on patients who were deemed inoperable. Cohort B, shown here in the red circle, is the subject of the PMA being discussed today.

In Cohort B, patients were randomized to receive either the test valve via transfemoral placement only or standard therapy. Those patients whose anatomy was not amenable to transfemoral placement were not enrolled because the Sponsor felt that these patients were too sick for any surgery, including transapical placement.

We move now to endpoints. As you've heard, both the primary endpoint of freedom from all-cause death and the co-primary endpoint, a composite of death and recurrent hospitalization, were met in this study. We will also provide our analysis of several key secondary endpoints that we believe are critical to the overall evaluation of safety and effectiveness for this device.

The key secondary safety endpoints that FDA will focus on are the time to major adverse cardiac and cerebral events and the serious adverse events listed here.

The key effectiveness endpoints that FDA will focus on are those listed on this slide.

I will now turn the presentation over to Dr. Wang, who will present the summary of FDA's statistical review of this submission.

DR. WANG: Thank you, Lisa.

Good morning. I will be presenting FDA's statistical review of this study. I will briefly recap the study design, patient enrollment and accountability, present the results of the primary and secondary endpoints, and summarize the study from a statistical point of view.

The study is a prospective, non-blinded, randomized, controlled, multicenter trial. A sample size of 350 was estimated to provide 85 percent power. The first patient was enrolled on May 11th, 2007. By March 16th, 2009, a total of 358 patients, or 179 on control and 179 on SAPIEN, were enrolled from 22 centers, including four OUS sites.

The Sponsor's statistical analysis plan was finalized on February 18th, 2010, about 11 months after the last PMA patient enrollment.

For this PMA, a data cutoff date of November 1st, 2010 was used. All events observed before the data cutoff were included, and all events occurring after the data cutoff were excluded.

Patient accountability. For control, there were five withdrawals by the cutoff date. With respect to compliance, about 16 percent of the eligible control patients missed their one-year in-window visits.

For SAPIEN, there was one withdrawal by the cutoff. There

were about 10 percent of the eligible patients who missed the one-year in-window visit. In addition, there were nine SAPIEN patients who did not receive the device.

There was no statistically significant difference detected for the distributions of patient demographics and baseline characteristics between the two arms. However, there may be a clinically significant difference between control and SAPIEN with respect to the factors listed on this slide.

There were two analysis populations defined in the protocol. The intent-to-treat, or ITT, population includes all randomized patients. The as-treated control arm was defined as randomized control patients and those patients who were randomized with SAPIEN but did not receive the implant. The as-treated SAPIEN arm was defined as a group of randomized treatment patients for whom the study valve implant procedure was begun.

The analyses of the primary and secondary endpoints based on the ITT population, which was prespecified in the protocol, will be presented.

The primary safety and effectiveness endpoint was freedom from death over the duration of the trial. The goal is to show the superiority of SAPIEN. Log rank tests were performed, and the results significantly favor SAPIEN.

This is a Kaplan-Meier curve of the primary safety and effectiveness endpoint over the duration of the trial. The yellow and red survival curves and their confidence intervals are for control and SAPIEN

respectively.

The proportion of survival at one year was 50.3 percent for control and 69.3 percent for SAPIEN. The median survival was 0.97 years for control and 2.18 years for SAPIEN. Please note that the numbers of patients at risk after two years were small. The survival results after two years, from this PMA, are subject to large variation.

A composite endpoint, defined as a hierarchical composite of death and rehospitalization, was proposed after the study was begun. For this endpoint, the null hypothesis was neither survival nor rehospitalization was different between the two arms. The alternative hypothesis was at least one and possibly both survival and rehospitalization were different between the two arms. Finkelstein-Schoenfeld method was used to test the hypothesis. The result significantly favored SAPIEN.

Here's a brief introduction of Finkelstein-Schoenfeld method. It is a non-parametric rank sum test where each patient is compared to every other patient in a pair-wise manner. For this study, all patient pairs are compared first on survival, if possible; otherwise, patients are compared on time to rehospitalization.

I'm going to review the secondary endpoints that have prespecified hypotheses.

The secondary safety endpoint, MACCE, was defined in the protocol as time from randomization to the first occurrence of death,

myocardial infarction, stroke, or renal failure within one year. Patients were censored at one year. In other words, MACCE after one year were not considered in this analysis. Log rank test results significantly favored SAPIEN. An FDA clinician will review the MACCE components.

Please note that the MACCE definition, using the Sponsor's presentation, was not the one prespecified in the protocol. Please consider their analysis results as post hoc.

The secondary effectiveness endpoint for hospitalization was defined as total hospital days through one year. The median was 8 days for control and 12 days for SAPIEN. Bootstrap test result was significant, with p-value 0.019.

An additional analysis was performed to compare the days alive and out of the hospital through one year. This analysis was proposed after the study was begun. The control had a median of 233 days and SAPIEN, 348 days.

The next effectiveness secondary endpoint was New York Heart Association functional classification at one year. The numbers are presented in the table. Those in yellow are unobserved data either caused by death or missing.

Several sensitivity analyses that used different missing data imputation methods, including a worst-case scenario, were done to address the unobserved NYHA. Their results favored SAPIEN.

Please note that this is a non-blinded trial. The assessment of NYHA may be subject to serious systematic bias.

The third secondary effectiveness endpoint was six-minute walk test at one year. Based on the observed data from the test performed at one year, patients in the SAPIEN group were able to walk farther. However, there were 66 percent and 55 percent alive control and SAPIEN patients who did not complete a six-minute walk test at one year.

Multiple sensitivity analyses were performed to address the missing data issue. Their results were not consistent. We think the amount of missing makes it difficult to draw any firm conclusion for this endpoint.

Please note that the results of six-minute walk tests presented in the Sponsor's presentation were not based on the prespecified hypotheses. Please consider their analysis results as post hoc.

To summarize, the study met the primary safety and effectiveness endpoint. This presentation highlights the primary and secondary endpoints with prespecified hypotheses. An FDA clinical reviewer will further review other key effectiveness and safety issues.

This concludes my presentation. Dr. Julie Swain will present the clinical review.

DR. SWAIN: Good morning. Well, as you can see, unfortunately the red is not showing up in our slides. It shows as a black line. I don't know you guys have any way of quickly correcting that because I've

got a fair number of slides with red.

There have been several trials of this device, and I'm going to concentrate on the randomized, controlled IDE trial. And as you can see from Ms. Akin's presentation, there's over 7,000 patients in trials and registries in Europe. The problem is defining who those patients are. They have different inclusion criteria, high risk versus inoperable. They use EuroSCORE primarily, which is not validated for this and we know, from many studies, predicts mortality, and there was no requirement for surgeon determination of inoperability. Although that did occur in at least some centers, it wasn't a requirement.

So, again, we're looking at the right side of this, which is PARTNER B, and noting that the control treatment was multifactorial. Well, in the randomized B, this is transfemoral TAVI versus standard treatment, and these are inoperable patients who are anatomically eligible for transfemoral approach. That excludes what we as surgeons generally think of as the true vasculopathies. And the transapical approach was studied in Cohort A arm only.

And it's careful to note that inoperable really does not mean short-lived. And Dr. Smith presented a great patient, a 61-year-old, with anatomical reasons for being inoperable. So, again, we have to keep reminding ourselves that inoperable does not necessarily short-lived, which is why we'll be needing some more long-term data in postmarket studies.

And the FDA actually asked that the transapical patients be included because I think that would be a group that would be well served by this device, but the Sponsor declined. Therefore, the population for labeling is limited.

So what are the key procedural data? And notice that these are excellent interventional cardiologists who did this. The average procedure time was four and a half hours up to 10 hours; fluoro time, 30 minutes; general anesthesia in all of the patients; a fair amount of contrast media; and a procedure success rate around 72 percent.

So the question will be, that you've all asked so far, what about the learning curve? As it gets expanded to a couple hundred more interventional cardiologists perhaps in the next year or so, what will that do to the key procedural data?

Again, you've seen this slide and you can't see the circle around the two-year and on. We have really minimal data from this study on the effects of this device for survival at two years and beyond.

There was a co-primary endpoint of mortality and hospitalization, and hospitalization is traditionally used in a lot of drug trials. The problem we always have in the device group is the necessity for unblinded trials, so that you know your own data, you know the other investigators' data because we all sit together in investigator meetings and share that, so -- and because the patient knows what they have, whether they

won or lost the coin flip to get the great, new device versus control, nothing, standard, however you want to view it, that there is a possible treatment bias, assessment bias, and placebo effect.

And the magnitude of that is not well characterized, and we know that in many other studies, such injection into vertebral bodies, knee arthroscopy, that the treatment had a wonderful quality of life, decreased hospitalizations, things of that sort, but the placebo had an equal amount.

So the characterization of the placebo effect is extremely difficult, and we know there's very good data, that it's proportional to ritual, and in this interventional cardiology device that's highly invasive, that the ritual is really a lot.

Well, what about days alive and out of an acute care hospital? Unfortunately we did not measure whether the patient went back home, if they came from home, so that being out of the acute care hospital is what is counted, not whether you went to an acute rehab or even a chronic nursing home. And this showed a great improvement with the device. These are the median days, and that's excellent because that's a good indication of quality of life.

What about the other secondary endpoints? And again I think, as Dr. Smith pointed out, as surgeons, you know, it's difficult. Quality of life is vitally important, but I'm not sure that we have great ways of measuring that in unblinded trials. It's really difficult to interpret.

The six-minute walk test, with half of the data missing, is a big problem, and it really doesn't work to do paired data because you exclude anyone that wasn't able to have a test in the postprocedure period, and those really are not missing at random, so that we have a very difficult time interpreting the six-minute walk test.

Well, what about the MACCE? And it's important to note that MACCE was predefined as all stroke, and that's different than the publication that came out on the trial. So what we see is that the death component of MACCE, which is the primary endpoint, is what overwhelmed any MACCE determination. Even though the stroke rate was considerably higher, the improvement in mortality was what drove this endpoint.

It's also important to note that both myocardial infarction and renal failure were not considerations in this trial. It's also important to note that the vascular complications were not included in the MACCE rate. Likewise, pacemakers have been an issue with this class of devices, and it really wasn't an issue in this trial.

So I'm going to talk about six different important considerations on evaluating the data of this trial, and the first is the heterogeneity of the control. As Dr. Leon pointed out, a great slide showing the early and late use of other modalities to treat these patients, we see many presentations where it's the control group, what is the treatment of aortic stenosis in the control, and then the next slide is blank. I've seen that

at several meetings, saying there is no treatment.

Well, these patients had mostly invasive procedures, but they weren't done within the first 30 days, many of them, up to 40 percent of these invasive procedures. So if they're done after 30 days, they counted as a hospitalization; therefore, time to hospitalization, that would be a failure. So it makes evaluation of time to event very difficult in this particular trial.

But you can see the various modalities. You can also see that there's probably a huge variation in selection of the modality. You can imagine the patients that were selected to be essentially too sick for balloon valvuloplasty, or it's not used, versus the four patients that went to Germany to get TAVI in Germany. There's probably a whole lot of different risk.

So when we look at the results of this trial, the superiority in mortality is what we can say is to no SAPIEN implant because the control treatment was not protocolized and, therefore, as in fact was mentioned, that there's selection bias in determining the control treatment. Some people, you know, like to do balloon valvuloplasties, others not, and various others. Some people used apico-aortic conduits.

So this study was not powered to compare SAPIEN with individual treatments. So it is incorrect to say that, you know, balloon valvuloplasty did better than medical treatment because those are very different patients, most likely, that got balloon valvuloplasty versus only medical therapy versus the open AVR versus apico-aortic conduit.

So we do not have any statistical proof of superiority. It was not designed or powered to study that question.

What about post hoc adverse event definitions? And this has been a considerable issue. We worked very hard, before the study started, to have common definitions for significant adverse events.

Once the data were analyzed, the results were known in this unblinded trial, the CEC was then asked to redefine some of the adverse events, the ones that were the major issues, stroke and vascular, not all of them that were defined with VARC, such as renal failure, myocardial infarction, and things of that sort.

The FDA was not informed of this re-adjudication, and the CEC very appropriately noted this and they said -- let me read an excerpt from their letter, that the Sponsor executive committee and the PARTNER CEC agreed that this adjudication is an adjunctive process to the primary adjudication process for PARTNER. This review is occurring after the unblinded assessment has been completed, and as such there is a clear variation from the primary adjudication process for PARTNER, as described in the CEC charter.

And if you notice, many of the publications and presentations, including today's, regarding this trial used the adjunctive data rather than the prespecified data. And the FDA will use the prespecified data for this presentation and for labeling.

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What about neurological damage? We've heard a lot about that this morning. The prespecified definition of stroke, it was suggested that may be a very strict definition. I'm on three different DSMBs for the NIH neuro institute that are all stroke studies, and this is the definition that are used in all of those. So it's a commonly used definition.

And then the effect of declaring things major versus minor. That's very different than the neurologists, especially the stroke neurologists, do to classify strokes acutely, whether to give clot-busting drugs or not. What we care about is classifying major disability, not major stroke like neurologists do, but major disability after the event and eventually, you know, out about 90 days where it levels off.

The Sponsor agrees that there is no retrospective Rankin. You really can't do it. Stroke patients are also very poor at self-evaluations, so depending on cardiology notes to determine whether the patient can still go to the store or buy the same number of objects, have the same interpersonal relations, can play golf three times a week for 18 holes like they used to, rather than, you know, one time a week for nine holes. So that's important to know, that we don't have a good idea of disability. Also notice that, again, in the MACCE, that all stroke is included in that prespecified definition.

So when we look at stroke, we can see that the less-than-30-day stroke rate is about 4.3 times higher in the SAPIEN group than the control group, and 2.5 times higher total at one year. And, again, the issues about a

standardized anticoagulation, an antiplatelet regimen, I think, is going to be very helpful for the new trials.

Neurological events, stroke plus TIA, it's important to note that some of these patients had imaging, but most of the images were CAT scans rather than DW-MRIs, so that the detection of strokes is difficult. So something called a TIA, if high-sensitivity imaging had been done, it may well have been determined to be dead cerebral tissue, a stroke.

So we look at the neuro events under 30 days, and again 4.3 incidence. Between 30 days and 1 year, 1.6. And notice in the control group, 2.8. We'll talk a little bit about those. This is not -- appears to be a high-risk stroke population that's described by the patients in the study. We don't really have enough events or enough patients after one year to compare. But when we look at the total study, we have about a three-times higher incidence of neurological events.

And what kind of events are we looking at? Well, mostly it's ischemic or unclassified strokes, 25 to 8 total events.

And when did these occur? Well, let's look at the control group. So there were seven ischemic or unclassified strokes. One of them occurred right after aortic valve replacement, four after balloon valvuloplasty, two of them very early, one moderate and one at six months, and only two with the medical management patients. One occurred on the day of randomization and one during the hospitalization three days after

randomization. Hemorrhagic stroke was not a consideration. No intracranial hemorrhages or TIAs.

However, in the SAPIEN group, there are 16 of these events. The vast majority occurred within six days of SAPIEN -- or were recognized within six days of SAPIEN implantation. And getting a neurological consult depended on someone recognizing that there was an event occurring on the cardiovascular team.

So we can also see that there were several late events after six months. So it's an issue of long-term antiplatelet/anticoagulation management of these patients, and I think we need a lot more experience with this device to understand that.

Now, to put this in context, there are five papers now that look at diffusion-weighted magnetic resonance imaging, which is right now the gold standard for determining stroke. CAT scan certainly is not the gold standard. And we can see that there's pretty good evidence that the DW-MRI lesion rate, which is ischemic and necrotic brain tissue, is around 70 to 80 percent or so.

And it's important that two of these papers, in fact, studied compared transfemoral to transatrial and showed really no difference between those two, which is very surprising.

When you compare that in the two left -- I guess they're yellow now. They're green on my computer. But 48 and 8 are open AVR, so that's

the DW-MRI lesion rate for cardiopulmonary bypass and open AVR. And then on the left, in blue here, is simply crossing aortic valves for diagnostic catheterization, a 22-percent incidence.

So what does this tell us? First of all, these studies are somewhat limited and that about 60 percent of the patients really didn't have postprocedure scans and they may not be missing at random. It could be death and complications and things of that sort.

And there was a limitation in assessment of the clinical impacts of these imaging-found lesions and there was no long-term assessment. One of the studies used a board-certified cardiologist to detect whether the patient had a stroke or not.

There are many possible mechanisms of injury. Catheter in the arch is what a lot of us would've thought would've been the main issue, but again, looking at between transapical and transfemoral, it's very interesting that there doesn't appear to be a difference. So you could see the list of possibilities here.

What we decided several months ago, that in all future TAVI studies, IDE studies, we will have at least 50 percent of the patients have a protocolized neurological assessment by neurologists, of these patients, so that we can detect stroke rate, because when you don't look for stroke, it's not found. And we know that from cardiac surgery and virtually every study done on cardiac surgery.

What about vascular injury? Well, what we found using the prespecified definition of hemorrhagic vascular complications as a significant adverse event, using these seven categories of injury, that there was about a 56-percent rate in the SAPIEN patients. I don't have the control patients here because they received so many different treatments that it really is not relevant.

So what are some of these vascular complications? And I think Ms. Akin talked about iliac on a stick, where you take the traducer out and the iliac artery comes out, a devastating complication that, you know, we see presented at meetings all the time.

But we can look at the amount of aortic dissection, iliac and aortic injury, femoral artery injury, and it's important to know that, you know, they get -- many of them got prosthetic grafts, and for those of us who do vascular surgery, it's, you know, the gift that keeps on giving. You have a lifetime risk of infection, thrombosis, things of that sort.

It's also a quality of life issue that really wasn't measured here. Do you have all your limbs and can you walk any distance, such as for claudication. So although we don't know of any amputations in these patients, and we really don't have European data to indicate that either, I'm not sure that's something that was noted or captured or measured.

What about aortic insufficiency? We worked very hard at the beginning of the study with the Sponsor to go over how this was going to be

captured. With the core lab, a great core lab at Duke, it was going to be measured as one plus, two plus, three plus, four plus. And then we had a lot of, let's say, somewhat disagreements with the Sponsor whether two plus was going to be considered an SAE or not, and we said we would have it all reported, we would consider two plus or greater as an SAE. And you can tell from the ACC/AHA guidelines from 2006 that when you look at moderate, it's two plus.

Now, Dr. Wang, our statistician, tells me that the SES dataset determines -- it calls two plus as mild, and that's not a standard convention that we would agree with or that we did agree with in the study. So it was not prespecified that we'd be talking about mild, moderate, severe, and all of that. We're talking about one, two, three, and four plus or zero aortic insufficiency. So when you look at that interesting color there, we can see that it's about a 15, 16-percent incidence with this.

Now, again, knowing that these are inoperable patients, but again inoperable does not mean short-lived, that that's a consideration. We need to follow these patients a whole lot longer.

And finally patient selection. And this has been mentioned a fair amount today. You can see from the inclusion criteria that there's a great deal of description about what is inoperable, what precludes an operation, and we have one exclusion about life expectancy less than 12 months. The problem is that the committee that looked at all of these patients, they did a

wonderful job figuring out whether they're inoperable. In fact, apparently disagreed in some cases.

We had some lists, whether the patient was inoperable as decided by a site, so it wasn't entered in this arm of the trial. We did not ever hear or have any evidence that this committee was also deciding, you know, who shouldn't have an operation. And in surgery, the hardest thing is to decide when not to operate.

So the whole question is can you, and then it's should you. And, you know, it's a qualitative judgment at individual sites. None of these patients were seen by the same individual in the test. So none of us saw these patients. Nobody at the FDA, nobody at the company, nobody in the executive committee laid eyes on these patients. We know that's a very important assessment.

And we know that in studies there's really enthusiasm for devices, and we test the limits of those devices in patient selection. That's why patient selection evolves over time during a trial.

The inclusion criteria really didn't address how you measure improvement in patients in long-term care facilities, so where hospitalization might be different than if you lived at home. We didn't have any measures of home visits, things of that sort, so we really don't have that answer.

We really need to consider when transcatheter valve implantation may not have a positive impact on a patient's quality of life, and

we'd like to ask the opinion of the Panel, to kind of throw that one around a lot.

And I'm just going to talk about three patients that came from CEC narratives. That's the only reason I have any knowledge of these patients. I don't have knowledge of patients that didn't have complications because I don't have those narratives.

So first an 87-year-old male with Paget's, debilitating rheumatoid arthritis, myopathy, post-herpetic neuralgia, and chronic pain. And it doesn't matter that his result was not ideal. That's peripheral to the discussion of, you know, who you would choose for this technology.

A 95-year-old patient with home O₂ COPD, macular degeneration, history of CVA and subdural hematoma.

And finally an 88-year-old lady, severe COPD, an FEV₁ of .5, home O₂, osteoporosis, spinal stenosis. And this patient was referred from an outside hospital and had a long history of intermittent left-sided weakness that was diagnosed as "recurrent TIAs." When she was transferred from the outside hospital, she had transient arm clumsiness at that outside hospital, then came into the interventional hospital, the left arm became clumsy again, an MRI showed an acute subacute stroke, and MRA angiography showed a decrease in flow to the important arteries. And then SAPIEN was implanted, and she died later from progression of the stroke.

It's important to note that CEC did not call this a new stroke

after implantation, so it's not listed in any of the stroke numbers because it was progression of a preprocedure stroke.

So these patient selection issues, I think, is really a big deal here and that we, the FDA, really made an error in not concentrating on bracketing who should get this device. We really put all of our concentration to make sure that they weren't operative patients in this inoperative arm.

We know that SAPIEN implantation is highly invasive. All of them require general anesthesia a good amount of time in the cath lab. And that's just the procedure time. That doesn't count all of the time in the cath lab to get monitoring catheters, TEE and things of that sort, or after you take the device out -- or the catheters out. It requires overdrive pacing, so no cardiac output for some length of time, and many of them required a vascular procedure.

So the key here is defining -- between the two yellows areas there's supposed to be a pink box of who might be expected -- what inoperable patient might be expected to benefit from this procedure.

So, finally, the inoperable patients who received the device had a very impressive reduction in mortality compared to those randomized to not receive the device. And we feel that this reduction of mortality in inoperable patients outweighed the significant risks associated with this device, especially stroke and vascular injury. And we think that long-term issues of aortic insufficiency and valve durability need to be looked at

because, again, inoperable does not mean short-lived; and that patient selection needs refinement, including judgment of whether a patient goes back to the same residential status, whether they go back home if they came from home, whether they go back to a -- go to a nursing facility, chronic nursing facility. If they originally came from home, is that a success?

So those issues, I think, we'll be refining as we look at trial designs for devices of this type in the future. Thank you very much.

And the next speaker will be Dr. Ritchey talking about the postmarket study.

DR. RITCHEY: Good morning. I am the epidemiologist on this PMA team and am responsible for the epidemiological review of the PMA contents and working with the Sponsor on development of a postapproval study protocol. I'll be presenting the postapproval study considerations for the Edwards SAPIEN Transcatheter Heart Valve. And in the event that the SAPIEN is approved, we will continue to work with the Sponsor to develop a protocol on which both the Agency and the Sponsor can agree.

Before we talk about postapproval studies, we need to clarify a few things. First, please be reminded that the discussion about a PAS prior to the FDA determination of device approvability should not be interpreted to mean FDA is suggesting that the device is safe and effective.

The plan to conduct a postapproval study does not decrease the threshold of evidence required by FDA for device approval.

The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate benefit/risk balance.

Second, please be reminded that in terms of study design, postapproval studies should contain a fundamental study question or hypothesis, a well-specified study population and study design, safety endpoints and methods of assessment, short-term and long-term safety and effectiveness endpoints and methods of assessment, and duration of follow-up.

For this PMA the FDA review team has identified the following postmarket concerns and recommends that a PAS be conducted to assess the following: long-term device durability, long-term patient quality of life, a learning curve assessment, and additionally a comparison of postmarket patients with a premarket cohort, as needed, to assess adherence to indications for use, differences in patient populations and outcomes, including stroke, device durability, and patient quality of life.

The Sponsor has proposed two postapproval studies to address the FDA concerns. The first study is an extended follow-up of the premarket cohort, which we refer to as PAS 1. This proposed study evaluates long-term device performance, including evaluation of device durability and patient quality of life. The second study is a new enrollment study, which we'll refer to as PAS 2. The study proposal includes short-term and long-term evaluation

of newly enrolled patients.

The following slides provide summaries of FDA assessment of the Sponsor's study proposals.

First is an overview of PAS 1, the extended follow-up of the premarket cohort. The study objectives are to evaluate long-term or a five-year valve implant durability, and long-term or five-year quality of life. Longer-term data collection is included in the proposed data collection section.

Enrollment of these patients is complete, as all patients were enrolled during the premarket stage of the study.

The proposed study does not have specific hypotheses for durability or quality of life, and a specific and predefined study hypothesis is needed to evaluate whether the study will adequately address the objectives.

As I said, all patients were enrolled during the premarket stage of the study. The Sponsor proposes continued follow-up through five years post-implant for patients who were enrolled in the premarket setting and who have not died and who have not withdrawn from the study.

The Sponsor indicated that about 10 to 30 percent of SAPIEN patients and virtually no comparator patients are expected to be alive at the five-year visit. Thus, the early long-term data will be fairly limited, but the limitation is acceptable as its inherent to the population under study.

The proposed PAS 1 will follow the premarket protocol with

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modifications to include analysis of echocardiography data at four and five years post-implant, and collection and analysis of four and five-year quality of life data via the SF-12.

To assess durability, the Sponsor proposed development of a linear regression model to study the progression of valve area, mean gradient, and aortic regurgitation over time, beginning with the 30-day visit.

To assess quality of life, the Sponsor proposed comparison of SF-12 physical and mental summary scores to baseline values and to published age group norms for the general population using a T-test. The Sponsor indicated that only actually observed data would be included in evaluations and that data from the four and five-year visits would be analyzed separately.

The sample size at five years is expected to include less than 100 patients in the SAPIEN arm and virtually no patients in the control arm.

Use of a study hypothesis will allow for power calculations, thus indicating the robustness of these findings to the alternative hypothesis.

Regarding outcomes, the current protocol of the IDE study is designed to collect data through five years post-implant, including echocardiography data at years four and five. However, quality of life data at years four and five will require a modification to the protocol and patients will need to sign a modified informed consent form.

Since patients using the device for the proposed indication

were previously inoperable, quality of life data provides the best data for the expected patient experience with the device and will be very useful for future patients and their clinicians in determining whether use of the device is the best option in their particular circumstance.

In light of the need for the re-consent of IDE patients to gain this very beneficial data, the FDA requests that the Panel discuss the practical clinical utility of the quality of life data from the IDE post-implant years four and five.

Next is an overview of the Sponsor's proposed design for PAS 2, the new enrollment study. The study objectives are to evaluate safety, including stroke, adherence to indication and learning curve assessment, and long-term assessments of valve durability and quality of life in the postapproval population.

The non-inferiority study hypothesis are that the event rates among newly enrolled registry patients will be the same or greater than the performance goal event rate for a composite safety endpoint at 30 days and a composite effectiveness endpoint at one year post-implant.

The proposed performance goals were derived from findings in the premarket cohort, with up to 1.3 times the premarket rates, or a 30-percent increase, considered as non-inferior. This means that with the composite safety event rate derived from the premarket set at 30 percent for 30 days post-implant, a difference of nine percent would be considered

non-inferior.

With a composite effectiveness event rate derived from premarket set at 50 percent for the one-year post-implant endpoint, a difference of 15 percent would be considered non-inferior. Due to these wide margins, FDA has requested a reduction to 1.2 times the performance goals.

Please note: the proposed study does not have a specific hypothesis for learning curve assessment or long-term patient assessment. The specific and predefined study hypotheses are needed to evaluate whether the study design is proper to address the stated objectives.

The Sponsor proposes to newly enroll 750 to 1,000 patients from a minimum of 75 sites which were not included in premarket studies. The Sponsor indicated greater than 99 percent power with the sample size, given the current delta, and no power calculations have been provided with the requested delta of 1.2.

Each site will consent a minimum of 10 patients and a maximum of 20 patients. All sites will be recruited in the first year of commercialization and perform at least 50 valve replacements per year. However, the outcomes at sites performing fewer than 50 valve replacements per year are expected to differ from the premarket cohort.

In addition, the learning curve may divert these low-volume sites. If these sites will be recruited in the second year of commercialization,

then extending recruitment to these smaller sites is warranted.

Data collection of long-term valve performance endpoints and follow-up are scheduled through five years post-implant.

The composite primary safety endpoint will be reported at 30 days and 1 year. It will only be evaluated against the performance goal at 30 days post-implant. It is based on the 2011 Valve Academic Research Consortium, or VARC, guidelines and includes the components listed on this slide.

The occurrence of stroke is a postmarket concern by FDA due to the premarket findings. However, only major stroke was included in the primary safety analysis, nor was an all-stroke hypothesis-driven comparison proposed. With the addition of all strokes to this endpoint, power at the proposed sample size is expected to increase.

The composite primary effectiveness endpoint will be reported at 30 days and 1 year but will only be evaluated against the performance goal at one year post-implant. The composite is based on the 2011 VARC guidelines and includes the components listed on this slide.

In evaluating outcomes, the Sponsor's primary safety and effectiveness endpoints are composites of multiple outcomes. Composite endpoints that are heavily influenced by one component, such as death, or contained components of particular interest, such as stroke, may not provide an accurate picture of the safety or effectiveness of the device.

The Sponsor proposed evaluation of a safety composite at 30 days and evaluation of an effectiveness composite at one year in the newly enrolled patients. Longer-term data collection is included in the proposed data collection study and will be included in a final report at five years.

In addition, the prespecified evaluation is needed to fully assess differences in outcomes when comparing postmarket patients to those included in the premarket cohort.

The full list of proposed secondary endpoints can be found in the Panel pack. Of note, all neurological events, including major and minor stroke and TIA, are defined in the VARC guidelines and are proposed as a secondary endpoint for measurement at 30 days and 1 year post-implant.

We've requested an analysis of this endpoint, including a testable hypothesis, and have asked for power calculations so that we may evaluate the robustness of the results, given the proposed sample size.

Another consideration is that vascular complications are not characterized within the study. However, a high proportion of major vascular complications were observed in the SAPIEN arm in the premarket study. If all major vascular complications were included in the safety endpoint, this would again increase the power in the Sponsor's proposed sample size.

In addition, we've requested analysis of vascular complications, including a testable hypothesis and power calculations, as with stroke.

In addition, the Sponsor proposes use of an anticoagulation

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protocol for pre-, peri-, and post-implant. However, the anticoagulation protocol is based on the stroke risk and atrial fibrillation patients and is not validated in this patient population, so it's unclear whether the anticoagulation protocol is appropriate for these patients.

The Sponsor proposed to assess a learning curve via analyzing composite safety and effectiveness outcomes according to the VARC guidelines.

In addition, the Sponsor proposes to conduct secondary analyses of outcomes using analysis of patients ranked by order of implant. The analysis will be repeated in separate models for implants by site and implants by interventionalists.

For example, in these analyses, the expected-to-observed ratios for each site will be considered in the overall assessment of site performance. Each implant will be given a rank order based on the number of implants at the site. The rank will be included as a continuous predictor in a logistic regression model and a curve will be constructed. Various early and late cutoffs suggested by the curve will be considered.

The Sponsor proposes newly enrolling 10 to 20 patients per site at a minimum of 75 new sites. With at most 20 patients per site, fewer patients will be enrolled for each interventionalist who's experiencing a learning curve. It is unclear whether this constitutes an adequate number of patients per interventionalist for evaluation using an indicated analysis curve.

The small number of patients per interventionalist may also prevent comparison of outcomes associated with earlier and later patients treated by the same person.

In addition, the learning curve associated with transcatheter valve replacement consists of two separate pieces: technical aspects of the procedure and appropriate patient selection. Both need to be learned by the interventionalist new to the device.

No assessment of appropriate patient selection was included in the study protocol.

The Sponsor has proposed two postapproval studies if the PMA is approved. The first study proposes extended follow-up of the premarket cohort, and the second is the Sponsor proposes a nonrandomized, prospective, consecutively enrolled registry of new patients undergoing transcatheter heart valve replacement therapy.

FDA requests Panel input on the appropriateness of the proposed postapproval studies, and in your discussion this afternoon you'll be asked questions which correspond to the following topics: the appropriateness of assessment to longer-term outcomes and quality of life, learning curve, and the postmarket patient concerns, the time frame, evaluation and presentation of learning assessment to the clinical community, the use of VARC composite endpoints, the use of the performance goals derived from the premarket data, and the proposed

objectives and study design.

And this concludes my presentation, and I'll now hand it back over to Matthew Hillebrenner for the FDA summary.

MR. HILLEBRENNER: Thank you, Mary Beth.

So we've talked about a lot of issues this morning. Certainly an important device that we're considering. I'd like to provide a few summary comments and introduce many of the issues that FDA is interested in your input on.

As you've heard, the primary safety and effectiveness endpoint was met. The inoperable patients who received the SAPIEN device had an impressive reduction in mortality compared to those who did not receive the device.

However, there are a number of other factors that we believe should be considered in the evaluation of the overall risk/benefit profile of the device, and we'd like to remind you of those issues here.

The proposed indications for use. We've clarified the issue of symptomatic, and we also have highlighted a couple of the pieces, the clauses in the indication that we feel identify the patient population who not only is inoperable, who were studied in this study, in this trial, but also who are most likely to benefit from the procedure. We're interested in your input on that.

Relating to patient selection, how do we ensure that those patients who are most likely to benefit will get the device? I think one step

would be the indication and the other will be, you know, in a training program. How do we ensure that this is consistent going forward?

We also talked about the heterogeneity of the control group, signifying that there really is no obvious standard of care in these patients. I think it reflects some of the limited treatment options they have, but also the opportunity for selection bias as we consider how to treat these patients.

FDA spent, as well as the Sponsor, talking about some of the key adverse events that occurred in this trial, notably, the neurological adverse events, and based both on the PARTNER trial as well as the worldwide experience with transcatheter valves, certainly stroke and TIAs, other neurological events, remain a concern.

What measures can we take to mitigate this risk? We've talked already about the anticoagulation/antiplatelet regimen, that it wasn't, you know, standardized in a protocol in this trial. So that represents certainly an opportunity to improve upon this risk as we go forward, whether it's additional premarket trials or in a postapproval study. We're also interested in any other thoughts you have about how to handle that.

Vascular complications. It was already acknowledged that this is a first-generation device/delivery system that is definitely part of the issue here. And, you know, I think obviously the Sponsor is making efforts to refine that technology and study additional devices and delivery systems.

But as we move forward with the commercialization of this

product, how can we minimize this risk? There's a comprehensive training program that the Sponsor has walked you through. Are there any additional features of that that you think would be helpful, or do you think this is the best we can do at this point, in terms of minimizing the risk?

Aortic insufficiency, I think, is something we've looked at in the short term. We have limited data, though, in the long-term setting upon which to base any judgment of the clinical significance, and I think this is something that we want to continue to monitor in a postapproval setting as well.

The valve-in-valve technique. It did not occur frequently in this trial. There were four patients who received a valve-in-valve operation. However, based on a number of literature references, it's clear that this is something that may occur more widely in commercialization. It happens in any number of formats, whether it's transcatheter valves inside transcatheter valves, transcatheter valves in surgical valves, or other configurations.

And I think the FDA is looking for answers on how to address preclinical testing for this configuration. We've had a number of discussions and public meetings. No one has the right answer here, and I think we certainly acknowledge that there are a lot of challenges to the number of different configurations and how you might go about demonstrating that safety or really making conclusions from those studies.

That being said, you know, we are looking at how to write a

label for this product, and we'd be interested in your thoughts, perhaps, as to how we might do that through the device labeling.

And just again looking at long-term data. Already it was a question about the Kaplan-Meier curves beyond two years, and it was hard to see in some of the FDA slides due to the coloring issue. But I think you get the sense of the limited data we have in the PARTNER trial beyond two years. We want to continue to follow that from some of the major outcomes, but also from a valve performance perspective. And, you know, can we look at the postapproval setting to try to do that certainly will be a key question we have for you.

So I think everyone agrees that we need a postapproval study here, the Sponsor and FDA. We want to find a way to determine adverse event rates in the real-world use. Certainly refine a way to assess the learning curve, which we've talked about already. Dr. Ritchey alluded to it.

A very specific question about quality of life: Do we collect these data in the PAS 1 study, where we have a limited number of patients left? But there's certainly an interest in understanding the impact on quality of life in this patient population.

In addition, we have the issue of unblinded trials in both cases where, you know, we need to decide on the value of quality of life data and how we might interpret it.

And then lastly, you know, what is the appropriate length of

follow-up for the postapproval studies?

So I want to thank you for your time, certainly as you've spent preparing for this meeting and looking at this application, as well as the discussion today, and I'll open the floor for questions for the FDA.

DR. PAGE: Thank you very much for a very well-prepared and efficient presentation.

We can now take questions from the Panel, who have brief clarifying questions for the FDA. Please remember that the Panel may also question the FDA during the Panel deliberation sessions later this afternoon.

And I see Dr. --

DR. ZUCKERMAN: Okay, to expedite the process, can we have the FDA presenters just come up to the table? Dr. Wang also will take your questions.

DR. PAGE: Thank you. Dr. Kato.

DR. KATO: Thank you. I would like to see Slide Number 23 redone with the -- you know, that dark line that came out because it's -- what we're seeing on the color printout, it looks like, at three years, the survival curves cross again. So, you know, maybe you can really fix that slide, you know, for this afternoon.

MR. HILLEBRENNER: I can work on that slide. I will say one thing. The point we really wanted to make clear with that slide is, though the curves do cross and the Sponsor mentioned the potential confusion that that

may create, the real point is that we have one patient between the two arms at that point.

DR. KATO: Correct.

MR. HILLEBRENNER: So I think we're really trying to illustrate the lack of data.

DR. KATO: Okay.

MR. HILLEBRENNER: But we will work on that.

DR. KATO: Okay. And I guess one quick second question is, if I remember correctly -- and forgive me if this is incorrect, but the history of valve performance used objective performance criteria that was established many years ago. What kind of caused the FDA to kind of go off on the path of doing a trial versus using OPC data?

DR. SWAIN: A totally new device and paradigm for valve replacement. So we made this decision probably a half a decade ago, that using performance data based on '50s, '60s, or so, data from open surgically implanted valves was not appropriate because there really are new questions of safety and efficacy regarding this approach, and you can see it from the neurological and vascular complications. So that is the paradigm that we plan to use for future devices in this field.

And you've heard the Sponsor talk about the newest study, which is new device versus this device, assuming it is approved. And because we don't view that there's probably ever going to be a possibility of doing a

trial versus "standard" or nothing or whatever the control is, that that's not possible.

We also realize that once you get -- every patient has an opportunity to get one of these two devices, those patients are going to be different than the ones studied in this trial. I don't think you'll ever have the same patients that the surgery group and the executive committee spent hours, you know, figuring out, can we really operate on them or not? Because, you know, you're going to be randomized to essentially nothing, nothing new. So those are all the issues regarding the trial design for this.

DR. PAGE: Dr. Borer.

DR. BORER: Yes. First, I want to tell you my bias. I absolutely, 100 percent agree with the FDA decision to go this route. So Norman asked the question, but I support it, that it was the right thing to do. We just didn't have the data and we've seen that we didn't have the data.

My question, though. Both you, Julie, and Matt indicated that there was an impressive reduction in mortality, and I want to understand that conclusion a little better.

The trial was a landmark trial. It was a magnificent effort. It's provided us with data that we never would've had. But the impressive reduction in mortality, when you look at the curves that we have, a relatively small trial, but most everybody's dead, you know, by the end of the follow-up period that we've got.

The data that we have and the data from Europe that support it suggests that even with the device and all the selection criteria and everything, more than half the people with this device will be dead in two years.

The way I calculated it -- and I think this was in the original paper -- the increase in life expectancy in this mid-80s, extraordinarily sick population was 1.7 years, and your median data showed that it was about one year, a little more than one year. That's a highly significant improvement in survival, but how important is that?

And both of you said impressive reduction, so I'd like to know how you come to use that word. It's important to me because I kind of think that quality of life here, even though it's so hard to measure and we've got to give heavy weight to strokes in considering this -- and we'll get to that later -- how impressive is this reduction in mortality, besides its extraordinary consistency and high statistical significance?

DR. SWAIN: Well, that was kind of a phrase I came up with because, in statistical significance-wise, it's impressive. And, you know, we all look at cancer trials where you have an incredibly statistically important result showing superiority and survival is an extra six weeks or something.

But here, you know, there are signals, and again the quality of life is huge. If you remember all the different trials, you know, getting your back injected and amazing with sham controls and amazing improvement in

the methods we have of measuring quality of life. So I don't know. But, again, you look at the diversion of this trial, the point estimates at one year, a 20-percent difference, then I think that adjective is pretty good.

DR. PAGE: Thank you. Dr. Naftel.

DR. NAFTEL: So I need just a little help with the language. I think, Dr. Swain, you're going to be able to help me here. You said there are two components. Can you do the operation and should you do it? And I get that.

The word inoperable, I always thought that was can you do it? It's like we need another word for should you do it? Inoperable doesn't sound like a very good word to me. Do you have any suggestions?

DR. SWAIN: That's a great point because we've all had patients come to us and say some other surgeon said we're inoperable. It turns out they're inoperable because they don't need an operation or shouldn't have an operation. So I would really appreciate if we had some other way of describing that group.

And Marty's slide was great in that it showed the whole group of inoperable and then the circle in the middle saying those that should get this device.

So that's the main thing we need help, and I think CMS needs help from you all of how in the world do you define a qualitative surgical judgment? Because inoperable to Val may well be totally different than

inoperable to the guy one day out of his residency who's the only cardiac surgeon in town. So this is hugely important.

DR. PAGE: Dr. Somberg.

DR. SOMBERG: I request a clarification from the FDA on the general concept of requesting the Sponsor to undertake evaluation when it is outside the label for the device, and specifically the valve-in-valve issue. I did not see any of that in the requested indications.

Because somebody goes way beyond the indications of a device, should a sponsor be required or is that an undue burden to investigate a potential interaction when it is outside the label? Can you give me a clarification on that principle?

MR. HILLEBRENNER: So I think you've hit on a great question, and it's not an easy answer, and I think part of the decision on the part of the FDA comes with, you know, what is the expectation that this is going to occur? And, you know, we need to make sure that the label adequately informs future users of the device and captures what data we actually have. So, you know, I think the Sponsor has made it clear that they do not intend to formally indicate this device to be used in that way.

So, you know, I don't know that we have data on a contraindication, but we put warnings, precautions, things of that nature into labels often for situations like this, where it's something that no one maybe has the data on, but we want to make clear what was and wasn't studied in a

trial.

So I think, you know, part of that, the FDA's effort, you know, we didn't uphold the start of a study or submission of a PMA because they didn't have those data. As you saw, it didn't occur very frequently in this trial. However, we have an anticipation, based on what's going on worldwide, that this will occur and we feel that we need to start pursuing this in one form or another.

DR. PAGE: In terms of clarification, the protocol did not prohibit valve-in-valve; is that correct? Certainly, if it did, it occurred in four cases out of 170 implants. So more than two percent of the cases in the best hands ended up having a valve-in-valve procedure in the setting of the physician assuming -- assuming the physician felt that that was the best thing to do in a critical situation. So it does occur.

DR. SWAIN: Yeah, it does not prohibit it and it's not something that was even thought of or mentioned at the beginning of the trial. I have to mention that, in future trials of devices coming through, we're going to require that data on that be captured really before the trial, hopefully before the trial starts or at least all of the trial starts.

DR. SOMBERG: Well, now that we're getting --

DR. PAGE: Dr. Somberg, do you want to comment again?

DR. SOMBERG: Yes, I would, please. Now that we're getting interested, I think Dr. Zuckerman might want to address this because I think

it's a fundamental principle of device development and regulatory affairs in that if something is not in the indications of it, what is the purview of your division to try to mandate? I just heard someone say to try to mandate something when it's outside the indications.

DR. ZUCKERMAN: Okay, John, you're raising a great point, and I think Mr. Hillebrenner gave a good initial answer. But I would remind you that we're a public health agency as well as a device approval agency.

And certainly we'll get into this this afternoon, but when you look at the warnings and precautions of the current label, specifically it's silent right now on this issue, and we know it's going to happen.

Just like within the drug-eluting stent arena, some unusual uses of drug-eluting stents occur, and wouldn't be so much better if, instead of saying as a warning or precaution, we have no data, we just proactively try to get a dataset that can help guide physicians for extremely difficult patients. I know that this will occur in the future.

We've heard from the Sponsor and Dr. Borer how sick these patients are. A practicing physician might really want to consider this option for a good reason, and if we can figure out, in a least burdensome fashion, which is another one of our cohorts, how we can do this, I think everyone would benefit. And we'll talk in more detail this afternoon.

DR. PAGE: Thank you. Mr. Barrett.

MR. BARRETT: Thank you. I have a couple of postapproval

study questions, in particular about PAS 2. They're probably best addressed by Dr. Ritchey.

I'm trying to get a little bit of a better handle on sort of the flavor or the extent of what the FDA is envisioning in this study, and as somebody who works in studies, I may take a slightly different tact to it. But as I heard describe the elements that the Agency is recommending or interested in, certainly there needs to be a protocol, which means there needs to be an IRB approval. I'm envisioning that the patients are going to have to agree to at least some assessments or some visits that would be outside of the standard of care, so there has to be an informed consent.

Would the Agency envision on-site clinical monitoring, or would this be more of a mail-in kind of postapproval study? That's my first question.

DR. RITCHEY: So as part of this proposed study, there would need to be information that would need to be collected via echocardiography. And so my understanding -- please correct me if I'm wrong -- is that that needs to be done on site.

MR. BARRETT: Right.

DR. RITCHEY: So it would be annual visit for --

MR. BARRETT: The patient would come back annually, okay.

DR. RITCHEY: Yes.

MR. BARRETT: So, you know, when I look at all of the elements, I look at, you know, a protocol, an informed consent, some on-site

monitoring, some nonstandard-of-care testing, which has some expense associated with it, a patient number and number of sites that's significantly larger than the study that is under discussion today, to support approval or not. To me this has all the elements of a well-controlled clinical study. In fact, the only difference is it's not randomized.

DR. ZUCKERMAN: Okay, Mr. Barrett, let me, for the sake of time, try to directly address your concerns. Number one, we evaluate devices, as you know, throughout the total product lifecycle. Our obligations don't stop with an approval. In fact, for many recent circumstances with transformative technology, it's actually more important to look at how devices actually are used and disseminated in the real world, rather than looking at a small to moderate sized IDE trial. That's only one component.

The Agency full recognizes your concerns regarding putting in elements that are reasonable and necessary and will have valued added. For that reason, there are a specific set of questions that we're going to really hone in on with the Panelists to help define a well and thoroughly executed postapproval study. But to indicate that the postapproval study is not a part of our regulatory mission is not a helpful aspect of device approval.

MR. BARRETT: No, that's not where I was going, and I was almost about to finish. What I was going to suggest is that those are the elements that are important and that, you know, at the highest level, when I looked at the list of questions, the questions are very similar to the original

study and then more extensive. And hopefully the Panel will help the Agency focus on the truly open questions. And I'm not making this comment just in relation to today's meeting and this Sponsor, but obviously because this is an important consideration for all sponsors, not just in this field, but in all of the fields. Thank you.

DR. PAGE: Ms. Patrick-Lake.

MS. PATRICK-LAKE: My question is also for Dr. Ritchey. I was hoping that you could help me clarify. So the postmarket study, it's showing follow-up to five years, but earlier I think we heard Ms. Akin say there may be a conversion of a study to a registry that's a partnership of professional societies, and I'm very unclear at what point that occurs and how that happens. And maybe it's premature and you don't know yet, but any information would be appreciated.

DR. RITCHEY: So the Post-Approval Study 2 is intended to be a registry from the beginning, and at some point that is still to be determined. So beyond that initial registry conversion to the professional society, we don't know the timeline for that yet.

DR. PAGE: By good timing, Dr. Brindis had his hand raised and he's an expert in registries. Dr. Brindis.

DR. BRINDIS: I'm still learning. Actually my question was along those lines. The Sponsor suggested the concept of a national registry following patients. I notice the FDA actually did not mention that.

And so with the concern of public safety, particularly with the appreciation of devices being used off label and the discussion, for example, that we've already had with valve-in-valve, I'm also kind of interested in the FDA's position in the concept of a national registry to be run concurrently or sequentially with the postapproval study. We have to understand there's a difference between a postapproval study and a registry, both of which have added value to the public health in the application of this new technology.

MR. HILLEBRENNER: I'll start out, Mary Beth, and if you want to jump in.

So I think I'll start by saying that FDA certainly sees the value of this registry. We are supportive of the effort. I think that, you know, we have some experience here from which to draw. The challenge will be how to design. You know, you said value of postapproval studies versus registries and can they actually be combined.

So I think, you know, we're trying to weigh what are the important issues we really need to see out of a postapproval study for this PMA, and I think it might be a separate question of can, then, a registry, a national registry be utilized to provide data to answer those questions. And I think, to the extent that we can work together with all of the various parties involved, it would be nice to be able to do those things in conjunction because it would be more efficient.

We have experience, you know, with a similar effort, the

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INTERMACS registry, which I know some of you are very familiar, that, you know, we were able to design a registry that included a number of different collaborators that fed a postapproval study into that. And we're even using it for some premarket trials. We're still working through the kinks there as well, but I think we were able to achieve this.

You know, the question will be, can the various parties who need to weigh in here agree on the data elements such that everyone could be satisfied?

DR. PAGE: Did you have a follow-up, Dr. Borer, otherwise I was going to be calling on -- okay, Dr. Good.

DR. GOOD: Yeah, I don't want to change this discussion because this is really important. I had a question, a different line, if that's okay.

DR. PAGE: Go ahead, please.

DR. GOOD: Okay. So a clarification question for the FDA. Based on the briefing document you provided on page 23 of 36 -- and this relates to the timing of the risk of stroke following implantation -- I think it's fairly clear that there's a risk early after implantation. The Sponsor also presented information that suggests that. But on this particular page, the comment is made that 48 percent of the neurologic events occurred greater than 30 days, thus indicating a continuing risk of neurological events with the device. And then that's elaborated on in the next paragraph, too.

So that seems to be a little bit different than what you presented today as well, and I wonder whether you might elaborate because I think it's important to know if there's a continued risk.

DR. SWAIN: Yeah, it's been, let's say, very difficult to get a handle on the strokes in this trial for a whole lot of reasons, and when you look at the slide I presented with days on it, and which I think is in that -- and I don't have a copy of that right in front of me and don't have my glasses on, so 0 for two -- that there appears to be a risk higher than control.

But, again, we don't have a control that you can judge because patients got a balloon valvuloplasty at day one or they got one three months later in the control group and then had a stroke. That's why I've looked at, instead of time from randomization, it's time from when I knew or could figure out whether they had some other invasive procedure.

So I just don't think we know very well the continuing risk, other than what's put up in that slide. And you can't make a lot of comments about this, but hopefully in the future we'll be able to make those comments.

DR. PAGE: Thank you. Dr. Borer.

DR. BORER: Yeah, just in the clarification mode. Again, we'll get to this discussion later, but I think quality of life, or whatever the components of it are, is a very important issue here, and I'm wondering if I can just know how you selected SF-12 as the instrument to use to capture this. This is not a value judgment question, just I'd like to know.

MR. HILLEBRENNER: Are you referring to the premarket trial or the postmarket trial?

DR. BORER: Postmarket trial.

DR. RITCHEY: That is what has been proposed by the Sponsor at this time. We're happy to have further clarification of that and comments from the Panel.

DR. PAGE: Dr. Somberg.

DR. SOMBERG: I want to return to the issue of stroke because now you've confused me with your answer, and I would appreciate if both the FDA and the Sponsor could give us some information this afternoon on this because I'm looking at the Sponsor's presentation on Slide C-93 and C-94, both for the ITT and the AT populations, in terms of timing of neurologic events, and it seems it's all clustered in the first five days, and I just think that's very different than 48 percent over time. So we have a difference in data.

Since I haven't looked at the data per patient, I think this needs to be resolved because, going back for a second, the most important side effect, I believe, in this process is stroke and there may be a factor on how you label it and how you therapeutic if it's in the first five days. If it's a continuous problem, it's totally different. So I wish we could clarify that as time goes on.

DR. SWAIN: And there's a difference between stroke and

neurological event, of those TIAs that didn't have DW-MRIs. So I think that 48 percent probably refers to neurological event. And we can look at those numbers again. It's just been extremely difficult to get my arms around the stroke issues. I probably spent 100 hours looking at these in this trial, and it has been extremely difficult.

DR. SOMBERG: I must say the Sponsor, on these two slides, calls it neurologic events.

DR. PAGE: Maybe we can get some clarification after the lunch break from the Sponsor. Dr. Somberg has an important question.

MR. HILLEBRENNER: And I think one other difference in the numbers is that slide went through one year. The numbers that -- I believe that 48 percent may reflect over the duration of the trial. So the data that we presented on Slide 53 does include data beyond one year, so that may make a difference in the numbers as well.

DR. PAGE: Thank you. Ms. Patrick-Lake.

MS. PATRICK-LAKE: Okay. So as the patient, I'm now thoroughly confused about the causality of stroke, and I think patients are going to know, in decision-making, is it going to be some type of, I guess, thrombosis that's formed on the device that might let go later and be the cause of a stroke, or are we talking about a complication due to a large-sized catheter that's being manipulated in tight areas and releasing embolic material?

DR. SWAIN: A great question. So there are periprocedural events where strokes were recognized at maybe four or five days but may well have been present before then. But there's definitely incidence of these events that occur after the periprocedural time period.

And there's one slide that was, I think, shown at a meeting that came out of the Cleveland Clinic, looking at kind of a rawness on this and the different opportunities for turbulence and a stasis of flow.

So I think that it really is multifactorial, and if we thought it was just going around the aorta, then, you know, you'd expect transfemoral and transapical to have a big difference.

So we just don't have the answer on strokes. That's why months ago when we first saw this data, and I think we were the last one to see the data at the FDA, that we decided that we need a whole new way of doing things on evaluating patients in this study, and that's why we worked with Dr. Marler and several others on the FDA stroke team to get a way -- and for all the companies that are sitting here that have other devices, we have a little white paper recommending how these patients should be studied.

MS. PATRICK-LAKE: So I think this is going to be incredibly important for patient decision-making. If you're going to prescribe an anticoagulation profile, patients are going to expect a certain level of protection. They're going to be very disappointed if they have a stroke. So I think maybe there's no clear answer, but it's something to be considered as

we go forward.

DR. SWAIN: Yeah. And what the Sponsor has provided is really a mechanism to have a protocol and, you know, it's based on CHAD scores which exclude patients with valve disease and they have A-fib, well, neither of which were kind of included in this trial. I mean, it's the opposite. But it is a rational way of going for it and, you know, it'll represent the first study and it'll need to be refined, but it's a great step forward for future studies and for postmarket recommendations.

DR. PAGE: Ms. Patrick-Lake, if I can put you on the spot a little bit here with regard to the definition of stroke. We've already heard from the FDA that there was concern about basically changing the rules in the middle of the game or after the game was over in terms of definition of stroke, minor versus major. And in terms of assessment of safety, I think we need to go with the predetermined definition.

On the other hand, as a patient representative, would you say it's important to know the degree of stroke, Rankin 1 being minor effect versus kind of all strokes put together, as a patient would be considering this procedure?

MS. PATRICK-LAKE: Patients are concerned, I think, with quality of life and level of disability, and the information that's been provided, particularly in the patient brochure, which was in general very good -- I appreciate the work the Sponsor put into that -- the table that lists the

risks for stroke, patients aren't going to know the difference. Basically it says 1 out of 10, and the next one says less than 1 out of 10, and it's meaningless to patients.

That same document also lists stroke and TIA as neurological changes, when, throughout the literature that was provided to us in the briefing document, it was consistently listed as neurological event. So I think it minimizes an event, but I don't think what is seen here is meaningful to patients yet.

DR. PAGE: So this will be valuable to discuss after the break with both the Sponsor and the FDA.

Dr. Borer.

DR. BORER: Yeah, I was going to save this one for later, but this is a good time, especially with what Ms. Lake has said. I'd like to know -- and this isn't a trick question; it may seem so -- if the FDA has an equation for stroke and death. The Sponsor showed two slides, and I've seen them before, in which stroke and death were added and the device improved the situation significantly, compared to control, when stroke and death were added together.

I find that very difficult because it presupposes that there's some equivalence between stroke and death. In this population, I don't think there is. But I'd like to know if the FDA has an equation for stroke and death, you know, whether it's kosher to put the two together like that.

DR. SWAIN: No, we don't have an equation. We, for many years, have used -- and I hate the term major and minor because it really confuses stroke neurologists because that's a specific acute term. But, you know, major stroke-free survival, you know, or major disability-free survival. And for LVADs, it was a Rankin 4 or 5, which is just horrible, you know.

But the question becomes what kind of disability. You know, the famous stroke patient at UCLA in one of the studies who had this "minor stroke," that he couldn't calculate anymore. It turns out he was an accountant. So, you know, it's in the eye of the beholder, of what minor is.

Now, we have a problem with the Rankin, somewhat, we're trying to work out, to make it uniform, that in one measure of Rankin by one group, Silva from Stanford, that wrote the structured interview, and it's used in England a lot, is that it means a significant disability, which means, if you can't do 49 percent of what you used to be able to do, you're still a Rankin 1. That's not a significant disability. And then there's the other phrase, able to do all usual activities. Those two really don't fit together.

So we're working out with all of the companies, and especially John Marler and our stroke neurologists, that, you know, able to do all activities is really a one. If you can only play eight holes of golf two times a week instead of five times a week, that's a two. But there's a lot of other things in the stroke group. If you used to be able to go and buy all of your groceries once a week shopping, but now you can go to store and you can still

buy something but you only can buy one thing, in some ways, to assess it, that's a Rankin 1. That's no significant disability. I would view that as a disability. If you can't be an interventional cardiologist anymore, but you can be a cardiologist, or you can't really operate anymore, but you can be a surgeon and work for the FDA, you know, is that different from what you want to be?

(Laughter.)

DR. SWAIN: So, you know, we have big problems with -- we've got to get on the same page on how do we define these Rankin terms. And Dr. Good may have some comments about that.

DR. ZUCKERMAN: Okay. So Dr. Borer, to sum it up, we don't have a simple mathematical equation. The only thing we can do from a mathematical perspective is, as you point out, combine the two endpoints so we can get a reasonable sample size and develop a clinical trial.

We really are going to be asking the Panel this afternoon to think about this critical point, and we look forward to your comments, as well as those of Dr. Good and others, on this critical issue because, as Dr. Swain indicated, this has very significant ramifications both for this Sponsor, multiple other sponsors and, most importantly, the American public.

MR. HILLEBRENNER: I'd like to add one other thing, though, to address Dr. Borer's question about that figure; that, I think, from the FDA perspective, as you heard, first, I think we prefer to see that as death plus all

stroke. There's obviously limits to the interpretability. I think, though, the other slide that the Sponsor presented was, you know, the correlation between some of the serious adverse events and mortality. So what you're seeing in that slide is that, I think -- and they can clarify this, but that a majority of the patients who did have those strokes also died. So there wasn't, you know, a shortening of the gap because the patients really did fail the primary endpoint anyway. But I think they could probably clarify that later.

DR. PAGE: Dr. Good, did you have a comment?

DR. GOOD: Well, I agree with everything you said about the modified Rankin, and it's sometimes very difficult to go between a one and a two and determine exactly which is a one and which is a two. There are strict criteria that you're supposed to use, but in real life it's difficult.

And, you know, I think your comparison of the surgeon who can't do surgery anymore but can serve on the FDA is a good one. You know, I had a patient -- I don't want to tell anecdotes, but I had a patient who was a piano player and she scored very well in the Rankin but she could never play piano again and, you know, it was horrible for her. So, you know, I mean, I think you have to be kind of careful about how you use these terms. Enough said.

DR. PAGE: Thank you. Dr. Naftel.

DR. NAFTEL: So composite endpoints, we have them, as Bram

said, for sample size and statistically you're only supposed to look at that composite endpoint. You're not supposed to peel back and look at the components. But that's just so illogical. We have to do that. And, Julie, you showed us how and the Sponsor showed us how death is driving so much of the composite endpoints.

What I will be doing over lunch mentally is trying to figure out everything that we've seen, and I'm going to try to pull death out of it and say, if these two arms had the same death rate, then which one would I pick? Because I'm really trying to figure out the strokes, the procedural problems, and just figure it all out.

And of course I think you know what I'm leading to. I am not as impressed with the survival benefit as everyone else seems to be. It's impressive that there's such a difference, but it's very depressive and very unusual that it's an incredibly poor survival rate in both groups. So it's really bad survival. And after lunch, we'll go into those extra deaths, and I hope I'll have the opportunity to tell you what I think about the sample size dwindling.

But it's not 10 percent that you've got left at two years. You've got 60 patients. That's a third of the patients, and near as I can tell, 12 of those died after two years. So there's a lot of information there. So we'll do that after lunch.

DR. PAGE: Speaking of lunch, I'm going to call the lunch break now.

We will reconvene at 1:00. I'd like to start at 1:00.

(Whereupon, at 12:00 p.m. a lunch recess was taken.)

AFTERNOON SESSION

(1:00 p.m.)

DR. PAGE: It's now after 1:00 p.m., and I would like to resume this Panel meeting.

We will now proceed with the Open Public Hearing portion of the meeting.

Public attendees are given an opportunity to address the Panel, present data, information, or views relevant to the meeting agenda.

Mr. Swink will now read the Open Public Hearing Disclosure Process Statement.

MR. SWINK: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency during the Open Public Hearing session of this Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement,

to advise the Committee if you do not have such a financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. PAGE: We have eight requests to speak today, including three cardiovascular societies. We ask that each of you speak clearly into the microphone to allow the transcriptionist to provide an accurate record of this meeting. Please identify yourself, your relationship to the issue at hand, and as Mr. Swink mentioned, any conflict that you are willing to disclose.

We'll start with the individual speakers, given five minutes each, and that will be followed by the three societies for 15 minutes each. And we're starting with Marvin Ward.

Sir, go ahead and press the button at the bottom of the microphone, please. Great, thank you. Welcome.

MR. WARD: My name is Marvin Ward, and I'm 88 years old. I've had a long history of heart disease beginning in 1987 when I had my first heart attack at the age of 64. Twelve years later, in 1999, I had another heart attack. This time I had to undergo quadruple bypass surgery. It was the most traumatic medical experience I've ever undergone in my life.

My family described to me the intense pain that I was obviously experiencing in the recovery unit after the surgery. Fortunately, I cannot remember that, but I do clearly remember the long and very painful recovery I had.

I was 75 years old at the time. I stayed in the hospital about a week and then went home to recuperate. Every step I took after that surgery was difficult and painful. It was at least two months before I was feeling anything near normal. I never wanted to go through anything like that again.

Several years later, my aortic valve quit functioning as well as it should. This gradually got worse to the point that I would get short of breath every time I exerted myself. Something had to be done.

I went to see the surgeon who performed my bypass surgery in 1999. He said he could replace the aortic valve using the traditional open heart method, but he warned that the risk of mortality was very high given my age.

I felt like I was between a rock and a hard place. I had been very active my entire life, but I could no longer function fully without a new valve. I had serious doubts about my ability to withstand another open heart surgery at my age, and even if I decided to try it, the risk seemed way too high. But I wasn't ready to give up on life yet.

Fortunately, I learned that there was an alternative to open heart surgery at Washington Hospital Center. I met with the doctors there who determined that I was eligible for their research study, which would allow me to get the new valve in a noninvasive way. I eagerly added my name to the list of patients who wanted this procedure.

During the months that I waited for the new valve, I continued

to deteriorate. Even walking to the end of my driveway to pick up the newspaper was extremely difficult. Although active my entire life, I was now at a point where essentially all I could do was sit in my recliner. I would even wake up in the middle of the night panicked because I could not catch my breath.

It was finally my turn to get the new valve in May of 2010. The procedure went very smoothly, and the doctors and staff took great care of me. I left the hospital three days after the procedure. In all honesty, I believe I could've walked out of that hospital on my own two feet had the hospital staff permitted it.

The day I returned home I was out watering my garden in the afternoon. The next day I was planting more tomato plants. I couldn't believe that I felt as well as I did and breathed as well as I did. I am back to being nearly as active as ever. I continue to work in my garden and I walk every day, weather permitting, for about 30 minutes. I walk rather briskly for over a mile. I still don't cut my own grass; as my wife says, it's time to leave that to a younger man.

(Laughter.)

MR. WARD: But I know I could do it if I wanted to. I feel very fortunate to have been part of this research study. I know I wouldn't still be alive if I hadn't gotten the new valve. And to have gotten it without the trauma of an open heart surgery made it even better.

I hope that this procedure will soon be available to everyone in this country who needs a new aortic valve. I urge you to approve the procedure and make it available to anyone who is a candidate. Thank you very much.

DR. PAGE: Thank you, sir.

The next speaker is Harold Schoendorf. Mr. Schoendorf.

MR. SCHOENDORF: Chairman Dr. Page and members of the Panel, thank you for this opportunity. My name is Harold Schoendorf, and I'm from Miami, Florida. Edwards Lifesciences provided my travel here today, but I am not a stockholder of the company, nor am I being compensated to be here. I am pleased to address this Panel so that I may share my personal experience with the SAPIEN Transcatheter Heart Valve.

Up to 2007, when I was 81, I was leading a very active life. I worked full time, I traveled, and I would walk up the stairs to my third floor in my condo carrying groceries just to keep in shape, and I could swim laps in our pool. But all of this changed. I started developing symptoms of aortic stenosis that kept me from leading an active life. I could not take the stairs anymore, and just carrying grocery packages was an effort.

At this point my cardiologist sent me to see two cardiac surgeons for possible open heart surgery. The news was not very encouraging, and they were concerned that I was at high risk due to my previous five-way bypass in 1988. So this was 20 years later that I developed

aortic stenosis, and I was concerned about it.

The news was not encouraging, and they were concerned that I was high risk due to my previous five-way bypass surgery 20 years before when I was 61, and they told me, if they had to reopen my chest cavity, they weren't sure what they would find in there because of the bypass work that was done, and they didn't think I was a good candidate for open heart surgery.

So I managed to find that the University of Miami Hospital had a new procedure that was going to be performed by Dr. William O'Neill after my exam. Dr. O'Neill said I was a candidate for the SAPIEN Transcatheter Valve procedure, but I needed to wait for the University of Miami to become a study center.

My condition continued to get worse, and then in 2008 I was selected to have the procedure. I went into the hospital remembering how difficult my open heart bypass surgery had been. But what a surprise this procedure was.

The transcatheter procedure took just a few hours, and I was wide awake that night reading a newspaper. But I needed my own test, so the next day I went out for a walk at the University of Miami. I snuck out of my room is really what I did.

(Laughter.)

MR. SCHOENDORF: And found the University of Miami main

entrance to the hospital was a ramp similar to what's in front of this hotel, about the same slope, only it's longer. And what I did this past Sunday, I went back there to that ramp that goes up there. It's a combination vehicle and pedestrian ramp, and there's only room for one pedestrian ascending or descending that ramp. It's about 200 feet long. I paced it off at 100 paces, and it's about 200 feet, and it sloped, I would say, about 15 to 20 degrees from the horizontal.

And this part, the transcatheter procedure took just a few hours, and I was awake that night and reading a newspaper, but I needed my own test, so the next day I went out to walk on the University of Miami -- I call it cardiac hill. The driveway ramped to the front of the hospital. It's so steep that, before my surgery, I remember before the surgery, checking into the hospital, I had to stop two or three times to navigate that slope to check into the main entrance. And I could --

DR. PAGE: Mr. Schoendorf, I'm sorry, we're going to have to have you wrap up in the next 30 seconds or so.

MR. SCHOENDORF: Okay. All right, thank you. Well, I just wanted to go on to say how important it was for me to get this transcatheter valve. The part I liked the best about it was the recovery. There was no recovery for me. I mean, I was up and running the next morning. And, again, I appreciate this opportunity for you to hear me. It's just my experience with -- I've been wearing the valve for a little over three years now.

DR. PAGE: Thank you so much for addressing the Panel, sir.

MR. SCHOENDORF: Thank you.

DR. PAGE: Our next speaker is Tiffany Charleston. Or
Charleston, I should say.

MS. CHARLESON: So, first of all, thank you for giving me the opportunity to speak for my patients. And I'll start off by saying that Edwards Lifesciences did pay for my travel and accommodations here and has paid for my travel to other meetings pertaining to the administration of the PARTNER trial, but I am not being compensated for my time, nor am I a shareholder in the company.

I'm here today because, for the last year and a half, I have been the research nurse coordinator at Brigham and Women's Hospital in Boston and have run the PARTNER trial from that site, and I have to say that this job has come with both its challenges and its rewards.

And the challenges have come in the form of patients that I've dealt with who were randomized to medical management at the beginning of the trial and, you know, we've continued to follow those patients, and I've continued to care for them over the years and have watched them progressively decline, and kind of with that watched sort of the resignation in those patients who looked that their future is not going to be one of feeling better. It's going to be one of feeling sicker.

And, you know, it comes to mind a specific patient who was

actually at his one-year eligible to cross over into the trial and be offered the therapy of the SAPIEN valve, but at that point had become sort of what we call the Cohort C patient. At that point he was clinically too sick to be enrolled. So, you know, even despite the best medical therapy possible for this gentleman, you know, he was looking forward to not feeling better.

In contrast to that, you know, the rewards of the job have been plenty and, you know, it has been in stark contrast to the folks who do not get better. I, you know, can speak for many patients like Mr. Schoendorf, who, you know, having been told that an option to treat their condition really doesn't exist and, you know, that this trial was available and these patients come to me with hope and come to the trial with hope that -- you know, that there is an option that can treat their condition. And these are the people I see who, the day after the procedure, immediately say, like Mr. Schoendorf, my breathing feels better. Immediately the day after, it's noticed, and it's like the first thing they say to me.

And I have a patient who comes to mind, who is a gentleman who's in his mid-70s, who -- he was actually not able to leave the hospital before the procedure. He was right on that ledge of either having something done or not, you know, and he went home three days after his procedure. He lives in a log cabin in Vermont. It's on about 40 acres of land which he works and he loves, and he winters in Florida as an artist, and I've seen him now, and he's back, you know, spending the winter in Florida and painting, back in

Vermont, you know, on his tractor on his land. And, you know, this is, again, someone who couldn't leave the hospital before we put a valve in him.

And his daughter Sharon wrote me a letter after the procedure and after he spent the winter in Florida, saying that she views what was done for her dad as nothing short of a miracle and that she can now look to the future with hope of having her dad back, having him be the man he has been, living the quality of life that he has been independently at his home, and that her children have the chance to spend even that much more time with him to get to know what an amazing man he was.

And sometimes it's not as drastic as that. You know, the goal of being able to go farm 20 acres is not everybody. I have another patient who was essentially housebound and bedbound and is now back going out to the ice rink with her grandchildren and staying out of the hospital for a year.

And I think that this has been the greatest reward for me, is to be able to give hope where there was none before. And I look forward to the future and to continue to be a provider of that hope to my patients. Thank you very much.

DR. PAGE: Thank you very much.

Our next speaker is Marian Hawkey.

MS. HAWKEY: Thank you for this opportunity to speak. My name is Marian Hawkey. I am a nurse with the valve program at New York-Presbyterian Columbia University Medical Center, and I have been working as

a nurse coordinator on the clinical trials of the Edwards transcatheter aortic valve for the last five years. Edwards Lifesciences did pay for my travel and accommodations. I've not received any other compensation for this. I am not a shareholder. And during the course of the clinical trials, Edwards has also paid for travel and accommodations to attend study-related meetings.

There was a lot of discussion this morning, and I'm sure there will be a lot later on, on quality of life and what it means, and I hope, when I tell some of my few patient stories, it will get to the heart of what it means on an individual level to have quality of life. Some of the comments and comparison to the heavier data may seem very light, but I think that it really does get to the point as to what it means to an individual person to have their life back.

One of the first patients I'm going to speak about is a lady who was 99 years old at the time of her transcatheter valve replacement enrollment in the PARTNER trial. She had undergone, previously, four balloon valvuloplasties for palliation of her symptoms of aortic stenosis; was ultimately able to be enrolled in the PARTNER trial. It's now four years since her enrollment. She will be 103 in November. She has not been hospitalized in those four years. She's an absolute delight to see when she comes back for follow-up. She continues to live independently in her own apartment, of course with, you know, appropriate family support.

Another patient, a very patriotic World War II veteran with very

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severe COPD received the valve. He was able the following Memorial Day to actually be the grand marshal in his local Memorial Day parade, which probably made him happier than anything else in the world.

Another patient, also severely symptomatic before his procedure, at almost a year after the procedure was able to return to the house that he had in Italy and spent the summer there, to some strenuous objection from his daughters that he was going to venture off to Italy by himself for the summer, but he did it. He got a chance to see his brother and he got back safe and sound.

Another patient recently celebrated her 100th birthday. She's a very vivacious social lady who had the valve implanted when she was 95. Definitely had some vascular complications postprocedure, got through them, and as I said, she is really quite the social butterfly at 100 and had a very big party to celebrate.

Another patient, he was 88 years old when his valve was implanted. He is, in fact, someone who had a late neurologic event in the year following the valve but did have complete recovery. He's a widower. He's since relocated to West Palm Beach, Florida, to the assisted living community where his brother lives. For his 90th birthday he took his children and his girlfriend on a cruise to the Bahamas, and he refers to his girlfriend exclusively as a petite, blonde, older woman of 92.

One of the patients that Dr. Smith mentioned earlier, a 61-year-

old gentleman who had had chest wall radiation when he was 19 years old, was hospitalized for weeks in advance of him being able to have the procedure. He needed frequent procedures to remove the fluid that had continuously accumulated in his lungs. Since his procedure, and almost immediately after the procedure, he just kind of jumped out of bed and he hasn't stopped since. He's now a year out, and he is looking and feeling wonderful. And he's another patient who often refers to this as a miracle, both for him and for his family.

Then there are a couple of stories that are on the flip side. One of our patients who was randomized to medical management, a 78-year-old woman who had a prior bypass surgery, a prior CVA, was deemed to be inoperable, was randomized to medical management, did have a balloon valvuloplasty, did reasonably well for a few months, then her symptoms started to resolve -- to recur, rather, and she actually at that time really kind of pleaded to be considered for surgery again, even though she was clearly inoperative. One of her big concerns was that she was the primary caregiver for her husband, who had Alzheimer's, and she soon after that passed away.

Another patient --

DR. PAGE: I'm sorry, we've reached the end of our time. Can you wrap up in a few seconds?

MS. HAWKEY: Sure.

DR. PAGE: Thank you.

MS. HAWKEY: So we do go through a very extensive evaluation process for these patients, but I think the biggest thing that we offer them by having this as a potential treatment option is the opportunity for choice, which I think is really important for anyone in a situation such as this. Thank you very much.

DR. PAGE: Thank you very much.

Our final speaker from this group is Dr. Greer.

DR. GREER: Hi, I'm Dr. Steven Greer. I'm a trained surgeon and a healthcare sector analyst. I've performed hundreds of open heart surgery cases, and I know the medical device industry pretty well. I'm speaking today to urge caution to the Panel in approving the SAPIEN valve. A bad chapter in medical device FDA regulation is set to repeat itself if the SAPIEN valve is allowed on the market for broad use.

In 2003, the CYPHER drug-eluting stent was approved with only one-year follow-up data. Dr. Marty Leon of the CRF was leading those studies. Now, in 2011, the Edwards SAPIEN percutaneous aortic valve is up for approval, again with only one-year follow-up data. And Dr. Leon is also one of the principal investigators.

The PARTNER trials to be reviewed today followed the SAPIEN valve for only one year. Traditionally, mechanical valves have had the highest regulatory hurdle, and for good reason. Many of you here remember decades ago the Bjork-Shiley valve that was a bad experience. When the

valve failed, there was rapid death. That's one of the reasons mechanical valves have to go through such rigorous long-term follow-up.

Back with the CYPHER valve -- the CYPHER stent as an example, a comparison here. It was only after one year when aneurysms started to show up and form, otherwise known as late stent mal-apposition.

What will we see with the SAPIEN valve after one year? Will we see more retrograde leakage? Will we see even higher stroke rates? Will we see heart block requiring more pacemakers?

In 2003, the CYPHER stent was granted rapid Medicare approval even before the FDA. As a result, off-label usage skyrocketed. At one point more than 90 percent of all PCI cases involved a drug-eluting stent.

Then came the evidence: stents just don't work compared to medical therapy. COURAGE, BARI 2D, SYNTAX, and then the safety data in the 2006 ESC drove the adoption and usage of stents down.

Tens of thousands of Americans, in the meantime, were killed or severely harmed by the first-generation drug-eluting stents. That's an example of aneurysm on this cross-section.

Just some of our estimates. With 25 million drug-eluting stents that were implanted since 2003, with an estimated one to three percent aneurysm rate, that translates into approximately one million coronary aneurysms. In addition, the lifelong Plavix that required, as stroke and significant bleeding.

And the CYPHER stent. It just was recently announced by Johnson & Johnson that they're exiting the business altogether.

Now with the SAPIEN valve, we've already seen at least seven-percent stroke rate in the very short study so far, per the FDA analysis. In addition, the significant bleeding and 50 percent of the patients getting femoral artery damage and iliac artery damage and aortic dissection.

Per the FDA documents, Dr. Leon et al. changed the definition of stroke to major stroke in the PARTNER trials, presumably to decrease those numbers.

The PARTNER study, it's important to note, is not even fully published and fully analyzed. We're just looking at the Cohort B here. Just the easy comps to this medical therapy, whatever that means, are published. The tougher comparison to surgery is not published yet. Why the rush? Is this a business move to get ahead of the Medtronic trials?

By the year 2015, according to J.P. Morgan estimates, an estimated 400 implanting medical centers will be replacing 26,000 SAPIEN valves a year. That translates into approximately 18,000 strokes per year caused by the SAPIEN valve. The cases we just heard were the lucky ones, and I'm very happy for you.

Many patients would rather die from heart disease than be crippled by a debilitating stroke as an octogenarian.

In the United States, FDA approval lets the genie out of the

bottle. Unlike Europe where reimbursement doesn't happen quite often, approval by the FDA almost certainly means reimbursement and rapid usage of a device of like this.

Related to that, a recent *JAMA* study that was helped -- conducted by the American College of Cardiology showed that 50 percent of coronary stents were implanted with any appropriate indications.

Edwards is already preparing -- we know this -- is already preparing to launch the SAPIEN in hundreds of hospitals, not just the Centers of Excellence. Again, similar to what we saw with the stents.

A perfect storm is brewing, creating a major public hazard. First of all, there's a pro-medical device climate in Washington. From President Obama to Speaker Boehner, with the high unemployment, it's viewed that the medical device industry is a priority --

DR. PAGE: I'm sorry, we're at five minutes.

DR. GREER: Yeah.

DR. PAGE: I'll need you to wrap up in 30 seconds.

DR. GREER: Yeah. And I've got three more slides. The other one is that investors desperately want this device, and lastly, doctors need to pick up the slack in the cath labs since the stent usage is down.

How will inoperable be defined? What is inoperable?

Michael DeBakey got aortic work at age 97 and lived well after that. Will cardiologists self-refer these valves just as they do now with the stents? The

so-called oculostenotic reflex. Two more slides.

I urge the Panel, if you do find the risk/benefit worthy of some sort of approval, that it should have a strict limit, a strict label, and that Medicare, just as they do with carotid stents now, should reimburse this only for specific populations.

Recently published were the ACC guidelines that should be adhered to.

DR. PAGE: Right, we've got the guidelines.

DR. GREER: Yeah.

DR. PAGE: We know you've got it up there.

DR. GREER: There you go, that's the last slide.

DR. PAGE: Thank you very much. I want to thank all five speakers for taking the time to address the Panel.

Do any of the Panelists have any specific questions for the speakers so far in this Open Public comment section?

(No response.)

DR. PAGE: Seeing none, we will proceed with three presentations from cardiovascular society representatives. The first is from SCAI. Dr. Pichard.

DR. PICHARD: Good afternoon members of the Advisory Panel, FDA staff, and guests. My name is Dr. Augusto Pichard. I'm the Director of the cardiac cath labs at the Washington Hospital Center. I'm a Professor of

Medicine at Georgetown University. My conflicts of interest include being the principal Investigator for the PARTNER trial at the Washington Hospital Center. I've been a proctor for the SAPIEN valve. Today I am speaking on behalf of the Society for Cardiovascular Angiography and Interventions, SCAI or skī.

SCAI is the leader in science, education, and advocacy for interventional cardiologists and their patients. The society promotes excellence in cardiac cath, angiography, and interventional cardiology through physician education and representation, and through quality initiatives to enhance patient care. The society represents over 4,000 invasive and interventional cardiologists. The society is committed to providing the best care possible for patients with severe aortic stenosis.

Well, you all have the statement. You should have it to follow what I'm reading.

The society believes the recent advent of transcatheter treatment of aortic stenosis is a viable alternative to standard open valve replacement in select patient populations at specialized heart centers with expert physicians. Inoperable patients with severe stenosis are currently treated with medication, since they may be too sick or too old to undergo surgery, despite the extensive historical information that medical therapy does not work.

The Edwards SAPIEN device clinical trial demonstrated that

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TAVI is a superior alternative to medical management in select inoperable patients and is non-inferior in patients at high risk for open heart surgery. In addition, many patients that could not enter the trial could've benefited from this therapy.

The society believes the PARTNER clinical trial provides a foundation for the essential requirements of a percutaneous valve program, and if this medical device is deemed to be reasonably safe and effective by the Agency, these requirements must be implemented in the real world to help assure successful patient outcome.

The clinical trial provides evidence that the most successful patient outcomes occur under the following circumstances: (1) performance in a specialized heart center with sufficient patient volume; (2) management using a multidisciplinary team with expert members; (3) access to a modified conventional cardiac laboratory or hybrid operating room to provide excellent technology; and (4) a planned approach to co-management decision by the heart team, as has been said this morning.

The society, in partnership with other medical societies, is committed to ensuring that these essential requirements of a percutaneous program continue in the real world so that this technology continues to benefit the sickest patients who have no other treatment options. SCAI and other medical societies are committed to the development of expert consensus statements, guidelines, use criteria, credentialing criteria, and

training paradigms, thereby supporting responsible diffusion of this technology.

Specialized heart centers should be accredited through Accreditation for Cardiovascular Excellence, ACE, an organization currently accrediting facilities for other invasive and interventional cardiovascular procedures. The society agrees that the Sponsor's proposed comprehensive training program for new practitioners is essential to evaluate operator experience level and management of vascular complications.

The society recommends a nationwide TAVI registry be developed to track long-term follow-up in the real world and provide data to answer critical research questions not addressed by the clinical trial.

The society is leading the development of a SCAI, AATS, ACC, and STS multi-societal competency statement on institutional and operator requirements to define the essential criteria for optimal patient outcomes. We agree that defining these characteristics is challenging and is not a single rigid set of criteria.

I'm going to now provide answers to the questions addressed by the Advisory Panel.

With respect to Question 1, regarding patient selection, the society believes the proposed wording for indications of use is adequate and addresses patient selection factors. The multi-disciplinary team needs to be accountable for these joint decisions, especially among patients who are too

ill or too high risk to benefit from surgical heart valve therapy. A similar multi-disciplinary approach has been implemented in the real world for other treatment options in high-risk situations, such as cardiogenic shock.

Regarding Question 2 on heterogeneity of the control group, the society believes that the natural history of medical treatment alone is well established and known to be dismal. The society believes that the control group reflects current best practice and that the heterogeneity of the treatment does not impact the positive benefit in mortality of the THV program. No existing therapy other than surgical valve replacement has been demonstrated to significantly improve survival.

Question 3, regarding stroke, the society is concerned about patients who may suffer stroke after THV. The society fully supports the proposed anticoagulation/antiplatelet protocol in Question 3b as a counterbalance to the risk of stroke. However, the frequency of this complication does not offset the significant benefit of mortality observed in the trial.

Question 4, regarding vascular complications, the society believes that vascular complications are important and are also manageable and in most cases reversible. The society supports the Sponsor-proposed comprehensive training program as one approach to reduce vascular complications. However, the frequency of these complications does not offset the significant mortality benefit observed of the trial.

Question 5 was about hemodynamic performance of the SAPIEN valve. The society is impressed that the aortic regurgitation in this high-risk population did not counterbalance either the survival or the sustained clinical patient improvement. The society believes that the data are clearly favorable.

Question 6, about valve-in-valve, the society believes that the operator should have the option to use THV therapy for inoperable patients with degenerated valves. There is a body of international experience with valve-in-valve therapy that supports this approach in patients with no other option.

And finally Question 8 is reasonable assurance of safety and effectiveness of the SAPIEN valve. The society believes that there's significant concern about the risk of stroke and the overall survival of this therapy is very significant. An absolute survival advantage of this therapy of 20 percent far exceeds the penalties of adverse events such as stroke and vascular complications.

The society believes that appropriate physician expertise will lead to a reduction in the number of complications as observed in PARTNER trial. Cohort B versus Cohort A showed a strong decrease from 5 to 3.8 percent, and vascular complications from 16 to 11 percent, respectively. Therefore, the society hopes that patients with severe AS will have access to this treatment option.

In conclusion, thank you for accepting our testimony today. The society is fully committed to providing the best patient care possible and welcomes all opportunities to provide recommendations to the Advisory Panel and the Agency. The society is encouraged by the information provided to date and looks forward to the Advisory Panel's recommendations and the FDA's final regulatory decision. Thank you very much.

DR. PAGE: Thank you very much.

We'll go on with the next presentation from the ACC, by Dr. Holmes.

DR. HOLMES: Good afternoon. It's great to be here. Thanks, Dr. Page and Panel members and FDA. I'm Holmes, and I'm here on behalf of the ACC. More importantly, I am here as a spokesperson for all of the patients with cardiovascular disease, a terribly important piece of information.

I'm also here in a collaborative, very extensive partnership with STS, as we try to provide some help in bringing along rational dispersion of truly transformational technology. Think about that term, rational dispersion of truly transformational technology. And that is the goal of my presentation and Michael Mack's presentation, the president of STS, to bring along and to reach those goals of rational dispersion of truly transformational technology.

I don't have any conflicts to disclose about this.

What is the ACC? What does it do? It advocates for quality

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cardiovascular care through education and research promotion and development and application of standards and guidelines. And we've heard about that. And we try, then, to have a way to influence healthcare delivery systems so that we can achieve the goal of quality cardiovascular care.

We have heard a lot about team-based care. The big tent of ACC includes a lot of team members. We have 40,000 members. We have structural heart disease people. We have cardiac anesthesiologists. We have cardiovascular surgeons. We have interventional cardiologists. We have echocardiography. We have primary cardiologists. And so we have many of the members that are going to be involved in this team care. That's the first piece of information.

What does the portfolio look like of the college? Well, it's lots of manuscripts, 7,000 submitted; 20,000, as you can see, live event attendees; 11 million patient records in the National Cardiovascular Data Repository. I know that's wrong, but rather than registry, we're changing the word of that; and 100 million patient visits; terribly important. So we have a huge amount of data that we will build on with STS.

What are the goals for ACC, for society, for TAVR? We want to have high-quality patient care. That's the first thing. We want to have efficient and appropriate access to new technology. We heard that from the patient testimony. We'd like to have appropriate patient selection for and the safe application of the technology. We would certainly like to have rapid

response to continued evolution of the specific device iterations. Everybody wants this year's model. Do we have it yet? We don't. Will we? We will at some point in time, but everybody wants this year's model. We're interested in the development of new scientific studies and approaches for specific diseases. And that's what will come out of some of these initiatives. And then we need cooperation among all people who are involved.

Collaboration is an interesting concept. We think of that as the cornerstone of everything, unless you live within the Beltway.

(Laughter.)

DR. HOLMES: Think about that. These are some of the collaborative partners. The primary stakeholders are physicians and government and industry and patients. The patients are stakeholders. Within the physician community, it's primary cardiologists and interventional cardiologists and it is surgeons and it then is multiple professional societies, SCAI and ATS and STS, and a whole host of other professional societies represented in the big tent of ACC. The common goal is high-quality patient care.

How have we been working with those other societies to make this happen? Well, we have a whole family of clinical documents in development. One is the societal overview by Michael Mack and myself, from the college and STS, that is now referenced in your Panel pack. It was just presented and published earlier this month, a societal overview.

The second is the SCAI-led competence statement that Gus has talked about, addressing institutional and operator requirements.

The third is an ACCF-led expert consensus document on pre- and post-procedural issues, including patient selection, that will have seven societies represented: European societies, North American societies, medical societies, interventional societies, surgical societies.

And then the update on structural heart disease guideline, which will be coming along from ACC and from AHA. These are all the multi-societal efforts to indeed include all the physician stakeholders.

As we think about this process, how could we plan for success? That is what we want. We need to have the multidisciplinary heart team. And I'll mention a couple of things, but you've heard a lot of about that. We'll talk about patient selection. We need the right patient, the right place, the right time. And there are issues then of the double-edged sword of futility and frailty. A very, very important concept, and we'll hopefully talk about that later this afternoon. We have some issues about facility requirements and operator experience, and then we will spend some time on postmarket surveillance, which I think is going to be crucial.

We've talked about the multidisciplinary heart team. I think at the center of that is the primary cardiologist. That is the person that saw the patient before you saw the patient, is going to see the patient after you see the patient and follow them up. And so that is going to be the central person,

the primary cardiologist that takes care of these patients that have advanced cardiovascular disease. There's then going to be that partnership of interventional cardiology and cardiothoracic surgery; the echo people that are going to tell you what size valve are going to help you guide that; the cardiac imaging specialists that are going to say we think you can get up here, it's tortuous, but we think you can do it; and the heart failure experts and then the other components of the paramedical team for team-based care.

What will be some of the requirements for the facility? Well, we've talked about they will need to have a multidisciplinary heart team. They'll need to have structural heart disease experience. You do not want to have a center that doesn't do structural heart disease. That doesn't make any sense. We think that they need to participate in national clinical databases such as ACC, NCDR, STS.

And ACC and NCDR and STS are in the middle of developing a specific module that includes a clinical and administrative claims database that will allow us to track patients early and track patients late. Obviously you'll have to have the equipment, the catheterization laboratory, whether that be a modified catheterization laboratory or a hybrid operating suite.

How about operator training and education? We've talked about that. Edwards has presented their plan for it. The medical specialty societies need to conduct the education on patient selection, the pathophysiology of the disease, expected outcomes, treatment, selection,

and timing. Industry is going to have to say, this is how you use this widget. This is how you turn it or you don't. It's a green button or a blue button. They'll have to do that. And then there will be joint training and team training. And ACC and STS already have developed joint educational programs for TAVR. We'll need that as part of operating and training and selection.

This is a terribly important slide. We all struggle with keeping up with data. I have *JACC* and I have *Circulation* and I have *New England Journal*. I try to keep up with other data, and this is an important example. I try to keep up with what is going on in Lake Wobegon. So we listen to Garrison Keillor.

And so I can tell you that, at the Chatterbox Cafe, I can tell you what Lars Svelund (ph.) eats for breakfast. I can tell you whether he likes it, whether it keeps him filled until noon. However, I cannot tell you, from knowing what Lars eats, what the rest of the people in Anoka County eat or what the rest of the people in Minnesota eat.

I do not know the denominator, and that has been missing in terms of postmarket surveillance. And so what we need is a numerator as well as the denominator. We need the top and the bottom of the equation.

And so as we think about postmarket surveillance, the primary goal should be assessment of the effectiveness and the safety when it's applied in clinical practice for all patients, all patients who receive the device,

not the subset. You don't care what Lars Svelund eats at the Chatterbox Cafe. It has nothing to do with what you eat in Southern Minnesota or Washington, D.C. You need to know what everybody is eating. You do not need a subset.

And so what we would like to propose is that there should be the use of existing infrastructures of national clinical data repository to capture all patients undergoing device placement, all patients undergoing device placement, all patients using ACC, NCDR, and STS established registries.

What's going to be involved? Well, you're going to have to have the infrastructure; you're going to have well-designed data forms that are going to allow seamless -- the emphasis is on seamless -- collection of data for new iterations; new adjunctive strategies, whether that be for stroke prevention with embolic protection or whether that be for aspirin and -- or whatever it is that you want. It will allow us to look at changes in approach.

It'll be the same module. You'll just check off a different box. It's going to have to be a very good module, and you'll have to check it off, and you'll be able to study transapical or subclavian or transfemoral, and it will allow you to look at changes in patient selection criteria and outcome over time because it will be every single patient. So you'll then be able to say, well, valve-in-valve, I've checked that off. We'll then be able to follow those patients earlier on and longer-term outcome and plan the next group of scientific evaluations.

What will these clinical data repositories give us? Patient safety. We'll be able to look at quality improvement. We'll be able to look at compliance. We'll be able to look at drift, drift in patient selection criteria. We'll be able to follow that, get data on that. We'll be able to look at specific devices and look at comparative effectiveness.

What do we have now? Well, we have existing national clinical databases. What we need to do is harmonize those, scientific and clinic expertise with claims administrative data. And so we have been in negotiation for this module that will include clinical things from NCDR and STS. It will include claims administrative data from CMS MEDPAR. And that is the goal of this in a very short period of time, to have this data that can be used in every single patient undergoing TAVR, no matter whose TAVR it is, no matter whose TAVR it is.

What are the benefits? Well, we can leverage, then, existing relationships. In this particular case we can leverage NCDR, ACC, STS, and MEDPAR data. We can then leverage the existing relationship between physicians and hospitals and that series of clinical data repositories. We can look at data collection and data standards and make sure that they're uniform, so everybody talks about and defines stroke in the same way. Great.

And then we will have a national registry, hopefully, for therapies for structural heart disease. It would be very helpful. We are talking about TAVR here. It would very helpful. Maybe they're a group of

patients who are early on in the disease that should have treatment before they get into problems. Maybe we would see about and learn about under-utilization of this technology by having a national registry that includes medically treated patients as well as surgically treated patients as well as interventionally treated patients.

But then, at the end of this time, what's the bottom line? What is the bottom line that you want, that we want, that that fourth group of stakeholders, the patients, want? This is that bottom line, to provide expert care by expert teams in expert centers for carefully, appropriately selected patients to optimize the results obtained with this truly transformational technology that we call TAVR. Thank you.

DR. PAGE: Thank you very much.

Our final speaker from the cardiovascular societies is Dr. Mack representing the STS. Welcome.

DR. MACK: Thank you, Dr. Page, members of the Panel, members of the Food and Drug Administration. I appreciate the opportunity of speaking on behalf of the Society of Thoracic Surgeons.

My travel expenses here were paid for by the society. My conflict of interest disclosure is that I am an uncompensated member of the PARTNER trial executive committee, which means that my travel expenses were paid by the trial Sponsor to attend trial committee meetings.

I might just parenthetically say that, although this is clearly

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breakthrough technology that's going to change the treatment of patients with aortic stenosis, perhaps the larger legacy of the PARTNER trial may be the cooperation and collaboration between specialties that you've heard a lot about. And I've spent the last four years in many hotel rooms around the country with three other surgeons and four cardiologists, and this collaboration is not just lip service, but it is a true partnership that has led to the partnership between the societies now and hence Dr. Holmes and myself presenting in collaboration here today. So I think that may be the ultimate legacy of the PARTNER trial.

So who are we at the STS? Well, we represent the entire cardiothoracic surgery team. There's more than 6200 cardiothoracic surgeons, researchers, and allied health personnel. We represent more than 85 percent of practicing cardiothoracic surgeons in the United States and 65 countries from around the world.

You've heard a lot about the databases, the ACC, NCDR, and the STS. The STS adult cardiac database gathers outcomes from more than 95 percent of U.S. surgical groups in the United States, contains more than four million patient records, and has almost 100 published papers.

The responsibility to patients and leadership in quality improvement by the STS database is exemplified through its innovative public reporting initiatives, that you can now find out the results of cardiac surgery in the United States in *Consumer Reports*. And there are now more than 1100

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open heart centers in the United States represented.

The concept that you've heard is rational dispersion of TAVR into centers that have sufficient experience and patient volume to maintain the reported results of PARTNER B, that you've heard this morning, in inoperable patients that are symptomatic with aortic stenosis.

The key center requirements, it is our thoughts, as you've heard, is the multidisciplinary heart team, as you've heard Dr. Holmes outline who the members of that team are; secondly, significant experience in the management of aortic valvular and heart disease. Well, that sounds fine, but what exactly does that mean? There are about one-sixth the number of aortic valve operations done in the United States as there are coronary bypass operations. So there is about 35,000 patients in the Medicare population.

If we look at the top 200 centers doing aortic valve surgery in the United States, they do 93 aortic valve replacements per year. If we look at the top 400 in the United States, they do an average of 53 aortic valve replacements a year, one patient undergoing surgical aortic valve replacement per week.

Now, we have to realize that we're talking about a very small population. We're talking about, as was alluded to this morning, the top tenth percentile of risk of patients in both PARTNER trials. So we're talking about a miniscule number of patients. And so how this experience spreads

out to sites so that there's adequate procedural volume and, more importantly, cadence is an issue that needs to be determined.

The proper facilities. Imaging is key here, so a hybrid operating room or modified catheterization lab to accommodate an operative team is critical for this, adequate infrastructure and personnel to provide the proper preprocedural assessment with selection of joint decision-making by the heart team. The optimal place for this to be done is in heart valve clinics, and it's not just a surgeon signing off on a sheet that says this patient is inoperable. It's joint decision-making and heart valve clinics together, intra-procedural multidisciplinary teams of interventional cardiologists and cardiac surgeons working together.

There are many reasons for the success of the PARTNER trial. Some of it has been we have learned from the experience of Europe, and they have attenuated the learning curve for us with that. But there's a lot of other components, and I think that this is one of them, the cardiologists and surgeons working together.

And then lastly, providing an optimal postprocedural care setting including intensive care units staffed with hospitalists, gerontologists, social workers, physical therapists, cardiac rehabilitation. In other words, this isn't just a procedure, it's a program, and needs to be treated like a program in the order of a transplant center concept; that it isn't just an operation you do, but it's a large infrastructure that's built around that care delivery system.

Regarding postmarket surveillance, as you've heard from Dr. Holmes, we think that mandatory participation in the STS database is not a high bar, since 95 percent of the 1100 programs in the United States already participate in the STS database. And of the 1500 cath labs in the United States, 80 percent of them now participate in ACC/NCDR. So the infrastructure is in place.

As you've heard what the proposal is, that we expand the linkage between the STS and ACC database to form a new TAVR module. The current form of the STS database, which went live July 1st, now captures TAVR, but nowhere near in the manner of all the details that need to be. In addition, such issues as porcelain aorta and liver disease that weren't captured before now are, and there has even been a frailty parameter, the five-meter walk test, that's been added to this.

The teams from the ACC and STS databases have met. They assure me that this new TAVR module, once the data fields and definitions are defined and decided, we can have this up and running in 60 days. Both are warehoused at DCRI, they have spoken with DCRI, and this can go live later this year.

The ultimate linkage of these two databases with the Social Security Death Master File, CMS MEDPAR data, is not a new concept. It's been done, it's been proven, and it can be done. The ASSERT trial has done exactly that, which is a collaborative effort funded by NHLBI for looking at

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coronary revascularization. The other model, to think of this, is the INTERMACS trial, which tracks all patients receiving ventricular assist devices, also under an NHLBI grant.

So, in effect, what we'd have is a national database for all treatments for patients with aortic stenosis, medical therapy patients, surgical patients, and TAVR patients, so that comparative effectiveness and cost-effectiveness outcomes can be analyzed. It would also create, in our mind, the infrastructure to facilitate postmarket surveillance of expanded populations and device iterations.

So in very short order, PARTNER A trial will come before a panel like this, the next iteration of devices now in trial. There's now another device in trial in the United States. Creation of this infrastructure should be able to facilitate postmarket surveillance and not have to reinvent the wheel every time. And, in addition, it will become the model for assessment of outcomes of future devices, not only within the cardiovascular field, but beyond.

What is the professional society role of this? You've heard from Dr. Pichard and Dr. Holmes that there is extensive professional society collaboration here: the overview that's referenced in your pack, the operator and institutional requirements that is a four-society collaboration, the expert consensus document which 11 societies have agreed to collaborate to look at the evidence in this area, and the STS and ACC have partnered with

educational programs that are over and above the specific device training that the trial Sponsor has mandated. The first of these happened in June, the next one will happen in December, and there's three planned for next year.

So, in summary, we view this as a breakthrough technology with a potential to offer a lifesaving treatment to inoperable patients with aortic stenosis. We feel that the experience of adoption in over 40 countries outside the United States will help the introduction into the United States. We have learned significantly from that learning curve already. Rational dispersion of TAVR to centers with multidisciplinary heart teams and sufficient personnel and infrastructure to support a TAVR program is key. Expansion of existing databases and linkage to administrative databases to capture early and late outcomes should be mandated. And the professional societies have established a cooperative partnership to help facilitate the safe and effective adoption of TAVR in the United States.

I began my career 30 years ago and spent the last 30 years in a tug of war with my colleagues in interventional cardiology, between which is the best method of coronary revascularization, CABG or PCI, and the patient was caught in the middle. Having lived with that for 30 years, I'm absolutely convinced that we could do it different this time, and the societies hope that we have shown the leadership, that we will help to get this right and facilitate the safe and effective introduction into the United States. Thank you very much.

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DR. PAGE: Thank you, sir. That brings us to the conclusion of the Open Public comments.

I want to ask the Panel whether they have any questions for the representatives of the cardiovascular societies. Ms. Patrick-Lake.

MS. PATRICK-LAKE: I had two questions for Dr. Mack. So from the conclusion slide, I was a little unclear on what the professional society role in rational dispersion would be. Do you see it as an advisory panel to a sponsor? Could you let me know how you see that?

DR. MACK: So I think the actual process of how that happens and what role we could lend to facilitate that is contained in those documents that I mentioned on the previous slide.

So, for instance, regarding credentialing of centers and credential of operators, SCAI, which is the interventional cardiology society, is leading the effort, with the American Association of Thoracic Surgery, of which Dr. Smith is the president; ACC, Dr. Holmes; and STS, myself, to help establish criteria for adequate training, adequate credentialing of both individuals and centers. That is a work in progress.

There are two source documents that have been generated already, one by the STS and one by SCAI. They're being melded together, and the intent is to have that completed in 60 days so that there is robust, specific criteria of center and operator qualifications to be able to deliver this technology.

MS. PATRICK-LAKE: So you see it as site selection would still be left to a sponsor, if the site was credentialed?

DR. MACK: Ultimately, site selection has to be left to the Sponsor, and we would propose guidelines to help facilitate and work with a sponsor to do that.

MS. PATRICK-LAKE: Okay. My second question was, you mentioned that, I think, DCRI said that they would be prepared to go live later this year. Any feel on what happens if there were to be an approval today?

DR. MACK: So I think the first thing to happen if approval happens today, the infrastructure is in place already with the existing clinical databases that all patients could be captured. So we would at least know who is receiving these in the United States, simple demographics, and 30-day outcomes of mortality and major stroke. So I think that is already in place. However, it's not --

DR. PAGE: I'll just remind the Panel and the audience that this body is advisory to FDA, so approval --

MS. PATRICK-LAKE: Right.

DR. PAGE: -- we will recommend approval, but actual approval will follow --

MS. PATRICK-LAKE: Correct.

DR. PAGE: -- subsequently if that were to occur.

MS. PATRICK-LAKE: I'm just theorizing.

DR. PAGE: Thanks.

DR. MACK: So, you know, we've got a very fast timeline to do this, and clearly, by the end of the year, we feel confident that a larger, expanded registry ultimately being able to be linked to administrative databases and track long-term outcomes can be in place, and both the ACC and STS have committed the resources to make this happen. DCRI is the vendor and the warehouse for both of the databases, and they have given us these timelines as doable.

MS. PATRICK-LAKE: Thank you.

DR. PAGE: Dr. Brindis, then Dr. Lange.

DR. BRINDIS: My question is for Dr. Holmes. Thank you, David.

One of the concerns that the Panelists are going to be wrestling with is how we recognize who the Cohort C is. That's the term we've learned today. And one of the suggestions was that potentially a national registry would not just have -- follow patients who undergo this technology but also those who do not, the natural history.

Has the American College of Cardiology and STS given some thought on how -- should we take on this role and how we would actually go about such?

DR. HOLMES: Sure, Ralph, I think that's an incredibly important question. We need to know the natural history of several different subsets of patients within aortic valve disease. Some of those will be the truly

inoperable, untreatable, un-TAVI-able group that we shouldn't do, and we should be able to identify why we shouldn't do them, either because they're too frail or it's futile to do that. The other part of that will be those patients before they get to that and seeing. So we would favor, as part of an expanded registry or data analytic approach, the patients with severe aortic stenosis be identified.

Now, some of that, then, would be linkage with American Society of Echocardiography or potentially through the valvular structural heart disease group that deal with that. So we would then link that data using electronic names to make sure that they are rolled in and so we can then have information, particularly as you think about adding claims data, long-term outcome in those patients.

So at the end of the day, at some point in time we'll be able to identify patients that haven't gotten anything, either because they shouldn't get anything or they don't want to get anything, or before they should've gotten something. So that's a really important point. We have talked with people about that and there's great interest in that. That really completes the family of science of data around a specific disease state. A great question. Thank you.

DR. PAGE: Thank you. Dr. Lange.

DR. LANGE: A question to Dr. Mack and Dr. Holmes both, and that is, in light of the national registry that you all -- that is being proposed or

jointly worked on in collaboration between the societies, would you talk about the relationship between this and the postmarketing or the postapproval studies? Are you suggesting that this would replace postmarketing or postapproval studies? The first question.

And then the second is related to that. Is the data collection robust? You've seen the information that's going to be requested for the postapproval study, that is, PAS 1 and 2, and is the registry information you're collecting, is that robust?

DR. MACK: Well, in answer to your first question, the decision about that is not ours. I mean, it's the trial sponsor and the FDA and the advice of the Panel that ultimately decides that. We simply are presenting an infrastructure that we think can help facilitate postmarket surveillance of this device and all devices in the future.

There are some key elements of a postmarket surveillance that could not be captured in this. So, for instance, echo follow-up at five years are not part of current databases, nor would they realistically be. Quality-of-life issues aren't currently part of these databases but ultimately can be incorporated into them.

The other aspect of this, in terms of Dr. Brindis' question, is that patient selection has been a huge issue for this, and how you identify the inoperable patient. And we use current scores based upon surgical replacement, and we know that they do not translate over to this.

So this registry will allow us to have a TAVR risk score, if you will, just based and validated in patients who are receiving this procedure. So we will be able to hopefully determine those patients whose risk is too high, so not only where the floor is, but where the ceiling is for these patients.

DR. HOLMES: I think a crucial added piece of information is it would have all patients. It's not a subset of patients. I think that you can get a lot of information with detailed analysis in a subset of patients. There is no question about that.

But if you think about the whole field of people that are undergoing this procedure, if you had a platform, like we are talking about, that then could be added to, that would have the same definitions so you could then add information when you have a transapical procedure, so when you have the next model, so that you could then seamlessly add that on, have identified a place that you could say that's what they got, was the next model, you would have the same metrics and then it would be seamless. But you would have all the patients, not just a subset. So you would have a good feel of the whole field.

DR. PAGE: Go ahead, Dr. Lange.

DR. LANGE: Can I follow up with that, and that is, how -- obviously one of the limitations of all registry data is 100 percent participation, both 100 percent participation by site and 100 percent registration of all data. So talk to us and tell us -- you guys have obviously

talked about this -- how you accomplish that.

DR. HOLMES: I think that there are a couple of approaches to that. One is at the national level. So for example, Michael has talked about NCDR PCI registry. That's now been selected by Leapfrog as that quality indicator of PCI performance. Everybody's going to be involved with the issues of quality of care. And so that can then become the standard of quality.

The second piece of information is to say, as part of facility selection or site selection, that you could say, in order to be involved with this, in order to work with CMS in terms of some of the other things that we can't talk about here but are very real, you would have participation in this registry or a registry like this. And that is something that obviously FDA and CMS would have to work with. And maybe you'll want to comment on that. Bram, that's a good point.

DR. ZUCKERMAN: I think the key components are (1) to define the best or an optimal public health system for this type of technology, and then the federal government, as a stakeholder, will be very interested in trying to figure out how it can be implemented.

As Dr. Holmes stated, this is really going to be for this technology or for other transformative technologies in HHS effort where the Agency, meaning FDA, will work with our CMS colleagues who are here in the audience.

DR. PAGE: If I'm seeing no more questions from the Panel, I want to thank again all eight speakers. And with that I'll pronounce the Open Public Hearing officially closed, and we'll proceed with today's agenda.

It's now time for Panel deliberations. Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. In addition, we request that all persons who are asked to speak identify themselves each time. This helps the transcriptionist identify the speakers.

Now, this morning we had a number of questions for the Sponsor. Is the Sponsor prepared to respond to the Panel's questions from this morning? I'll take that as a yes. Come on forward, please.

MS. AKIN: We're ready, yeah. Did you want us to proceed?

DR. PAGE: Yeah, why don't you go ahead and proceed with the questions --

MS. AKIN: Sure.

DR. PAGE: -- as they were posed to you.

MS. AKIN: So we did our best to compile the questions. I think to start, since stroke is of the greatest interest, we collected the questions and created a collective response. So I'm going to start by bringing up Dr. Leon to address some of the stroke questions.

DR. LEON: Actually, I'm going to try to navigate us through this whole series of stroke issues because I think that there was a lot of confusion,

and I think it's best for us to be very transparent and to clarify some of that confusion. So we're going to orchestrate this next session by having several speakers provide their perspectives.

The first speaker will be Tom Brott, who's the neurology consultant for the PARTNER trial and will provide some perspectives on stroke. He's seen the data and, I think, will help to clarify some of the questions raised this morning.

After Dr. Brott, we're going to have a representative from the CEC, who's director of the CEC, to better explain how the stroke events were adjudicated and how they were defined. There was some confusion about that.

And then I'd like to present some additional data that was not presented this morning, to again help clarify some of the stroke issues, and we'll conclude with Murat Tuzcu from the Cleveland Clinic providing some of his perspectives on the stroke issue as it relates to PARTNER.

So Tom.

DR. BROTT: Thank you, Marty. And I'm here as a consultant to Edwards and really was not involved in the PARTNER trial, but I will try to be succinct with regard to a perspective which I think or I hope will relate to the questions that you're faced, Question 3 and Question 10, as well as the questions that you raised this morning.

I've been taking care of stroke patients for not quite 30 years

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and very early on I became interested in the issues that were raised today, and I was the principal designer of the NIH Stroke Scale, then went on to -- in the NINDS t-PA stroke trial, I had the opportunity to lead a team that randomized 150 patients out of the 624 patients in that trial. We examined everybody at baseline, 24 hours, 7 days -- excuse me -- 90 days, 6 months, and 1 year.

And, you know, you learn in trials, and one thing that we learned then was that the scales that we used for a given patient were a moving target. The patients that we treated were fall-down strokes, 911 strokes. Their NIH Stroke Scale median -- and you'll hear some numbers on NIH Stroke Scale -- was 14. And with an NIH Stroke Scale of about 10, you've got an occlusion of an intracranial artery about 80 to 90 percent of the time. So 14.

And yet, as we examined them over time, all of our scales changed. So we realized and we, of course, were forced in our publications that when addressing severity, one had to be disciplined with the individual patient with regard to examination at fixed time points from symptom onset.

In that study, which led to the labeling for t-PA, an excellent outcome was considered to be a modified Rankin score of zero to one. Okay, modified zero to one. And I mention that because I think the greater than one in that context used to define major stroke is relatively conservative. Following the t-PA trial, the PROACT trial of prourokinase with intra-arterial

endovascular techniques, major stroke was considered to be greater than two. The study of desmoteplase as a potential replacement for t-PA, major stroke was considered to be greater than two. And in the recent MERCI trial, which underwent approval by a different panel, major stroke was again considered to be greater than two. So I do think that there is a conservative measure that you've been dealing with.

Just a week ago -- and this has to do with the patients. The t-PA patients were age 68, and I had a lot of experience with the 150 patients, following them over those time points. The CREST trial -- and many of you participated in the review of that trial -- the average age was 69.

And I was just going over some of our quality of life data. Let's see, if I push the -- oh, okay. Great. If I push this, this is just -- as you can tell, this was just a few weeks ago, just talking about selected secondary endpoints, and the next slide was the one that caught my eye. I mean, we expected that the surgery patients would have more difficulty with eating and swallowing, and the stent patients might have a little bit more difficulty, as you can see in the slide, with walking. But what caught my eye at the time was the limitation of the elderly patient. So if you look at the bottom left, and it's hard to read, unable to drive at baseline is between 12, 14 percent.

By the way, Dave Cohen was our quality of life individual.

And, you know, we tried with our own assessment of major stroke, many of you will recall, was also a greater than one. We tried to have

patients come in at fixed time points because, in contrast to this trial, CREST was a stroke trial. And we did our best, but we weren't as successful as we would've liked to have been.

So the measure, I think, is conservative. Obtaining the measure, it's important to have fixed time points, but it is difficult, particularly in patients who are octogenarians. And the patients in this trial who have sustained stroke were a little bit older than the cohort overall.

I did notice, as well, today that the absolute number of events was about 50 percent, in absolute terms, after the performance of the procedure, and that caught my attention as well. But the denominator -- you know, I might remind all of us that twice as many women are hospitalized for stroke in the United States, yet the rate of stroke is the same, age adjusted, and it's because there are so many more women alive at risk for stroke.

And so we were able, over the lunch period, to look at at-risk, you know, looking at these events with regard to the at-risk population, and they're about the same. That doesn't mean that Edwards should relax, by any means. After all, some of the patients -- many of the patients in the control group had the balloon treatment, but we don't see a significant difference. Anyway, those are just a few comments with regard to context and Questions 3 and 10. And thank you for your attention.

DR. PAGE: Great. And I just want to remind the Sponsor, we're not addressing the questions the FDA is posing, that we're going to be talking

about later. What we're really looking for is follow-up from the questions that we had during the morning sessions. We've got about 25 minutes to do that, and I just want to remind, Dr. Good had a question needing follow-up, Dr. Slotwiner, Dr. Lange, about ejection fraction, and Dr. Good, about quality of life, and I think you had a question about surgical follow-up.

And I trust that the Sponsor took note of those, and I don't want you to spend all of your time talking about neurologic endpoints when we had other issues to address.

DR. BROTT: I apologize if I went beyond the scope --

DR. PAGE: No apology necessary. I just want to keep us so we're able to get all of our work done today.

Dr. Good, are you satisfied that the questions you had have been addressed, or is there more?

DR. GOOD: Yeah, I think so. One of my concerns was what the risk was going forward, not the risk that was periprocedural, but following that, and I think that was addressed quite nicely. I think that was an important question. I still have a little -- I don't think we should get too blasé about this, as Dr. Brott said. There may be some ongoing risk. But I think that answers it for now. That was one of my major questions.

DR. PAGE: Thanks.

MS. AKIN: Okay, I'll switch gears for a moment and go to the left ventricular ejection fraction question and bring up Dr. Becky Hahn.

DR. HAHN: I'm Dr. Rebecca Hahn. I'm an associate professor at Columbia University. I have nothing to disclose with relation to Edwards. They did pay for my travel and hotel for this meeting.

This will be AA-99. So the data, very, very briefly. The next slide up. The ejection fraction you can see in Cohort B showed a slight statistically significant increase in the TAVI group, from 53.6 up to about 56.2. But importantly, when one looks at -- and I think this is what was asked. When you stratify it by baseline ejection fraction, you could see that there is significant improvement in ejection fraction seen in the lowest ejection fraction group. So in those patients who came to us with an EF of less than 30 percent, there was a 26-percent improvement in ejection fraction, and progressively less improvement was seen as the ejection fraction increased.

The increase that you see in the standard therapy, again in the setting of 78.8 percent of patients getting BAVs, is in all likelihood secondary to that procedure. And I hope that answered the question.

DR. PAGE: Dr. Lange.

DR. LANGE: This is great information. I guess what I was really interested in was, in terms of mortality associated with the procedure, was there a mortality difference based upon those that had a normal EF or those who had a depressed EF? In other words, your follow-up data, your ejection fraction improvement only tests survivors of the procedure. So I just want to make sure and see if there's any relationship between the periprocedural

mortality and EF.

DR. LEON: I'm sorry. In the TAVR group, there was no significant relationship between baseline left ventricular ejection fraction in either 30-day, which is periprocedural, or one-year mortality.

MS. AKIN: The question on the results of SF-12 and EQ-5D, I'll bring Dr. Matt Reynolds.

DR. REYNOLDS: Sure. That's the one. So the question was asked this morning, could we show the results for the other quality of life scales? These are just raw means. There's a lot more analysis that's been done behind the scenes. But briefly, this shows SF-12 physical and mental scales on the top parts of the Panel and then EQ-5D utilities on the bottom.

For those not familiar, SF-12 summary scales are scaled to a population average of 50, so the baseline scores on the physical are more than two standard deviations below the population average. Obviously older patients tend to have lower baseline physical scores anyway.

The difference, there's a measurable difference at one month. It's in the range of four and a half points on the SF-12 physical, and that increases slightly from 1 month to 12 months. On the SF-12 mental, the scores -- you can leave that up, actually. The SF-12 mental, the scores were less depressed at baseline so that sort of remarkably the baseline mental scores in this population were not that far below population averages. They were in the mid-40s. There was no difference at one month, but the groups

did diverge such that there was about a six-point difference in SF-12 mental scores at 12 months.

And the EQ-5D utility scores, these are scaled from zero to one, and again, the differences were in the range of about .08 to 1/10th of a point on one-point scale. And all of those differences were statistically significant.

Any other questions about that data?

DR. PAGE: Any further questions? Dr. Good.

DR. GOOD: Just a clarification on the EQ-5D, which I'm not quite as familiar with. You mentioned that disability adjusted life years are part of that. Is that rolled into or --

DR. REYNOLDS: So we are not showing you any of those, but EQ-5D utility scores are used commonly in health economics research to estimate quality adjusted life years. So these are simply to get from a life year to a quality adjusted life year. You just multiply the life year by the profile of utility scores seen over time.

DR. PAGE: Thank you.

MS. AKIN: On the subject of quality of life, a question was asked, why did we choose the SF-12 for the postapproval? The answer is actually simple. It seemed like a simple instrument in the postapproval, it's widely accepted, and there is population data. We have no concerns to use other instruments equally. Okay.

So let's see, another question would be, did you use the NIH SS

stroke for patients and what were the scores for patients who had a stroke?

DR. LEON: So yes, we did have NIH Stroke Scales at baseline for both groups and at the various follow-up intervals, including 30 days, 6 months, 1 year. And maybe we can show this next slide.

The ascertainment isn't perfect, but we had NIH stroke scores on survivors. It varied at baseline. As you can see, it was close to 100 percent had drifted down to between -- to as low as a little over 50 percent at a year, but certainly NIH Stroke Scales were performed and were equally administered to both groups. Can we go to AA-40, please?

These are the absolute mean NIH Stroke Scale data for all patients at the various groups. As you can see, the baseline numbers are quite low, less than one. This Y axis is only up to 10; slightly higher in the TAVR group, but only a mean of .8 at the 30-day visit and showing no significant difference during the follow-up periods.

If you look at the 24 patients that had any neurologic event -- just to keep out of trouble, I'm not going to say TIA, minor stroke, major stroke ever again. I'll just say all neurologic events. There were 24 neurologic events in the TAVR group and the baseline NIH Stroke Scale for those patients was 2.3. Several of those had previous strokes. And the peak after their event was 5.1. In the control population, of the eight patients that had neurologic events, the baseline was 2.2 and the peak was only 2.7. So these are the NIH Stroke Scale data that we currently have available.

In addition, we did analyze the KCCQ in all of the stroke patients to see how well they felt from the standpoint of quality of life, and it was interesting. We do have data. If we can show AA-39. The majority of patients who had strokes and survived actually felt much better than they had at baseline, principally because the valve was fixed. So the overall quality of life, even though they did experience a neurologic event, was generally better in the stroke patients. But, again, this is our crude effort to try to assess quality of life in these patients.

Is that helpful?

DR. PAGE: Dr. Good.

DR. GOOD: So did you do NIH Stroke Scale prospectively on the entire cohort?

DR. LEON: Yes, yes, yes.

DR. GOOD: Okay.

DR. LEON: Yes.

DR. GOOD: A preprocedure?

DR. LEON: Preprocedure --

DR. GOOD: Okay.

DR. LEON: -- predischarge, 30 days, 6 months, every clinic visit, yes.

DR. GOOD: Okay. And then as soon as person had an event, they had the NIH Stroke Scale registered again at that time? Or are they just

at regular time intervals?

DR. LEON: They were at regular time intervals, but if they had an event, remember, predischage encompassed more than 50 percent of the events.

DR. GOOD: Okay.

DR. LEON: So I don't know if it was within 24 hours or 48 hours of the event, but they always had a predischage NIH Stroke Scale after the event. And then the time points would be because many of the other strokes were outpatient strokes. We had no way to administer temporal-to-the-event NIH Stroke Scale, so it would be at their next clinic visit.

DR. PAGE: Thank you.

MS. AKIN: There was a question about longer-term follow-up. We do have Slide 8A. Eight is a three-year mortality curve or survival curve -- mortality curve similar to shown by FDA. I'd also like to bring up Dr. Josep Rodes, who has done a longer-term study in his series.

DR. RODES-CABAU: Hello, I am Josep Rodes-Cabau. I'm working at the Quebec Heart and Lung Institute in Canada. I am a consultant for Edwards, and Edwards paid my travel and the hotel for this meeting.

Remember, this study was investigator initiated, not supported by any sponsor -- the trial in Canada, including 339 consecutive patients. We only excluded the patients included in the PARTNER trial. And this is the update of this trial that was published about one year ago in *JACC*, and you

see at that three-year follow-up we have a number of patients, a significant number of patients, around 25 percent of the study population. The survival rate at three-year follow-up is 53 percent. The number of patients at risk at four-year follow-up was pretty low.

The patients included in this trial, this was a compassionate clinical use program approved by Health Canada, each patient had to be approved by Health Canada, and most of these patients were non-operable patients. There were some patients considered at high risk, but most of them non-operable. All of them were weighted by a heart team, involving, for sure, a cardiac surgeon. And this is still the case in Canada nowadays. The next slide, please.

And the next slide is only a brief overview of causes of death during the follow-up. This is only death at follow-up. Most of the patients died of non-cardiac causes. About one-third of them died of cardiac causes. In five patients we didn't know exactly the cause of death. Next slide. Next slide, please.

When you look at the non-cardiac causes of death, in fact, most of these patients died of respiratory problems. We found the COPD an important marker, an important predictor of this mean to end-term mortality, then followed by renal failure, and six patients died because of a stroke. A total of 10 patients had a stroke during a median follow-up above two years, a median follow-up of 27 months now. And this means on a stroke grade per

year during the follow-up period of about 1.5 percent in this population.

Next slide.

And this is showing the causes of death among the patients who died because of cardiac causes. Most of them had died because of cardiac failure. There was certain number of patients who died because of sudden death. And there were two valve explanations in this study. There were two patients who had endocarditis several months following the procedure, and the valve was explanted. One of them died and the other one survived. But importantly, there were no cases of valve explantation due to structural valve failure during the follow-up period in this trial.

DR. PAGE: Thank you. Dr. Naftel, I think that was in response to your question. Do you have a further comment?

DR. NAFTEL: Well, yeah, absolutely, but not for you.

(Laughter.)

DR. NAFTEL: Could we go back to my question? That was a little bait and switch there. Now you went to Canada. I want to stick with the study in front of us, so please go back to the first curve that you showed.

MS. AKIN: Okay.

DR. NAFTEL: And the question was how many deaths are in each curve. And also your curve looks very different from the FDA curve. I need to understand that.

MS. AKIN: Okay.

DR. ZUCKERMAN: Okay, Dr. Naftel, when you say it looks different from the FDA curve, what FDA slide or figure are you referring to?

DR. NAFTEL: Yeah, the very first slide on all-cause mortality, the very first mortality curve that FDA showed.

DR. PAGE: Was that the primary endpoint curve?

DR. ZUCKERMAN: Okay. For reference, are you talking about -- because it's blown up bigger -- page 16 of 36 --

DR. NAFTEL: Yes, yes.

DR. ZUCKERMAN: -- of the FDA Executive Summary?

DR. NAFTEL: Yes, sir.

DR. ZUCKERMAN: So if the Sponsor and their team could go to the FDA Executive Summary.

MS. AKIN: I'm a little confused by the question. If we can -- let's see, next slide up here. All right. So I'll show this curve again. I think that FDA showed a survival curve, and we're showing a mortality curve, I guess the flip of that. I'd like to bring up Dr. Bill Anderson, who maybe can better answer your question.

DR. ANDERSON: I'm Bill Anderson, and I worked on the trial as a statistician, as a consultant to Edwards, and I'm paid for my time and my travel.

If you look at this curve and compare with the one in the FDA book, they're virtually identical out to 24 months. The distinction is, at the

time of data close for the submission, which was November 1st, there were very few follow-ups past two years. So most of the data we had would be either because a patient died, we get current death data, or because a patient had some other adverse event and we would get data, and those, of course, tended to be the sicker patients, as they had an adverse event.

The particular data in this curve is based on the data extracted June 24th, and as it says on the slide, we have not yet submitted data that late to the FDA. Certainly, after having shown this slide, we anticipate a request for that.

(Laughter.)

DR. NAFTEL: Okay. So just let me get it straight. So this line is follow-up through June of 2011?

DR. ANDERSON: This is the status of the database on June 24th, 2011.

DR. NAFTEL: And then the curve that FDA shows is quite a bit different from this because it's got that high mortality right after two years. So their curve is a different dataset. Is it the one that's through January 1st, 2011?

DR. ANDERSON: The extract was done in January, but the data -- the close for all of events is November 1st, 2010. That was the agreed-upon analysis close date for the update PMA.

DR. NAFTEL: Okay. So I mean, this is really an important point

to me because the FDA curve shows a really big increase in mortality after two years and yours isn't showing that at all. So I'm still confused.

DR. ANDERSON: It's the denominator difference. We have a lot of three-year follow-ups of alive patients.

DR. NAFTEL: Okay. So let me just try one more time. How many deaths occurred after 24 months?

DR. ANDERSON: I do not have that number at hand.

DR. NAFTEL: Because, just looking at the FDA, it looks like 12 steps, near as I can tell, and it'd take a lot of follow-up to push that up. But I mean, I hope this right and I'm listening to you very carefully, but I was just so jarred by the FDA Kaplan-Meier and the fact that this is so different is a bit unsettling to me and I wish -- I just don't quite understand how a little extra follow-up would push that up. I totally understand patients pushing through the death times and all, but it's unnerving to me that your curve is so different from FDA's.

DR. PAGE: And if I may, Bram, maybe you can help us, or somebody else from FDA. Page 16 actually only has a single patient out at three years. Leave that slide up, if you would, please. It only has a single patient at three years, whereas the chart that was just seen, there it has six patients out at three years. I don't know what to make of any mortality curve when only one patient exists in follow-up.

DR. ZUCKERMAN: Let me try to help the Panel. And

unfortunately, this didn't come out well when we showed the FDA slides, but I would refer the Panel members back to Slide -- I believe my vision is bad. It's C-36. That actually has the red lines, as well as the actual Kaplan-Meier on page 18 of 36.

And in general I think the problem is, post two years, we just have very limited data right now, and in retrospect, one could make a suggestion that we should not have shown anything post two years. We don't really have a difference in interpretation with the Sponsor and Dr. Anderson. It's a matter of data and denominator.

David, that hasn't been an issue as opposed to, I think, when we get to Dr. Somberg's question and why there's a discrepancy in some of the neuro percentages.

DR. NAFTEL: Okay, I'll almost let it go. But just even looking at your curve, at two years there's 61 patients and 12 deaths after that. That's a hunk of information, so I will not ignore it myself.

DR. ZUCKERMAN: We would certainly agree, and I think a key Agency question is to get better follow-up and data post two years. These patients just live, fortunately, longer than two years, many of them.

DR. NAFTEL: Okay. So thank you. So I'm backing off a tiny bit, but you didn't answer the first question. How many deaths are in each group? From the best, your latest follow-up, how many deaths in each group?

DR. PAGE: Please speak in the microphone. It's the button of the base. There we go.

DR. ANDERSON: I do not have that number with me at this moment. I can possibly get it in the next 10 minutes.

DR. NAFTEL: Yeah, okay. And that actually was my question, how many deaths in each group was my original question. And I'm sure, Bill, that you don't have it on the tip of your tongue, but quite frankly, I would expect the Sponsor to know that number from memory. So I'll wait for somebody to tell me how many deaths in each group. A very simple question.

DR. SOMBERG: Can I just ask a quick follow-up to this?

DR. PAGE: You bet.

DR. SOMBERG: It says at the bottom of the slide that this has not been submitted to the FDA, but it's been validated in the company, and this is what the company stands by as a truthful representation of the dataset that they are going to present to the FDA.

DR. ANDERSON: As of the data extract at that date. We did not put this slide in our original slide set but presented it in response to the question.

DR. SOMBERG: Excuse me, it's been validated and vetted by the company but not yet presented to the FDA. Is that a correct statement?

DR. ANDERSON: That is correct.

DR. SOMBERG: Thank you.

DR. PAGE: Has the Sponsor adequately answered the Panelists' questions that were left over from this morning? Dr. Lange?

DR. LANGE: No. Jodi, you were going to show us the data from the patients that have continued access to the valve but weren't included in the original analysis?

MS. AKIN: Yes, I have that. Dr. Leon, do you want to come up? And that is Slide -- let's see. Can you bring up the -- let's see. Slide AA-17, please. Actually, I'm sorry, that's roll-in patients. It would be AA-21. There were two populations of continued access, just for purposes of clarification, and then I'll bring Dr. Leon up to walk through any questions.

At the end of the inoperable cohort we were still enrolling in Cohort A, which means we were required to continue to randomize in continued access so as not to bias the Cohort A protocol. So the first series of continued access were randomized, followed by a subsequent series that are nonrandomized.

The datasets again are from the same extract of November for the current PMA update, and we'll present to ITT. We have all-cause mortality, mortality/rehosp, and mortality and stroke. If you have any other questions, we'll see if we can accommodate.

Do you want to come up, Dr. Leon? Which specific data point were you interested in?

DR. LANGE: I was just going to walk through this. I mean, it's flashed up there and so kind of walk -- just as you walked through the other slides, walk us through the endpoints with the TAVI group and the standard treatment group.

MS. AKIN: Okay. So this slide is just -- this is straight from the clinical report in the PMA submission. This is ITT population. There were 41 patients in randomized continued access and 49 patients in standard therapy, and this is showing your Kaplan-Meier survival at 30 days, of 90.2 percent versus 97.9 percent at 30 days. The next slide should be one year.

DR. LANGE: Before you leave that for second, it's randomized or it's not randomized? I'm confused.

MS. AKIN: The first series of continued access were randomized. They had to be randomized because we were continuing to enroll in the operable group.

DR. LANGE: Okay.

MS. AKIN: Yes.

DR. PAGE: Dr. Jeevanandam had his hand up, or Dr. Kato. Either.

DR. JEEVANANDAM: So I'm looking at death at one year, which is 31 percent of the TAVI group and 20 percent of the standard therapy group. So in the continuous access protocol, is there less mortality in the standard group?

MS. AKIN: Okay, this is -- not all patients were full follow-up, so this is a little bit -- a snapshot in time for a smaller sample size. Secondly, we did see -- in the very beginning of continued access, we did see a higher death rate early on, and I'd like Dr. Leon to explain that phenomenon. You can come up.

DR. PAGE: Let me just remind the Panel that all our comments should be with the microphone on, please.

Dr. Leon.

DR. LEON: Yes. So, again, this is a small snapshot of, as you can see, less than 100 patients that were randomized after the formal randomized portion was completed and before we had completed enrollment in the Cohort A operable patients. Thereafter, the continued access Cohort B, or inoperable patients, were followed as part of a prospective observational registry.

There was a significant delay in initiating this randomized portion of continued access, and under those circumstances, at each one of the sites, certainly patients were clustered who had the highest risk characteristics.

So I think we felt that there was an anomalous increase in mortality in this early randomized phase of continued access due to the fact that, again, we had no therapy available and only the sickest of the sickest of the sick were actually initially randomized, and these one-year mortalities, I

think, reflect the fact that they had extraordinarily high morbidities.

DR. PAGE: Dr. Kato.

DR. KATO: You know, I'm not a statistician, but the problem that I see in this is that if you look at every event, early deaths, 9.8 percent on the TAVI side, two percent on the standard, so TAVI has a higher early death rate. The death rate at one year is higher on the TAVI side. Late deaths greater than 30 days, it's still higher. Whatever the next death is 31.7 percent versus 20.4 percent. Death rate per early death rate -- you know, every number on the TAVI side is higher than the standard therapy.

And yet the Kaplan-Meier curve says 90.2 versus 97.9 percent. You know, from a very simplistic view, it doesn't add up because all the death rates are higher on the TAVI side and yet the Kaplan-Meier survival curve is improved on the TAVI side.

MS. AKIN: So I apologize. This is actually survival, not mortality, in the columns.

DR. KATO: Okay. Well, then you have -- then what I would read off of this slide is that you do better with standard therapy because you have a better survival, at 97.9 percent versus 90.2 percent on the TAVI side. And you have a higher mortality in every category on the TAVI side.

MS. AKIN: The rate shows survival, 54 versus 31. I'm sorry? Yes.

DR. KATO: The 54.72 that you're referring to is death --

MS. AKIN: I know.

DR. KATO: -- at one year.

MS. AKIN: I'm saying that it's not correctly -- there was a -- the slide doesn't accurately -- it is survival. We can reproduce the slide or the analysis, but it's survival.

DR. SOMBERG: Is it correct to say that --

MS. AKIN: Yeah.

DR. SOMBERG: -- this is the subset of patients -- excuse me? Is it correct to say that this is the subset of patients who were continued to be randomized in the B arm of the study?

MS. AKIN: Yes.

DR. SOMBERG: So some of these people, if that's the case, so what you're -- so what some of my colleagues are saying is, in this subset, from this dataset, it's going a different than the overall. That's still acceptable because the overall is what they presented in the previous slide at two years and three, overall mortality. So this is not all the patients; this is only 41 and 49.

MS. AKIN: We also have additional slides to show the nonrandomized continued access, which we can bring up as well.

DR. PAGE: Well, before we do that --

MS. AKIN: Yeah.

DR. PAGE: -- I think it should be clear to the Panel that these

are patients who were randomized after closure of the randomized trial that was presented to us. This is a smaller population. But I think what's troubling the Panel is that the 30-day and the 1-year mortality appear to be higher with the valve than with control. Are we interpreting that correctly?

MS. AKIN: The survival is higher in the TAVI than the control. The mortality at 30 days was higher in TAVR than control. So I need to confer with my team.

DR. PAGE: Are you statisticians agreeing with this? Because something's wrong here. Either the slide or the interpretation of the slide is wrong.

Dr. Lange, could you clarify for us?

MS. AKIN: I can come back and clarify, just to make sure that we're presenting this accurately. I did want to turn back to Dr. Naftel's question. Deaths as --

DR. PAGE: Before you do that, Dr. Lange had a comment.

MS. AKIN: Okay.

DR. PAGE: Yes.

MS. AKIN: I'm sorry.

DR. LANGE: No. And the reason I -- and I saw this when I was reviewing the data, and what I'm just trying to get my hammer on is why it's different than the -- because this is randomized.

MS. AKIN: Um-hum.

DR. LANGE: It's a smaller patient population.

MS. AKIN: Um-hum.

DR. LANGE: There's no question about it. It's not 380 patients, it's just 100 patients, but it moves in an entirely different direction. And while you might say, well gosh, it's the sickest of the sick people, but the standard therapy group, if it's randomized, should have a very high mortality, too.

MS. AKIN: Um-hum.

DR. LANGE: So I'm just trying to figure out what's different about this --

MS. AKIN: Um-hum.

DR. LANGE: -- since the trial closed, as opposed to the trial. That's all.

MS. AKIN: So, again, the short answer is that, in early phases of randomized continued access, the trend was actually noted in the acute period by the Data and Safety Monitoring Board, which took weekly reports of death and stroke, and again it normalized as the backlog of patients. I can't explain the phenomenon, but it's not evident in the full continued access population.

DR. PAGE: I understand that another population may be different. What I just want clarity on is, looking at this small group --

MS. AKIN: Um-hum.

DR. PAGE: -- the control patients did better than the valve patients. Are we correct in that interpretation?

MS. AKIN: Again, I want to make sure I have the correct answer to that with a statistician.

DR. PAGE: Maybe you can get back to us --

MS. AKIN: Yes. Yeah.

DR. PAGE: -- pretty soon.

MS. AKIN: Okay.

DR. PAGE: Thanks. Let's move on to the other questions that we had.

MS. AKIN: Um-hum.

DR. PAGE: And then we need to wrap up for --

MS. AKIN: Okay.

DR. PAGE: -- this section of the meeting.

MS. AKIN: I wanted to answer the total death question for Dr. Naftel. As of the March update, the test, there were 79 deaths, and control 119 deaths.

DR. PAGE: As of June when that --

MS. AKIN: As of March.

DR. PAGE: As of June when that slide was made, how many deaths were there?

DR. NAFTEL: Thank you.

MS. AKIN: Dr. Anderson is pulling those numbers.

DR. PAGE: Dr. Good.

DR. GOOD: Do you have any stroke information on that group as well?

MS. AKIN: Yes, we do. Yeah, we can pull that up. Slide A-24, please. And that's showing here. Do you need me to comment on it?

DR. PAGE: Dr. Good, do you have any comments or questions?

DR. GOOD: Well, you know, just making a quick eyeballing here, it doesn't look that there's any difference in the stroke events in either group. So the mortality, if the mortality is real, must be certainly related to something else.

DR. LEON: Yeah. Again, there was one stroke early in this population. It's a small subset. I think the other point that we neglected to mention was only 21 of the 26 PARTNER sites had enrolled in Cohort B, and during this randomized phase we were integrating five new sites. There may have been some early learning curve issues amongst those five sites, and it doesn't take very many more early deaths to create some imbalance in this very small randomized trial.

DR. PAGE: I think we understand. So this is a small subset, and in a small subset that's not powered for mortality or stroke, we see at least a signal of higher mortality and actually lower stroke overall. But, again, it's a smaller study.

Dr. Borer.

DR. ZUCKERMAN: Okay, before we switch gears, because this has been an important issue as to the veracity of that slide, I would ask the Panel members to look at pages 95 and 96 of the briefing document where Edwards gives their review of the data. Presumably, these data are correct and the relationship of increased mortality in this small continued access, randomized trial is seen.

DR. PAGE: Dr. Zuckerman, you're looking at page 96 and looking at page --

DR. ZUCKERMAN: Ninety-five and ninety-six of the Sponsor's briefing document.

DR. PAGE: So Table 20, specifically?

DR. ZUCKERMAN: Yes.

DR. PAGE: Which shows, indeed, a higher mortality in the small group, among the valve patients.

Ms. Patrick-Lake.

MS. PATRICK-LAKE: Okay. So I'll be the blonde person. I've gotten a little lost. When we're talking about the continued access population, were they more sick, less sick, or comparable to Cohort B?

DR. PAGE: I think we've heard from the Sponsor that they believe they may be more sick.

MS. PATRICK-LAKE: Thank you.

DR. PAGE: I'd be interested in our statisticians commenting on whether we need to spend more time on this small group in that it is an underpowered small group that wasn't randomized. I think we could discuss whether this gives us concern about safety and efficacy.

Dr. Naftel.

DR. NAFTEL: Certainly it's obviously a small group. You know, it still is a piece of the evidence, but it's a small piece of the evidence. It's not going, you know, the way I'm sure they hoped it would. So I'm willing to back off from it.

DR. PAGE: And I think, in fairness to the Sponsor, they wanted to comment also about continued -- the continued access, the nonrandomized point, in terms of ongoing mortality. I don't want to give the impression that these were the only individuals that received the valve after, although this was the only randomized group.

MS. AKIN: That data is forthcoming because now we have hundreds of patients, but that was not part of the November snapshot. It was still early in continued access. And Dr. Leon made an important point that there were a number of new centers that initiated in that continued access period. And, finally, the access that we had was 32 patients per month for the entire U.S., which allowed us about one to two patients per center. And we did have a backlog.

We observed, ourselves, that it felt like more Cohort C, you

know, patients that were kind of getting into that early group. I believe that when we have the hundreds of patients in continued access at 30 days, which should come, you know, later this year, we'll have a more accurate snapshot.

DR. PAGE: Dr. Somberg.

DR. SOMBERG: Just to make sure that I understand this correctly, is that with the continued access population, the small group, was that also counted in the overall two- and three-year that was closed in March?

MS. AKIN: No.

DR. SOMBERG: Pulled together in June?

MS. AKIN: No.

DR. SOMBERG: So that's not?

MS. AKIN: No.

DR. SOMBERG: Well, then, could you -- I think it would be very important for me and maybe for other Panelists as well, could you provide an overall statement on mortality now, based on this continued access, which is a small population, but still 41 and 49 should be included in all patients, plus all the data that you have at two years and three years that was closed in March? That, I think, is a fair representation because it's unfair to look at this, but it's unfair to look at the other as well. We should look at it all combined.

DR. PAGE: If you could get that for us, that would be great.

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Dr. Borer and Dr. Brindis had their hands raised, and then we are going to need to move on to questions to the FDA for follow-up.

DR. BORER: Yeah, I'm sorry, it is a little unfair. I didn't expect that the answers to the pre-lunch questions would take so long. But the population, as I see it, that we're really going to be honing on here is an extraordinarily sick population, predominantly in the mid-80s in age, but there was a relatively wide variation in age. There was 83 plus or minus 9, which was the standard deviation, and there were some people who were as young as 49, as I recall.

The question I would ask, and you may not have the answer immediately and it doesn't take more than a sentence to respond, was there a difference in survival of the people who got the valve and of the control group based on age? Was there -- did you have a substantial number of people who were -- you must've had a substantial number of people who were under 80. Did you have some who were under 75? Can we say something about the duration of survival, on average, about those younger people compared with the older people?

MR. WOOD: I can give you a partial answer. We think the reason that there's that broad range has to do with the bimodal distribution based on the subset that has low STS score, relatively young with technically inoperable causes for inoperability. There's a whisker plot, you know, a forest plot that we didn't show you, that demonstrates that age had no

significant impact on outcome. As far as the duration of survival related to age, I don't know that we have that.

DR. BORER: Okay. I mean, I can certainly understand the variation in age. That's not a problem for me. I think it would be important at some point to know whether there was a difference in survival based on age, but we'll come to that in the discussion.

DR. PAGE: Dr. Brindis.

DR. BRINDIS: Going back to the previous issue about the increased mortality in the group, post the original study, I actually am less concerned about this, and I'll share that. Again, the one-year mortality in the TAVR is consistent with the study one-year mortality. In fact, I don't take on the issue of the new training groups. It's consistent with your study per se. It's three extra deaths, if you will, in the standard care group. The confidence interval is such that it doesn't cover that. And off the back of the envelope, I would imagine that if the three extra deaths pooled in -- if you pooled the two together, it would still be statistically significant, but I would like to have that data.

DR. PAGE: Panelists, have the questions from this morning been adequately addressed? And is our Sponsor satisfied that you've had the opportunity to respond? Thank you.

Let's go on to any questions that were left over from this morning with regard to the FDA presentation. As I recall, Dr. Kato had a

question about Slide 23. One problem was the --

DR. KATO: It was really an imaging thing. I just wanted to make sure that we had -- because of the red line on the black background. But, you know, again it's going to rehash this other issue, but we just want to see it again.

DR. PAGE: Okay. Were you able to reconfigure that? Please turn on the microphone.

MR. HILLEBRENNER: We can load that up. I'm not sure how long it would take. This is Matt Hillebrenner, for the transcriptionist. But I would point out that the slides, the color slides you have in front of you --

DR. PAGE: Right.

MR. HILLEBRENNER: -- do show this in color.

DR. PAGE: Right, okay.

MR. HILLEBRENNER: So hopefully you'll get to see that.

DR. PAGE: I don't think we need to spend time on that.

Dr. Somberg, you had a question about CVA, I believe.

DR. SOMBERG: Well, that now becomes a sub-issue, but we had a question of the CVA rate was increasing, about 50 percent I think was stated; well, late CVAs, 48 percent or some number like that, as opposed to the Sponsor, which had essentially most of the occurrence of neurologic events in the first five days. We've just seen a new slide from the Sponsor showing that there is really no increment over time in neurologic events. Do

you have any data that is different than that?

DR. SWAIN: Well, from our statistician's dataset that we got, 46 percent of the neurologic events, meaning strokes plus TIAs, 46 percent were greater than 30 days, so late, not acute. That's 41 percent of the strokes. So, you know, that was the question you were asking, I believe.

DR. SOMBERG: You know, it's like asking one side the question and you get one answer. You ask the other side the question, you get the answer. I haven't asked the question, but I will just make the statement that it looks to me, from my interpretation of neurologic events, I think we're talking about the same events from C-93 and C-94, that most of the events are occurring in the first five days, not -- and I mean most, not half and half, as you're describing. So there seems to be a question about the important toxicity as well as the efficacy question. And I'm confused on that.

DR. SWAIN: The data we have from the Sponsor, 46 percent of the neurologic events, of 24 events, 11 out of 24 are after 30 days. It was extremely difficult to analyze these strokes for a lot of reasons.

DR. FERGUSON: A follow-up to that. What was the percentage of late strokes in the control group?

DR. SWAIN: You know, if you say time from randomization, that's different than time from some event, and you can see --

DR. FERGUSON: Let's say 30 and 31 days and a year.

DR. SWAIN: I'll have to look that one up again. I believe I have

a slide there to indicate that. There's four graphs on a slide, of various time periods, and my Slide Number 50. It's 50. And in the control group, the neuro events between 30 days and 1 year was 2.8 percent of the total.

DR. PAGE: Is it possible to project Slide 50, please? Is that a yes, it's a possible, or a no, it's not possible? There we go.

DR. SWAIN: So if you look at the upper right, between 30 days and 1 year, those are the neurological event rates. The total number of patients.

DR. PAGE: The question was, are those percentages? And I assume they are.

DR. SWAIN: Those are percentages, yes.

DR. PAGE: 4.5 percent --

DR. SWAIN: Yeah, percent of patients.

DR. PAGE: -- versus 2.8 percent at 30 days to 1 year.

DR. SWAIN: Correct.

DR. PAGE: So it's 1.6-fold greater but less than the 4.3-fold difference in the less than 30 days.

DR. SWAIN: Yeah. And, again, control is time from randomization, I believe. And the problem of most of the strokes in the control group were after -- close after an intervention, or many of them were close after an intervention.

DR. PAGE: Dr. Naftel.

DR. NAFTEL: So may I take a moment to compliment the Sponsor on their statistical analysis of this?

I think, when I read it carefully, this was percent of patients, and all of these are a percent of the 179 and the Sponsor earlier showed rates. And of course the experimental group, the transcatheter group, they have more time, they're alive longer, so the rates, the way the Sponsor did it, is far better than this. So I just want to tell you that.

DR. SWAIN: Dr. Wang actually has a competing risk slide related to that.

DR. NAFTEL: Oh, wow.

DR. SWAIN: And if someone can figure out how to find that in this group here, we'll see.

DR. NAFTEL: The issue is that the experimental group has more patient exposure. They have a higher -- a better chance to experience events because they're around longer.

DR. PAGE: While we're queuing that up, does the Panel have any further questions for the FDA? Because we're going to be moving on to the FDA questions as the next segment.

Dr. Ferguson.

DR. FERGUSON: Yes, I had a question. The FDA made a comment about vascular complications, and then they had just a qualitative assessment that many of the patients who had vascular complications

required stenting or grafts, but there were no percentages associated with that. Do we have any idea of how many patients with vascular complications actually had long-term or disabling complications?

DR. SWAIN: We actually don't have that data. We don't have it broken down by those with vascular grafts versus vascular material, patch graft angioplasty or something of that sort versus aortobifem versus fem-pop versus all of that. We just don't have the granularity to look at that. There was no measure or a place on the CRF for claudication, things of that sort. So it's not something that I can comment on.

DR. PAGE: Dr. Good.

DR. GOOD: I'm going to go out on a limb here as a non-cardiologist. One of the things when I was reading through this preparatory information was the endocarditis rate, and that hasn't been discussed at all today. Any thoughts about that? There were certainly some examples of pretty horrendous endocarditis, and I just don't know enough about it to comment.

DR. SWAIN: Not very high in what we would expect for a prosthetic aortic valve replacement.

DR. PAGE: Are you ready with the slide now?

DR. WANG: Yes. This is Chenguang Wang, FDA statistician.

To better understand an adverse event, especially stroke, on this trial, we did a cumulative incidence analysis on stroke, taking death as a

competing risk. Although we have a p-value here, please note that this analysis is post hoc. And if we look at the curve, the Y-axis is the cumulative incidence probability, and the definition is the probability of failure time less than a given time, T, and the type of failure to be stroke, and we see that that control is smaller than SAPIEN. That's for stroke.

DR. PAGE: Dr. Naftel, did you have any other question about that? Did you have any other comment?

DR. NAFTEL: No, that's very nice.

(Laughter.)

DR. PAGE: That being said, I really appreciate both the FDA and the Sponsor's efforts to generate responses to our questions. I know while we having lunch you were feverishly working on slides, and we appreciate that.

It's now time to focus on our discussion on the FDA questions. Copies of these questions are in the folders for the Panelists. I would ask that each Panel member identify him or herself each time he or she speaks, to facilitate transcription.

And let's put up the first question, please. And as we're getting that together, let me address -- the first issue we're addressing is proposed indication for use.

The Sponsor and the FDA propose the following indications for use. And the word symptomatic is inserted in here. I remember where.

The Edwards SAPIEN Transcatheter Heart Valve, model 9000TFX, sizes 23 mm and 26 mm, and the RetroFlex 3 Delivery System are indicated for transfemoral delivery in symptomatic patients with severe aortic stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis.

This wording is intended to reflect the process by which patients were determined to be "inoperable" before entering the PARTNER trial. There were several patients enrolled in the trial who may have been too sick to benefit from isolated treatment of severe aortic stenosis, since there were no specific inclusion/exclusion criteria in this study to eliminate these patients. The proposed indications statement also attempts to address this concern.

So Question 1 is as shown. Please comment on whether the proposed indications for use statement adequately addresses the concerns mentioned, as well as whether there are any other patient selection factors that should be addressed by refining the indications statement.

So I'll look to Panelists to comment, and we'll try to work through a couple of these questions before the break.

And Dr. Borer.

DR. BORER: I will say that once you've added the word symptomatic, that this statement is acceptable, but with a caveat. It's

acceptable to me, at any rate, for this population. And let me define what I mean by this population: a very sick population that is, by and large, in its mid-80s, and from the data that we have -- there may be other data, the follow-up may not be adequate yet, but from the data that we have, we expect that most of them aren't going to live all that long. Within that context, I think that this statement is acceptable.

The question of co-morbidities that would not preclude the expected benefit from correction of aortic stenosis, of course I would like that to be more explicit and more directive. But it can't be because we don't know what they are. If one were writing a label, one could get some examples of what people might consider, but we don't know that.

However, if the proposed -- if the device is approved and postapproval studies or further follow-up is performed and the data are collected appropriately, then I think we could learn what might be indicators of sufficient co-morbidities so that benefit could not be expected and the label could be modified. At present, I wouldn't know how to modify it because we don't have the data.

DR. PAGE: Thank you very much. Dr. Kato.

DR. KATO: I share that comment, with the exception that we have the inclusion and exclusion criteria from the -- you know, from the trial itself, which is -- I forget which page it's on. But, you know, for example, I think that while you brought symptomatic aortic stenosis, the inclusion

guidelines said New York Heart Association Class II or greater. I actually think that we should put that in there.

One of the co-morbidities that was specifically excluded was dialysis-dependency or creatinine greater than 2.5, I believe. And I think for the -- because of this, trying to find the best cohort going forward, using the inclusion/exclusion criteria, I think, is going to be important here.

DR. PAGE: Dr. Borer, did you have follow-up?

DR. BORER: Yeah, just one. I mean, I absolutely agree. That's why I say we could -- one could put in some examples like the specific criteria. The functional Class II or greater is interesting, but 93 percent of the patients were in functional Class III or IV. One could put those things in. My only point was that, beyond that, we can't go yet. We can't say any more because we don't know.

DR. PAGE: Thank you. Dr. Lange.

DR. LANGE: Rick Lange. And while I agree with comments of both, one of the exclusion criteria were life expectancy less than 12 months due to non-cardiac co-morbid conditions, and that covers a lot co-morbid conditions.

So, you know, as worded, it's sufficiently vague, where you can't think of anybody that would live through the procedure that wouldn't benefit. If they're going to get up the next day and walk out of the room, even if they got cancer and they're going to die next week, they'll benefit for

a day. So I think putting in something like this would help it be true to the exclusion/inclusion criteria and give some guidelines as well.

DR. PAGE: Dr. Ferguson.

DR. FERGUSON: I'd just be concerned that that New York Heart Association class is a measure of congestive heart failure, and there are other symptoms besides CHF that are associated with risk in aortic stenosis, including angina and syncope. So we could potentially be missing those patients if we put a Heart Association classification on it.

DR. PAGE: Dr. Jeevanandam.

DR. JEEVANANDAM: I think the crux of the matter is, you know, this definition of this inoperable patient. I mean, we heard from some consumers or patients that, you know, they determined themselves as inoperable because they didn't want a sternotomy, right? Let's say there's a 50-year-old who doesn't want a sternotomy. Is that an inoperable patient? So I think we need to define what inoperable means a little bit more and --

DR. BORER: I'm sorry, but I thought people who just said they didn't want to have a sternotomy but who otherwise were judged operable by surgeons were potentially -- were excluded from the trial. They couldn't just drop into it.

DR. PAGE: One patient gave the impression, it was a personal impression, that he didn't want the operation. I did not query him or his doctor as to the circumstance. But if that was a Cohort B, then the surgeon

made the determination that he was not eligible.

DR. JEEVANANDAM: I'm wondering whether, you know, there are other criteria that were more objective, such as EuroSCORE or STS, and do you need to put those in there? Because clearly, you know, different surgeons are going to have different bar levels for inoperability. And, you know, in the trial itself, it was two surgeons who had to make the determination and this says one surgeon. So you're going to have wide variations in programs.

DR. PAGE: Dr. Zuckerman, do you have a comment?

DR. ZUCKERMAN: Yes, I'd like to remind the Panel again about the difference between indications for use and another part of the labeling, which is the clinical trial section.

Traditionally, the Agency has looked for a crisp and direct indications for use statement, and the concerns regarding inclusion and exclusion criteria and replication of important data find their way into the clinical trial section of the label. And what the Agency is looking for is really any possible short modifiers that help a physician really understand the appropriate indications for use. But the bulk of the comments being made really traditionally go in the clinical trial section.

DR. PAGE: In that setting, Dr. Kato and then Dr. Somberg.

DR. KATO: I guess one of my main concerns, having participated on panels before, is the recent, you know, follow-up studies on

drug-eluting stents, that 50 percent are being implanted off label, or the 20 to 40 percent of ICD pacemakers being implanted off label.

I share with Val this notion that, you know, I really -- everybody calls this a transformational technology. I mean, the guidelines by the societies have already been published and released in anticipation of a positive response by this Panel.

But that's also why I believe, at least in my view, that the indications for use, because it's a transformational technology, need to be fairly tight in order to try to avoid going on this path of off-label use. In this particular age group where, you know, these people, these patients -- and we're all headed this way -- you know, are achieving their life expectancy and we're giving them even more time on top of that. You know, there's ethical issues and there's moral issues involved, but I'm trying to avoid the situation where this all of sudden goes off label and becomes rampant.

DR. PAGE: Dr. Somberg.

DR. SOMBERG: I agree with Dr. Kato on that point, but I also think that we have to -- there's a spirit here and the spirit is that these are going to be used in people who are very severely ill and who really are not surgically operable.

So with that said, I suggest that the word severe be bold. I certainly think symptomatic is excellent in front of patients, and I think instead of saying one surgeon, I think it should be said that it should be,

generally, surgeons would feel this patient to be inoperable. So it's not that one can seek out a surgeon who would feel that this is, but it would be generally. And I think then, when you go back to the very specifics, as Bram suggests, you would go through a whole host of criteria that this would fit in, and it's actually an extensive one.

But I got the feeling, I mean, when you go to the part, the trial presentation, the different meanings from Dr. Leon's presentation, these are people who, you know, most surgeons and surgeons at Columbia and other places like that are saying, no, I won't operate on them. But, you know, the medical people and everyone else feels that they have enough life that they can benefit from this.

So you want to put that in a few words, as Dr. Zuckerman said, and I think just underlining or bolding severe and making it not just one surgeon but surgeons would feel this person not to be an operable candidate.

DR. PAGE: Thank you. Dr. Brindis.

DR. BRINDIS: Yes, it's been mentioned twice that 50 percent of stents have been put in that are inappropriate, and I want to make sure that everyone understands there's a distinction between off-label use which could be appropriate and inappropriate use. The study was actually misquoted earlier today by the presenter. It turns out that about five percent of stents in that study were found to be inappropriately placed in the United States. That was a marked unfair characterization.

In terms of the ICD issue, it was really a function of coverage reimbursement and may have actually covered guidelines. I want to get those issues out of the way, that we shouldn't -- these are apples and oranges here.

The discussion related to the proposed indications for use, I see us going at both edges, making sure that we focus in on the Cohort B patients reliably, and at the same time make sure that we aren't taking on the Cohort C's, you know, if you will, making sure that we're doing the right thing. And I have to say that, in general, I find this wording excellent but appreciate that it's really in the eyes of the beholder on what the expected benefit is for correction of aortic stenosis.

And Dr. Lange, you said it perfectly, that, you know, somebody who's going to die in two weeks of cancer who could be not short of breath for those two weeks, he would get the benefits from the procedure.

So I don't know how to deal with this, but I kind of like the flavor of the exclusion of the guidance in the PARTNER B trial that the expectations that without the co-morbidities, that you could live a year. I like that, conceptually, to help guide our clinicians and not doing things inappropriately to the wrong people.

DR. PAGE: Ms. Patrick-Lake.

MS. PATRICK-LAKE: So I wanted to get back to what Dr. Lange said. I think the statement is concise as guidance, and if we're looking just to

add something, I like the thing about the life expectancy of less than 12 months.

But I just want to point out that, to all of you, there is no patient, and I don't care how old, that wants sternotomy, and it is going to be a challenge. And so I think as stiff as we can make a guidance statement, that would be wise.

DR. PAGE: Thank you. Dr. Slotwiner has been very patient.

DR. SLOTWINER: Thank you. I just want to comment. I agree with all the details that all the Panel participants have said. But I think, for the indications for use statement, I think this is really quite elegant and I agree with particularly the possibility of two surgeons evaluating. But I think, for the IFU, this is really very elegant and, from my perspective, sufficient.

DR. PAGE: Mr. Dubbs had his hand raised.

MR. DUBBS: I agree with what Dr. Borer had to say about the age sensitivity of the results and the fact that we have such limited data, and I'd like to see something in here similar to what he said about the limitation in terms of the population that has been studied thus far, and that we don't really know, on a broad range of ages, whether or not it's an appropriate indication or not.

DR. PAGE: Dr. Borer.

DR. BORER: I'd like to ask a question, actually, of the FDA, Bram. And Dr. Jeevanandam said it earliest and best, I think. What we're all

concerned about here is slippage to people who don't fit into this population. I believe that the FDA has other mechanisms than just stating the indication for use here that could be applied to severely limit that kind of slippage, like mandating that every valve be registered with some information about why it's being put in before it gets put in, or something like that. Am I incorrect in that or are these mechanisms available?

DR. ZUCKERMAN: Yes, that's why, in my comments this morning, I tried to indicate that FDA takes the dissemination of transformational technology extremely seriously, and consequently we're just not a device approval agency. And, frankly, one of the most helpful things that this Advisory Panel can help us with today is to offer ideas on how this technology can disseminate.

Now, while I recognize that indications for use statements are important, I would certainly underline the points that Dr. Borer is making. If this Panel thinks this device is approvable, the mechanisms suggested for FDA and CMS to take in the postapproval setting are extremely critical, and we will be all ears.

I think there's another difference between the drug-eluting stent example that Dr. Greer and others referred to earlier. It's an important example where there was a problem with dissemination of very important technology. As Dr. Brindis said, we don't want to lose the whole picture, though. We do have an entire ecosystem right today that's very different

from the drug-eluting stent era.

I think you've heard that the professional societies are aware of potential risks and benefits of this technology, and again, I think their input can be an extremely important mechanism to utilize with government regulatory agencies to make sure that the entire system works, Dr. Borer.

So I think I've tried to answer your question in a general context. Do you need specifics?

DR. BORER: No, no, that's fine.

DR. PAGE: If I may, then, I'd like to summarize that the Panel -- I've heard a number of people actually compliment the FDA and the Sponsor on this being succinct and, if anything, elegant with the additional word symptomatic, and I'd agree with that.

There is concern that's been expressed in a number of ways, bold this word, have more than one surgeon. But the fact of the matter is that this statement, from what I'm hearing, seems like a pretty good effort at an appropriate indications for use statement. There are the concerns that have already been mentioned, and what I'm hearing primarily is concern that this will end up being used in a manner that's not appropriate and it slips into other indications.

So, Dr. Zuckerman, have you received enough information on this issue, or does the Panel have any concern with that summary?

DR. ZUCKERMAN: Anyone from the Panel want to add anything

else before I respond?

(No response.)

DR. ZUCKERMAN: I think that's an extremely helpful summary, Dr. Page.

DR. PAGE: With that we have a number of more questions to go, but we're already past time for a break. So I'm going to break for 10 minutes. It's now 3:40. We will reconvene promptly at 10 of 4:00.

(Off the record.)

(On the record.)

DR. PAGE: Okay, we're going to come back and reconvene. I'd remind the Panel that while I very much hope we can finish by 6:00, we need to stay throughout to reach a vote.

We've handled one question already, but there is one issue that I want to bring up. There's been concern raised about the continued randomized portion that was as -- and let's make sure at least I have it straight, and then I'm going to ask Dr. Naftel to comment

As I understand it, that was a continued access protocol that was continued in a randomized fashion as long as enrollment was ongoing in Cohort A so as not to offset the selection. If you have one where everyone gets it and another where they're randomized, that would throw off selection for Cohort A.

But the data that the Sponsor showed us was truncated at the

end of enrollment for the pivotal trial, and you've made the argument that this was, perhaps, a different population. But in any case, you were called upon to perform the trial, the trial was terminated, and then those trial, Cohort B, patients were followed, and those are the data that you showed us.

The concern has been raised as to whether the further patients should be combined in a Kaplan-Meier analysis. And before you answer, I'm going to ask Dr. Naftel to comment on what's appropriate here.

DR. NAFTEL: Well, certainly, in my opinion, a randomized trial lives by setting up the rules ahead of time and then following them.

So in this case, I believe you had 179 randomized in each group -- and then you used the word truncated; I'm sure you really meant that the enrollment stopped once you got the 179 in each group -- and then all the p-values, the alpha testing, everything is based on the 179, and that's the strength of a randomized trial, and I think that's what we should go with.

The fact that you continued CAP and randomized them, that's incredibly fascinating to me; I love the way you did that. I think the right thing to do is to live and die by the 179 and 179, and then we'd look at the continued access as a piece of information. But to really keep the probabilities correct and to keep this as a pivotal trial, I think we stick with the 179/179.

DR. PAGE: Let's move forward, then.

DR. SOMBERG: Does that mean -- can I ask a question?

DR. PAGE: Yes, Dr. Somberg.

DR. SOMBERG: Does that mean that we cannot see if the 179 plus the continued access randomization data combine? Has that been censored, according to Dr. Naftel?

MS. AKIN: Just a quick comment, too. And, again, this is more of a statistician's question, but per protocol and per statistical analysis plan, it is specifically actually requested by FDA that the continued access series should not and could not be pooled with the randomized trial series. So this is not a priori preset analysis plan.

DR. PAGE: So is it correct that you do not have that prepared for us?

MS. AKIN: Correct.

DR. PAGE: Thank you.

MS. AKIN: I do have an update on the numbers of -- that Dr. Naftel asked for, the June 25th snapshot of deaths, because I know you don't want to leave that blank. Control 127 and tests 92.

DR. PAGE: Okay, thank you very much.

Let's move on to Question 2. This is Heterogeneity of the Control Group.

The Cohort B arm of the PARTNER trial was designed to demonstrate superiority of SAPIEN device to "standard" therapy. During the trial, however, the Control group received several different treatments, as

outlined on page 13 of the FDA's Executive Summary.

Although the majority of patients received balloon aortic valvuloplasty, it is clear that there is no "standard" therapy for this patient cohort, as evidenced by the various treatments received.

So Question 2 is: Please comment regarding the impact of the heterogeneity of treatment options received by the Control group on the evaluation of safety and efficacy of the SAPIEN THV in this patient population.

Dr. Borer.

DR. BORER: This doesn't bother me at all, quite honestly. Julie Swain actually said what I think had to be said. The question that was being asked, certainly the question that was posed by the Sponsor in designing the trial or by the trial designers, was what happens when you give the new device versus what happens when you don't give the new device?

There is no standard of care for patients with aortic stenosis who can't undergo operation; it doesn't exist. There's no consensus, there's no way of teasing out something. And if you thought there might have been, I would say that the PARTNER group resolved that issue as best they could by comparing the people who had balloon valvuloplasty with the people who didn't have balloon valvuloplasty and didn't find any important difference. So I'm just not concerned by this at all.

DR. PAGE: Thank you.

Dr. Brindis.

DR. BRINDIS: I share that response. I have no issue with this particular query. In fact, my own intuition is that the standard of therapy, of which there is none, is mostly medical therapy and that this control group had a much higher use of balloon aortic valvuloplasty than is done in the United States overall.

DR. PAGE: May I ask the Panel, from my own standpoint, is there any concern that there was a higher performance of balloon valvuloplasty, and as such, the mortality was higher in the control group than would've been in a control group at a less sophisticated medical center?

Dr. Borer.

DR. BORER: Well, you know, of course, anything is possible and we can't answer the question because the trial wasn't done that way. But, again, the PARTNER group showed us that when you compared people who had balloon valvuloplasty to the albeit much smaller group that didn't have balloon valvuloplasty, there wasn't any difference in outcome.

So I'm not -- although I might have been concerned about it, I'm not concerned about it. I agree with Ralph. This was a very high, a very frequent use of balloon valvuloplasty, in my experience.

DR. PAGE: And I agree with those comments. If there are other comments that differ from these, please let me know. Otherwise, we can move on to the next question.

Dr. Jeevanandam and then Dr. Somberg.

DR. JEEVANANDAM: I think, you know, we brought up the comment with the earlier question about having multiple surgeons or at least two surgeons deem these people inoperable.

Well, you know, there were 11 patients here who actually got AVRs and who were supposedly inoperable. And according to this data, it seems like 8 out of 11 survived greater than 200 days, and of the three who died after hospital discharge, so that means that all 11 of them were actually discharged from the hospital. And the ones who died after hospital discharge lived for 291 days, so they didn't do that badly, in these inoperable patients. And, actually, a lot of them had multiple procedures as well.

DR. PAGE: Dr. Somberg.

DR. SOMBERG: Addressing the issue of the balloon valvuloplasty, I did think it was very high. Some people say it's out of the ordinary, and I think, actually, in this type of group who is seen by these very aggressive interventions, this might be what is done now, but it may actually make things worse.

And Jeff, comparing 80 versus 20 doesn't really give you insurance, 80 percent, 79 percent.

So I think it should be pointed out someplace in the product insert, if you will, that the -- or the usage information, I always use the drug verbiage, but -- that an overwhelming majority had balloon valvuloplasty, and this could've influenced the outcomes, making it look better or worse.

DR. PAGE: Fair enough.

Dr. Zuckerman, do you have a good sense for the Panel's perspective on this question, or would you like me to summarize?

DR. ZUCKERMAN: If you could first summarize.

DR. PAGE: Well, I would say that, in general, it is what it is and it may well reflect standard of care; it certainly reflects standard of care at the institutions involved.

There is some concern that the high rate of balloon valvuloplasty could have affected the survival, but we don't know which direction that might have gone. Their data suggests that it did not have a major impact.

But perhaps including a description of this trial will be included in the package insert anyway, and I think this should be noted.

DR. ZUCKERMAN: Thank you. That's a very helpful summary. The FDA has no further questions on this question.

DR. PAGE: Great. Thank you.

We'll go on to Neurological Adverse Events.

As shown in the tables on page 22 of the FDA Executive Summary, there was a significant increase in the neurological event risk in the SAPIEN arm compared to Control, noting that the majority of the Controls had BAV, in both the acute periprocedural period and the longer-term follow-up phase of the PARTNER trial. The breakdown of neurological events by type

(stroke, transient ischemic attack, intracranial hemorrhage) is also presented. Those events may actually have been under-reported, since the identification of stroke in the current study depended on recognition of symptoms by the cardiovascular team, rather than rigorous neurological evaluations. While interpretation of the increased late event rate is complicated because of the higher mortality rate in the Control group, neurological adverse events remain an important safety consideration for this device and impact the overall risk-benefit profile of the SAPIEN THV.

Question 3a reads, Please comment on the clinical significance of the neurological adverse event risk observed in patients treated with the SAPIEN THV.

Dr. Good.

DR. GOOD: Okay. So I have several things to say.

Before I talk about the clinical significance, I think that we should state that there does appear to be an increased risk of stroke; the Sponsors agree. And it probably is under-reported. Although we are not looking at Cohort A, the material was provided to us by the Sponsors does show that in Cohort A there was a statistically increased risk of stroke in that population as well. And that's on pages 117 and 118 of the briefing document that was provided by the Sponsors.

The other reason to suspect that there is a high risk of stroke here are the -- and again, this is not directly related to this, but there are a

number of studies now that show that there are radiologic or MRI-related abnormalities, looking at diffusion-weighted imaging. You heard that there were seven studies. I wasn't aware there are that many, but obviously there are subclinical strokes that are occurring in this patient population.

This reminds me a little bit of the old days with CABGs and bypasses were -- although it's a totally different procedure, were -- initially it was thought that there was a low risk of neurological complication. But when this was looked at more closely with neuropsychological testing, that there were, in fact, neurological changes that did occur. And I don't want to make too close of a correlation there, but I think that cardiology teams and CT surgery teams will under-report these things. They're not really trained to do this. So I do think there's a high risk.

The question is, then, are these clinically significant? I would argue that it is. The Sponsors, unfortunately, mostly based -- when they realized that there is a high risk of stroke, went and did a post hoc analysis, they didn't let the FDA even know they were doing that, which is a little bit bothersome. And so I'm concerned about this. I think it's clinically significant and probably subclinically significant as well, in terms of burden of neurologic deficit that we're not even seeing here.

I'm reassured that the Sponsors are very aware of this, and the future studies are taking many steps to try to evaluate this. It's probably a multifactorial problem. There are probably a number of causes, as were

mentioned earlier today, and trying to prevent this is really going to be critical going forward.

That's all I have to say.

DR. PAGE: Thank you.

Dr. Borer.

DR. BORER: Yeah, I certainly wouldn't disagree with any of that. I'm a mere cardiologist. I think this is a very important issue. And let me preface my comment by telling you why.

As someone who sees large numbers of patients with heart valve disease, because one of my jobs involves running a valve disease institute, when I see patients who are in their mid-80s or older and have debilitating valve disease, they certainly don't, as Ms. Patrick-Lake said, they certainly don't want to have sternotomies. But what they don't want to have more than that is strokes.

In general, what I hear is I've lived a good, long life; I'm not worried about living any longer, but I don't want to live badly. And the greatest fear is a stroke, is becoming dependent, totally dependent, when they've already begun to experience losing some of their independence. And the five speakers in the public hearing all focused on this. The two nurses, most particularly, said something about independence. The three patients plus the two nurses all lauded this procedure because it made them feel better. Not because it made them live longer. Nobody said anything about

living longer; they talked about feeling better. So --

DR. PAGE: If I may, there were two patients. There were two patients, two nurses --

DR. BORER: Oh, sorry.

DR. PAGE: -- and then one other physician.

DR. BORER: I'm very sorry.

DR. PAGE: Just to clarify.

DR. BORER: Sorry about that. Two patients, two nurses, and a physician. So the two patients and two nurses.

Okay, so I think stroke is a very major issue, and I think it's worse than death for this population. And, again, my comments relate to this population because this is the population we ought to be considering, but although, of course, what Dr. Good says is absolutely right or, you know, the more events you have, the greater the burden, the more likely it is something worse is going to happen down the road.

Nonetheless, I tend to look at the functional outcome as being most important; can I get up and walk around rather than did I have a stroke, and I was comforted to hear Marty Leon's presentation of Slide AA-39, which showed that the Kansas City scores were actually better even among the patients who had strokes and the procedure than -- rather than becoming worse. That's good. Small numbers doesn't prove anything, but at least it gives me some comfort.

Our tools to determine, to tease out, what the strokes mean are gross. They have to be improved. And I'm concerned about it; it's a big deal to me. On the other hand, I think that, in general, the best information we can get right at this moment is probably from HQOL, of which stroke would be a big component, and those data all look pretty good.

So while I think stroke is very important, while I think we need a lot more information about it, and while I think that prospectively, a great deal of information in future studies, in postmarketing studies, need to be devoted to better understanding the impact of stroke from the data we have right now for this population, which wouldn't be expected to live a long time and therefore might not suffer the impact of the multiple small lesions before death.

I think that the stroke issue is reasonably dealt with, but just for this population, which gets back to the slippage issue. It's not for any other population.

DR. PAGE: Thank you.

I've heard two pretty consistent comments that stroke is important, their concern, hope that it can better managed, better measured in the future. Does any Panelist have a significant difference of opinion or anything to add to that? I can say taking care of atrial fibrillation, I've told many patients that I'm much more scared of stroke and arrhythmias, so it's an important issue for our patients' quality of life.

Bram, do you need anything further?

DR. ZUCKERMAN: No, that's a very helpful summary.

DR. PAGE: Bob Dubbs, do you have a comment, please?

MR. DUBBS: I'm bothered by the terminology in terms of neurological event. As an unsophisticated non-physician, non-scientist, neurological event doesn't convey to me the same meaning as using the word stroke. And to a patient, I would think that language using the word stroke would be more appropriate than the broader language, neurological event.

DR. PAGE: Thank you. You're echoing Ms. Patrick-Lake's comment as well, that the information for the patient might be tuned up in that way, to neurologic event does sound different than 1 in 10 or less.

Did you have another comment, Ms. Patrick-Lake?

MS. PATRICK-LAKE: So I echo most of what Dr. Borer said. I agree with a lot of that except for the part about patients being so afraid of not having a stroke. The way I would look at this, as a patient, is that there's a 50 percent chance that I'll be dead in a year and there's a 93 percent chance that I'll have an intervention and I won't have a stroke.

DR. PAGE: Okay. Any other comments on this question?

So Dr. Zuckerman -- Dr. Good.

DR. GOOD: I just have a question.

DR. PAGE: Yes.

DR. GOOD: We're going to be talking about the patient

brochure later; is that right? Okay.

DR. PAGE: Are we going to be talking about the brochure?

Bram? I don't think that's --

DR. ZUCKERMAN: I don't think we have a particular question on that, so how about -- Dr. Good, is it a short comment?

DR. GOOD: I'll make it short, I'm sorry.

DR. PAGE: Thank you.

DR. GOOD: The brochure needs major modification. Stroke is really downplayed, and if I was a person reading this or a family member reading this, I'd have no impression that the risk of stroke is as high as it is. First of all, stroke isn't mentioned, as was mentioned, and the risk is not enumerated here. It definitely needs to be emphasized.

DR. PAGE: Yes, Dr. Jeevanandam.

DR. JEEVANANDAM: You know, I completely agree. This is, you know, great new technology, et cetera, but, you know, we have to accept the fact that at least in this iteration of this device, there is a higher incidence of stroke. And, you know, we need to be able to communicate that to the patients with either warnings or the brochure.

I looked at the brochure. It says, you know, less than 1 in 10 in both arms. And I think something like that really, you know, one could also say it's four times higher in having this procedure. So I think that patients need to be made well aware of the fact that incidence of stroke is much

higher in this than in the other arm.

And I think, even in the -- I guess we don't change indications, but even warnings, if you look at the warnings on the label, you know, stroke is way down there mixed in with everything else. I think stroke should be isolated and bolded and put up front that this is a major complication of this procedure.

DR. PAGE: I'm seeing a lot of nodding heads.

Are you getting this, Bram?

DR. ZUCKERMAN: Yes.

DR. PAGE: Good. All right, moving on to, actually, Question 3b.

The cause of neurological injury with transcatheter valve implantation is multifactorial. One important consideration is management of coagulation and platelet aggregation. The PARTNER trial did not require patients to be on a protocolized anticoagulation or antiplatelet regimen. In light of this, as well as the increased neurological event risk discussed, the Sponsor has proposed a protocolized anticoagulation/antiplatelet regimen to be used for the proposed postapproval study.

Please comment on the proposed anticoagulation/antiplatelet protocol included in the postapproval study protocol as well as any other risk mitigation measures that should be taken into account to reduce the neurological event risk in patients receiving the SAPIEN THV.

DR. ZUCKERMAN: So for point of reference, we're looking at, I

believe, page 30 on Post-Approval Study 2, which is the last section in your briefing booklet.

DR. PAGE: Dr. Borer.

DR. BORER: Yeah, I think that the proposal is a reasonable proposal. It's a first effort; we have no data. We don't know if this one's going to work or another one's going to work better.

One could request the Sponsor to design a study that had alternative anticoagulation strategies and see whether there's a difference between -- you could do that. But that would mean you'd need more patients to be able to have the power to see something, if it's really there, and that would be difficult. I mean, I think that would be burdensome.

I think, as a first effort, this protocol is not unreasonable, and it will, at least, provide us information about this protocol, and if it happens to improve the outcome, well, that's pretty good. Remember, we have no data now, so I'm happy with this.

DR. PAGE: Dr. Somberg.

DR. SOMBERG: I think this is a critical area. Stroke is highly important, and as we saw with the stent, which is a mechanical device, if you will, placed in the vascular system and left there, I think we have another mechanical device left in the vascular system. And if it's true that everything -- or not everything, but the majority of the strokes, of clustering in the early procedural period, there's a possibility it comes from dislodgement and

there's a possibility it comes from new fibrin thrombi forming on the valve in that situation.

With that said, I think you should start out with a pre-force like they did with, after the original bare metal stents or all that problem, 50 percent acute, very acute, stent thrombosis. It was triple, multiple therapies; in fact, more than triple, at that time, and then you pare down, not that you work up. So I think this is inadequate, as a pharmacologist. I really think there should be 325 of aspirin.

I really think there should be heparin initiated intra-procedurally and maintained until the INR prothrombin time, if you're using warfarin, is adequate, and I do think there should be a loading dose of clopidogrel and it be maintained, and that drugs that interfere with clopidogrel should be relatively contraindicated in the situation.

So I think this is -- we need to be very aggressive in this situation to reduce the potential for a thrombotic --

DR. PAGE: So just so I'm clear, what are you stating that's different from the protocol as written?

DR. SOMBERG: Higher dose of aspirin, the interfering drugs with clopidogrel, preloading of clopidogrel before the procedure, not postprocedure, and the initiation or the continuation of heparin, whenever possible, until the INR for Coumadin is adequate. I don't see those things here.

DR. PAGE: Dr. Good.

DR. GOOD: I think many of those things are here. The dose of aspirin is not here, but the preloading with clopidogrel is here. And so I think much of what you're -- and you mentioned something about warfarin, heparin initiation until put on warfarin, that's only a small subset, I would think, that have atrial fibrillation.

DR. PAGE: That's the way it's currently written.

DR. GOOD: Right. So I'm okay with this. I think it's -- you might argue about the aspirin dose; that's a whole other discussion.

DR. SOMBERG: Clopidogrel is postprocedural.

DR. GOOD: No, I think if you look up --

DR. SOMBERG: I'm looking on page 30 here, anticoagulant regimen intraprocedural and then there's postprocedural.

DR. GOOD: I'm looking --

DR. SOMBERG: If you're right, that's fine.

And the other thing is to -- it's not -- the heparin and Coumadin is not just for atrial fibrillation because you have a surface now that's thrombogenic, the valve, itself, and that may be the source. So why not anti-thrombinase the person and then go forth? Yes, you have a downside of potential bleeding, and if they have a hemorrhage, worse bleeding, that is a possibility, but we see what's being done now and it looks bad.

DR. PAGE: So you're advocating warfarin for everyone?

DR. SOMBERG: Yeah.

DR. PAGE: Okay.

Do I have any comments? Dr. Kato and Dr. -- actually, Dr. Slotwiner after that.

DR. KATO: Although this is somewhat controversial in the cardiothoracic surgery literature, and I personally don't use Coumadin for my pericardial valves, I do know several heart surgeons who do, you know, who are very high-volume guys who, have over the years, have used at least three months' worth of warfarin, so -- I mean, I don't think that can be faulted, either, as a trial, even for straightforward Category 1 patients.

DR. PAGE: I think right now we're talking about how this would be used if it were approved, so you're saying a trial of warfarin but not making the package insert require warfarin?

DR. KATO: Well, I think it's a valid question because, you know, again, there is some disagreement even within the cardiothoracic surgery literature and -- with pericardial valves. And if you're thinking that pericardial valves, the valve that we put in by -- hand-sewn versus what is being implanted, you know, transluminally is roughly the same type of tissue, then you can make an argument, as many heart surgeons do, to put patients on three months of warfarin.

DR. PAGE: Okay, Dr. Slotwiner.

DR. SLOTWINER: As we said, stroke is clearly the most

important complication, and I feel comfortable with the anticoagulation protocol, but I think distal embolization protection devices, which I'm not an expert in, but that may be something that the Agency would like to encourage in postmarket approval studies if approval is recommended.

DR. PAGE: Dr. Jeevanandam.

DR. JEEVANANDAM: You know, I know we don't want to discuss this continuous access protocol, but the stroke rate and the continuous access protocol was dramatically lower than what we had seen with the original cohort, right?

So I'm wondering whether they did start standardizing some of the anticoagulation and if that's what is what's being recommended, and if they've decreased their stroke rate because of that, then we should probably follow what they've recommended.

DR. PAGE: Thank you.

Ms. Patrick-Lake.

MS. PATRICK-LAKE: So I feel like we really need to proceed with caution. I think we're lacking evidence on the causality of stroke, and this protocol is going to have a significant effect on quality of life for our patients.

I'm definitely not in support of warfarin at this time without further evidence, and I think we need to be careful about reevaluating in six months or a year. This is a population that's subject to the age of falls and

fractures, and are we going to inadvertently send somebody for neurosurgery because they end up with a subdural hematoma? And I think we really need to be careful about this evidence.

DR. PAGE: Thank you.

Dr. Brindis.

DR. BRINDIS: I appreciate all the particular concerns we have on stroke, and I applaud the concept of developing postmarket studies related to the use of dual antiplatelet agents and maybe with or without Coumadin.

I will reflect on a comment Marty made, which is that -- and that Bray also has made, that these are very sick patients with a lot of contraindications related to these drugs and that actually pushes me to -- that we need more data in the patients that aren't going to take them.

And so I'm hoping that one of the things that comes out of this Panel is the encouragement of a national registry so we can follow patients who are not just on a postmarket study such as this, but find out what happens in the real world to them related to what they're actually taking in terms of their risk of stroke.

DR. PAGE: Great, thank you.

So, Dr. Zuckerman, if I may summarize, I think there's general consensus that what's being put forward is probably reasonable but is based on few data; it's based on a trial where the protocol was not clearly followed,

and we're looking forward to a more protocolized anticoagulation/antiplatelet regimen in the future. It was mentioned that there's already work to reduce embolization such as the devices that are used in carotid stents to catch them.

The question of warfarin is a good one; we just don't have any data on that, and perhaps studies down the line might compare one regimen versus another to reduce stroke.

Any other -- is that a fair summary of the Panel's deliberation and any other questions you need answered from us regarding this?

DR. ZUCKERMAN: Yes. That's a very good summary. I think it's the general consensus of the Panel that, at least, this proposed anticoagulation/antithrombotic regimen will at least serve as a good anchor for a postapproval experience.

However, I would like the Panel, when they get to Question 9, to really delve into whether the stroke rate should be a particular endpoint with a hypothesis. One of the concerns from our epidemiologist was that the present postapproval study just is looking at a composite endpoint rate, is not drilling down on this critical stroke issue, and we look forward to your comments when we get to Question 9.

DR. PAGE: Great. And please remind us if we don't address that when we get there.

We'll move on to Vascular Complications.

The study results indicated that over half of the SAPIEN patients had serious adverse events relating to the access procedure, resulting in both short- and long-term risks for patients receiving the SAPIEN. The table on page 24 of the FDA Executive Summary, which FDA created based on a review of the CEC narratives, lists the most serious of the vascular complications. In an effort to address this risk, the Sponsor has proposed a comprehensive training program for new practitioners.

And we have Question 4a, which reads, Please comment on the clinical significance of the vascular complications observed in patients treated with the SAPIEN THV.

Dr. Borer and Dr. Ferguson.

DR. BORER: It's very hard to know what the importance of these complications was to these patients because that wasn't included in the collected data or at least information relevant to that point wasn't really included in the collected data, which is unfortunate. My intuition would be that these would be important problems.

But I think they would be -- their importance would continue, over time, and if they weren't immediately lethal or didn't lead to immediate major complications, bleeding, et cetera, et cetera, or infection. If they didn't do that immediately, they would continue as problems over time; it is a foreign body, it is in the circulation, it is a potential site for infection if you have to repair one of these things.

While that's true, once again I come back to what I've said several times now. We're talking about this population, with a relatively short expected lifespan even if they have the device put in. And in that context, these complications probably don't represent a showstopper, but I can't say with any assurance because we just don't have the data.

DR. PAGE: Dr. Ferguson

DR. FERGUSON: I'd just concur with that, and I don't think we were given enough information to know how these complications were managed or what the long-term effects were in terms of disability.

DR. PAGE: Fair enough.

Dr. Good.

DR. GOOD: Well, there were some comments that a number of these required vasc-surgical repair; I'm just not sure how many. So obviously some of these were moderately serious complications.

One question I have is whether training the operators will really make a difference whether this is strictly technology based. So how much is operator based and how much is technology, the size of these big catheters, I don't know.

DR. PAGE: Other comments?

Dr. Slotwiner.

DR. SLOTWINER: I think a new iteration of the device is already significantly smaller, and that may just be the main issue.

DR. PAGE: So, Dr. Zuckerman, in terms of 4a, yes, there's concern, but I think saying it's not a showstopper is probably appropriate and there is hope for improved technology. This is a very large catheter going through, at times, a relatively small vessel that's diseased already.

Do you have any other concerns regarding this question for the Panel?

DR. ZUCKERMAN: No, I think those are very helpful comments, but I would remind the Panel members that talk of a new smaller device is speculative. There's no PMA for that device before us, so I do want the Panel to think hard about how potentially the Sponsor and FDA need to drill down further on vascular complications in any postapproval study, if that's appropriate.

DR. PAGE: Yeah, that point is very well made, and this trial and the device need to stand on their merits for consideration by the Panel.

That leads us very nicely into 4b, which is, Please comment on the proposed training program for new practitioners as well as any other risk mitigation measures that should be taken into account to reduce the vascular complication rate in patients receiving the SAPIEN THV.

And it's already been commented on that is it technology or is training. Any other comments about the training protocol as it relates to vascular access and damage?

Dr. Ferguson.

DR. FERGUSON: Well, the only other question I had is if there's a minimum cutoff value at which operators should have on an annual basis or before they're effectively trained. We talked about trying to enroll centers that had higher volumes and a higher likelihood of, you know, enrolling patients, but we never talked about if there was a minimum value per operator that was considered safe.

DR. PAGE: Comments about that or comments about the training?

Dr. Brindis.

DR. BRINDIS: Well, I'm hopeful that with the company's training program, the professional societies' education and their own training program, the opportunity for centers to be accredited in terms of what they have to offer locally to assure that the patient safety is best in hand, that we, as a society, have done the best possible due diligence to ensure the decrease in adverse outcomes related to these large devices being placed in the groin.

DR. PAGE: Dr. Zuckerman, any other concerns?

DR. ZUCKERMAN: No, those were very helpful comments.

DR. PAGE: Dr. Lange had a comment.

DR. LANGE: Just one comment.

The one thing that will be missing from the training that's in the current study program is they were having conferences weekly or biweekly to discuss complications and how to mitigate those or alleviate those, and that's

obviously not in the training program, and so that will be missing.

DR. PAGE: Thank you.

We'll move on to Hemodynamic Performance of the SAPIEN THV.

The Sponsor analyzed valve performance based on responder analysis, where a responder was defined as maintenance of greater than of 50% of the effective orifice area (EOA) at the follow-up visit. The results provided on page 27 of the FDA Executive Summary show that the reduction in stenosis was maintained at least at a reasonable level (greater than 50% EOA) for the first year in the SAPIEN group.

In addition, as noted on page 25 of the FDA Executive Summary, the Sponsor reported the percentage of patients with moderate or greater aortic regurgitation based on data reviewed by the core laboratory at various follow-up points in the SAPIEN group. Note that these totals include all sources of regurgitation, including both central regurgitation and paravalvular leak. These data show that the amount of aortic regurgitation (AR) is appreciable and does not decrease over time in the SAPIEN group.

And Question 5 reads, Please comment on the hemodynamic performance of the SAPIEN valve based on the data available from this study. Please also discuss the potential long-term clinical significance of these findings.

Dr. Borer.

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DR. BORER: Let me start with the second part first because I've spent the last 35 years studying it, and that is the importance of the aortic regurgitation. If somebody started out with no AR or with very mild AR, minimal AR, and had a procedure and suddenly had severe AR, that's acute aortic regurgitation, and yes, I would worry about that. That was not what was seen in the majority of patients who had AR; it was actually a minority who had what was graded as severe AR.

But more importantly, although I don't think that the data was set out in quite this way, acute heart failure was not the consequence of that finding, you know, you correct me if I'm wrong, but it was not. So while I'm worried about that, it didn't seem to be as big a problem as I might have thought it is.

Once you go a grade below severe AR, the unfortunate fact is that we have no data from which to draw inferences. There really are no data about the long-term effects of moderate AR or mild AR on the natural history of patients with aortic valve disease. There are mitral valve disease now, a few, but not in the aortic valve disease.

And I have to put this in the context because the question is long-term effects, I have to put this in the context of the fact that I'm talking about what my concerns would be for this population. If we were talking about a less sick population, I'd be very concerned. But I'm talking about, basically, a relatively elderly population that is very, very sick and the life

expectancy of which is quite limited, even with the device, so that the long-term effects, which I think of as five years or longer, may not be quite so important as it would be for another population.

Am I totally secure in that I know the effects of AR? No, of course not. But I don't think that this represents a major problem. It's a problem that could be described within the information given to the patients so they'll know there's the potential for a problem here, but I don't see it as being, again, a showstopper.

The EOA maintenance is very important because the problem with balloon valvuloplasty is that the durability of an open aortic valve with that procedure is very poor. It lasts only a matter of a few months. Here we've seen that during the course of follow-up, the EOA was maintained. That's good. I'd like to have more long-term data.

I think the FDA has to mandate that and, in fact, it's been suggested as, in the postapproval studies, that this should be assessed and that longer-term follow-up should be obtained. I think that's very important to refine the label, if that's necessary, if this device is approved as is, but I'm comforted by the fact that this does not -- there is no loss of EOA, and also remember this is not the first tissue valve that's ever been put in.

We have a lot of experience with bovine pericardial valves, and by and large, they perform pretty well for a long time. The difference here is that they're on a stent with some open metal surfaces, open to the

circulation that a standard surgically implanted valve wouldn't have, and that leaves an unknown. But still, the data here are not -- they're reassuring to me, and they're not surprising because we do have experience with bovine pericardial valves.

DR. PAGE: Got it.

Any other -- Dr. Jeevanandam.

DR. JEEVANANDAM: I think it's impressive that the EOA is maintained and the gradients are low. I think that's actually fantastic for this valve, considering the fact that you're jamming it up against a whole lot of calcium.

In terms of aortic insufficiency, a lot of these patients have AI to begin with, so this is just a different type of AI and obviously are tolerating it. I think it's something that you follow, but I don't know if we could -- I don't think there's -- I mean, there's always things that are potentially concerning, but to me, that's a lot less concerning than other things like stroke, so I think from a human -- point of view, I'm very happy with this valve.

DR. PAGE: Is there anybody on the Panel who has significant concern about this or can we move on?

(No response.)

DR. PAGE: So, Dr. Zuckerman, you hear from us that there was already some regurgitation in the control group, that this appears to be

stable, although I've got to say the sixth month going down to about 10 percent is the one aberrant data point that I don't personally understand, but that in limited follow-up the function appears to be maintained for this prosthetic valve.

Anything else we can do for you regarding that question?

DR. ZUCKERMAN: No, that's quite helpful. I think you've summarized it nicely, and again, I would underline limited follow-up and again ask the Panel to consider what needs to be done in a postapproval setting.

DR. PAGE: Great. Moving on next to Valve-In-Valve Experience.

The FDA mentioned, as their unresolved issue raised was, an engineering review team regarding the safety associated with valve-in-valve implantation. To date, the Sponsor has not conducted any engineering testing to address implantation of the SAPIEN valve in this configuration. However, four patients underwent valve-in-valve procedures in the Cohort B study. In addition, there are reports in the literature of many cases of valve-in-valve implantation involving the SAPIEN valve in other countries, such as SAPIEN in SAPIEN, SAPIEN in another transcatheter valve, and SAPIEN in a previously implanted surgical bioprosthesis.

FDA is concerned that if the SAPIEN becomes commercially available, widespread use of the valve-in-valve technique might occur.

Without any preclinical testing and only limited clinical data, the FDA is unable to draw conclusions regarding the short- and long-term safety of SAPIEN valve-in-valve implantation. In addition to fretting corrosion and galvanic corrosion, other unknowns associated with valve-in-valve implantation may include long-term durability, valve migration/embolization, and access to the coronary ostia.

And Question 6 reads, Please provide input regarding the appropriate way to address potential valve-in-valve use with the SAPIEN valve, including device labeling, practitioner training, and/or additional testing requirements.

Mr. Dubbs.

MR. DUBBS: Is the Sponsor seeking any sort of direction or approval for valve-in-valve? I mean, they don't seem to have really addressed it. Maybe the best thing to do is to say it hasn't been appropriately addressed.

DR. PAGE: I think the Sponsor did not make any claim or indication for valve-in-valve. I think the reason this is raised is in a real-world situation where valve-in-valve could not be considered, there were four out of 170 implants, of the successful implants, that involved valve-in-valve. So 1 in 50 or more ended up occurring, and the concern is there's no bench testing of these devices in other devices. And the question for us to consider is what should be done, how should this affect labeling.

MR. DUBBS: Well, why don't we just say there has been no testing?

DR. PAGE: That certainly could occur.

Dr. Jeevanandam.

DR. JEEVANANDAM: I agree. I mean, you know, we haven't had any testing, so obviously we can't say it can be done. But in a real world experience, I think those cases, some of them were actually presented, were emergency cases where something escapes or something is malpositioned, so you're going to get valve-in-valve as rescue mechanisms.

I think somebody had like three in there or something, so -- it would be great to have it tested. I think they do need to have it tested at some point, but you're not going to be able to tell them you can't do it because people are going to do it when they need to.

DR. PAGE: I see Dr. Brindis raised his hand first.

DR. BRINDIS: So I think we have an opportunity to change the paradigm in how we follow how patients are managed to get innovative cardiovascular devices. To date, we have basically missed opportunities where we're not collecting data in devices that are used for off-label indications. That doesn't mean they're inappropriate; they're just off-label.

These are incredibly important questions for patients, for clinicians, for the FDA, for all of us, where we have, to date, missed opportunities to understand where these off-label indications are best suited.

We have other countries in the world that have registries where -- Sweden or Japan or others that have all this data in place. This is the perfect opportunity to collect this data, the valve-in-valve. We all know it's going to be done. There is no doubt in my mind.

Let's collect the data, let's learn and understand and how we approach these patients, what we have to learn and what is useful and what is not. In terms of benchmarking work, I'm not an expert there; I need to yield to other people who might have some idea that some bench work might be of value. But please, let's collect this in a registry.

DR. PAGE: Thank you.

Dr. Good and Dr. Ferguson

DR. GOOD: Well, it would seem quite unusual, but it -- address this to Dr. Zuckerman.

Is there any precedent to go back to a sponsor and ask for preclinical information where something might already be released? I mean, it's quite -- seems quite unusual.

DR. ZUCKERMAN: It isn't the usual paradigm, but we're not dealing with a usual device here. And, again, we're looking for some reasonable suggestions for finding out important data.

For example, Dr. Brindis, perhaps, has suggested asking the Sponsor, in a postapproval setting, to develop a worldwide registry of these cases. Perhaps durability testing would also be indicated, especially if the

results of a worldwide carefully looked-at registry experience don't prove to be as -- don't prove to -- don't allow us to see the clinical results that we would all like. We're asking for some input on whether this question should be investigated, how it should be investigated in a reasonable fashion.

DR. PAGE: Dr. Ferguson.

DR. FERGUSON: Well, we haven't specified native valve aortic stenosis in the indications, so I'm not sure we've, you know, clarified that it can only be used for native valves, the way the indications are worded now.

DR. PAGE: That's a very good point.

In terms of keeping, Bram, I understand the necessity of keeping the indications statement brief. As I'm looking around at the Panel, I wonder whether native valve aortic stenosis, that one word, would be valuable.

Do I see agreement from the Panel, at least for that to be considered? I'm sorry, go ahead.

MR. DUBBS: I don't understand what you're suggesting.

DR. PAGE: Well, the indications for use, we're assuming, and the trial was conducted that in such that the device was only placed in patients' original God-given valve, and the valve-in-valve use was only in the setting of the procedure with the safety in device when you need it as a bailout. That's different from coming up to a patient who already has a valve that's prosthetic and coming at them with this device, for which no study has

been conducted, as I understand.

DR. ZUCKERMAN: That would be a helpful addition, if it's the advice of the majority of the Panel.

DR. PAGE: Is it fair to do a show of hands, a straw vote? Bram, I'm looking to you. Is that acceptable?

DR. ZUCKERMAN: Yes.

DR. PAGE: Anybody disagree with this? I see two hands. Anybody disagree? So let's make that a suggestion from the Panel for the indications.

Moving on -- and let me help frame our discussion a little bit. It seems to me there are three issues that you've asked us to address. One is how to get more experience, perhaps bench testing. Another is in terms of how to give guidance to operators or mandate use.

If I may, since we just brought this up, in terms of prosthetic valve aortic stenosis, is there any Panelist who thinks we should have that anything but contraindicated in this package insert?

Dr. Borer.

DR. BORER: That actually was the issue that I wanted to speak to. I think that we should not proscribe the use of valve-in-valve in a setting where we have very little information, when there is no other option available. I don't think we have to suggest doing it, but I don't think we should proscribe it, and I think we should say, as Mr. Dubbs suggested, gee,

we have no data here.

But remember that there aren't exactly no data. We don't have bench testing data, which I think ought to be mandated now, whether it's this minute or whether the FDA approves the valve and postapproval, that has to be done. I think that collecting registry data is very important, getting some experience. But remember, there's not no experience.

In Europe, just last month I heard a presentation of the valve-in-valve experience. There's no question that it's going to be done, and it's not going to just be done in newly implanted prosthetic aortic valves. It's going to be done in any implanted prosthetic aortic valve, any surgically implanted prosthetic aortic valve that's not working. And there is experience suggesting that at least relatively short-term, that's okay.

So there's not no experience; there's some European experience that we can fall back on. Nonetheless, I think the key point is I don't think we should suggest to the FDA that the FDA flatly proscribe the use of this valve in another valve in a situation where there is no other option.

DR. ZUCKERMAN: Right.

DR. BORER: Or the caveats that we don't know anything is fine, but --

DR. ZUCKERMAN: Sure.

Dr. Borer has correctly pointed out our usual regulatory pathway. We only use a contraindication in this type of case where we know

a certain procedure would result in death or a significant adverse effect. Instead, in this sort of situation, we will have to indicate in a warning just the known data and the known data are limited, and that's the case right now.

DR. PAGE: Great, thank you.

Dr. Lange.

DR. LANGE: At the risk of complicating things, should it be native, trileaflet valve? Keeping in mind that bicuspid valves were excluded from this and PARTNER A, so at this particular point, to be true -- not trying to lengthen the statement, but it should be trileaflet native valve.

DR. ZUCKERMAN: Okay. And then, Dr. Lange, could you also note that in the contraindications for the labeling right now, they have contraindicated unicuspid and bicuspid aortic valves, so I think your point is a good one.

DR. PAGE: So, Dr. Zuckerman, you're suggesting that be in the indications for use statement or just in the package insert?

DR. ZUCKERMAN: I think it would be helpful in the indications for use, but I'd like to hear from the Panel. Dr. Lange is pointing out that you really need a trileaflet valve.

DR. PAGE: Anybody from the Panel disagree with that?

DR. FERGUSON: I guess I just have to clarify it, but congenitally or functionally bicuspid?

DR. SOMBERG: I think we're getting much too caught up in the

weeds here, and this is all for later in the follow-up information, you know, this is going to be a limited number of people who are going to be doing this, so I think, up front, you want to just give a general characteristic and not get involved if it's tricuspid, bicuspid, native or not native.

DR. LANGE: I'm going to respectfully disagree with my colleague there, and that is because 3 percent of the population's a bicuspid valve and lot of people running around with severe bicuspid aortic stenosis.

DR. SOMBERG: I'm not saying it's not important, but I'm just saying in the two or three sentences where you look to see its initial indication, I don't think you can put in every situation. I think that is for in the more definitive product insert where this will be stated. So I'm not disagreeing it shouldn't be stated, we shouldn't be going to, but where you put it, we disagree.

DR. PAGE: I'm not sure we really know how to best wordsmith this indications for use statement, and I hear both sides of this. What we have already, we've been working with, is it fair to say that this is not likely to change anyone's vote whether it includes this or that in the indications for use and go on using the indications for use we already have?

Dr. Good, you look concerned.

DR. GOOD: Well, the native valve thing seems to make sense. Maybe I'm --

DR. PAGE: Okay. I think we've gotten consensus on that one.

DR. GOOD: Yeah, okay. That's what I thought.

DR. PAGE: Okay.

All right, so at this point, we still have to -- we've talked somewhat about device labeling, practitioner training, or additional safety requirements regarding the valve-in-valve. Is there any other commentary? Have we given enough input to Dr. Zuckerman regarding this to move on?

Dr. Borer. Let's keep it concise, please.

DR. BORER: Okay. The only issue would be that we want the information collected in any postapproval studies or information collection that's going to be done, but I would think that there should be some instruction provided on how this might be done if, in fact, the people who have been doing it believe they have some information. I don't know if they do, but if they do, then it ought to be provided in case an emergency arises.

DR. PAGE: I don't know if there are enough data to support that that are available yet, but the interventionalists, are you aware of data that you could put, that could give guidance in this document?

Mr. Dubbs, you raised your hand.

MR. DUBBS: I just wondered, as a matter of information, in an open procedure for patients that can tolerate it, is valve-in-valve done rarely, never, periodically -- I have no -- nothing to put this into a context.

DR. PAGE: Perhaps one of our thoracic surgeons can comment on that.

DR. JEEVANANDAM: When we replace a valve that's already in place, prosthetic valve, we take it out and put a new valve in. Very rarely -- I mean, you can't really do a valve-in-valve. So it's not done.

DR. PAGE: It hasn't been available because there hasn't been a valve you could put through a blood vessel before. So, surgically, that's not been an issue. And if valve-in-valve were allowed, clearly it would have to be approved by a surgeon based on the way the indications for use is written and the surgeon had the opportunity of saying whether they thought the patient should have a standard surgical replacement.

Dr. Zuckerman, it's 5:00, and we have several more questions to go before we get summary statements. Are you comfortable with us moving on?

DR. ZUCKERMAN: Yes.

DR. PAGE: So let's talk about the Post-Approval Study.

The Sponsor has proposed continued follow-up of the premarket cohort in a non-randomized, prospective, consecutively enrolled registry of 750-1000 patients undergoing transcatheter heart valve replacement therapy to address FDA's postmarket concerns.

Please discuss the appropriateness of the proposed PAS (postapproval study). In your discussion, address the following -- and let's take Question 7 first.

The learning curve associated with TAVI consists of two

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separate pieces: (1) technical aspects of the procedure and (2) appropriate patient selection. Both need to be learned by interventionalists new to the device. Please discuss and make recommendations on the parameters of the learning curve assessment (e.g., technical aspects, patient selection, patient and provider outcomes, timeframe, and other) that would be most beneficial for evaluation and presentation to the clinical community.

Dr. Lange.

DR. LANGE: I'm going to address this in particular, Bram, with relationship to the post-study that was done with the continued access protocol and the fact that the results agree there are a small number of -- they're clearly different. And the proposal made by the company is not one that I would hope that they would stand by. One is that we enroll five new sites and they're not as good, that's not so good. Or now we have worse patients, we're now enrolling Cohort C. Neither one of those is good.

The alternative is, however, when you look at the control patients, only 20 percent of them died. It wasn't a high-risk patient group. So maybe we're selecting patients that really aren't as sick anymore and in an effort to try to get certified, and that is get the training, that now centers are now picking less sick people so that they can get the two or three or four or five people in to get proctored, and that's my concern.

The Sponsor proposes rolling out multiple sites, 75 sites, in a short period of time and what I would say -- and by the way, their training

protocol sounds terrific, but what I would say is do the first five or ten sites and pull back and make sure that the patients are appropriate and the results are as good as you'd like them to be because the initial results in the continued access protocol don't look quite as good.

DR. PAGE: Mr. Dubbs.

MR. DUBBS: Patient selection, as I understand, what's been done so far has been if a patient falls within the parameters, if they're frail and if they're certified, they can get the procedure. Should there be a specific requirement from a patient selection standpoint that we have certain ages, we have certain sexes, we have certain races, et cetera, et cetera?

DR. PAGE: All good thoughts.

Questions or comments with regard to Mr. Dubbs' comment or the question at hand, which is the learning curve and what recommendations we can put forward?

Dr. Somberg.

DR. SLOTWINER: I just wanted to support what --

DR. PAGE: Oh, I'm sorry. Dr. Slotwiner.

DR. SLOTWINER: Oh. I think Dr. Lange brings up a good point about the possibility of recruiting patients who may -- just to meet the enrollment criteria, and I want to just echo what Dr. Jeevanandam said about the fact that in the study there were two surgeons who reviewed each case, and I am concerned that with a smaller review group, without the weekly

conference call to review the procedures and prospective patients, that there will be this indication creep.

DR. PAGE: Other comments. Dr. Good.

DR. GOOD: You know, it seems to me that part one is pretty much -- it's just a registry of follow-up. It seems to me that that's fairly straightforward except there are no hypotheses, and we heard our FDA colleagues suggest that there should be some hypotheses even for that. But I don't see -- again, as a neurologist, I don't really see any real problems with the general design of that. I think the big problem is in Part 2, and that's where we're talking about the new sites and this kind of business. So I would say for Part 1, except for generate some hypotheses, that we can go ahead with that one and then focus more on Part 2.

DR. PAGE: Dr. Somberg, did you have your hand raised? Okay. Other comments?

(No response.)

DR. PAGE: This question is a little bit hard to address and frame, Bram, at least I feel. But what I'm hearing is that in terms of the Part 1 study, there is less concern. The Part 2, enrolling new centers, the issue is, and perhaps related to the signal that is seen in the continued access, is 75 new centers all at once, too fast.

DR. ZUCKERMAN: Correct. And Dr. Lange indicated that a more careful phased enrollment with a sequential look at data at appropriate

intervals would be appropriate. That's not really part of PAS 2 right now, and I'd like to hear more Panel discussion as to whether FDA and the Sponsor should move in that direction.

DR. PAGE: Dr. Brindis.

DR. BRINDIS: So I agree we're all talking about the second postapproval study, but I think we're also confusing two issues, that is, the approval study and the number of centers and the speed with which there's a rollout. Because if I -- I may have my numbers incorrect, but the vision of the Sponsor and the number of centers that they want to roll out in the first year is much more robust than the number of centers that were being talked about in the postapproval study, so that's two separate issues, the speed of rollout and centers, and how we would deal with the postapproval study.

First of all, I think we'd need to have a postapproval study. Maybe that's the first question. I think it's an absolute terrific idea. We still have questions we need to know, there are key issues related to key questions that have been posed in terms of the learning curve, the viability of the durability of the valve, the issues of -- we talked about creep, but basically, we appreciate the way we practice, that there may be changes in off-label indications, and we need to assess that and the other important issues.

The other question I have is the number of -- looking at 75 centers with some centers having very low enrollment worries me, so I don't

know what sort of conclusions you can have with a center with 10 patients enrolled. So I mean, there are aspects of the study that are -- (1) it's required, I think it's great; (2) it's very important, it's going to answer a lot of questions. We haven't addressed the rollout speed of how the Sponsor should take on the fusion of the innovation technology, and I have some concerns related to the size of the centers in terms of the small numbers that some of the centers will be participating in.

DR. PAGE: I'm actually going to take the Chair's prerogative because I think we're getting into number creep a little bit here and have us try to take Questions 8, 9 together with 7 because they all kind of fit together.

So let's go ahead and read 8 and then continue this discussion because I think it's very important, but I don't want to just focus on 7 and actually neglect 8 and 9.

Number 8: The Sponsor proposed evaluation of the learning curve with data from the first 10-20 patients at each site. Please discuss the merits of including this number of patients at each site for assessing the learning curve. Please comment specifically on the number of interventionalists at each site and the small number of patients available to assess learning curve by interventionalists.

And then Number 9: The Sponsor's PAS proposal includes comparison of the premarket data at 30 days for a composite safety outcome

and at 1 year for composite effectiveness endpoint. Please discuss and make recommendations on the following:

Do the proposed composite endpoints include the correct components?

Are these appropriate time points for comparison of safety and effectiveness?

What is an acceptable non-inferiority margin for the composite safety endpoint and effectiveness endpoint?

And (d) is it likely that patients receiving the device postmarket will differ from those receiving the device in the premarket period, and how long should a postmarket cohort be followed for comparison of the premarket cohort?

So with those kind of on the table, especially including 7 and 8, other comments in terms of this learning curve and how best to provide control?

Dr. Zuckerman.

DR. ZUCKERMAN: Yeah. Dr. Page, thanks for rolling the questions all together because I agree with you, we're really talking about the design of Post-Approval Study 2 and what are the important parameters that FDA and the Sponsor should work on. But before we get there, can we take another few minutes just to put Post-Approval Study number 1 to rest?

Dr. Good has indicated that it's logical to just continue to follow

out the original IDE cohort to a planned five years. I think the Sponsor and FDA agree to that. The only point of disagreement has been that the FDA has indicated that we would like quality of life metrics to be looked at in years 4 and 5. From the viewpoint of the Panel, is this a reasonable request, or what other additions would be suggested for just following out the original IDE cohort, which is Post-Approval Study 1?

DR. PAGE: Thank you for helping direct us. And let's try to move quickly through this, so if people are in favor, they can just say they're in favor without going into detail as to why.

Dr. Borer.

DR. BORER: Absolutely I'm in favor. I --

DR. PAGE: Good, thank you.

DR. BORER: -- can't see how you cannot do it.

DR. PAGE: Anybody -- Dr. Kato.

DR. KATO: Yes.

DR. ZUCKERMAN: In favor of including quality of life metrics?

DR. BORER: Yes, yes. Yes.

DR. ZUCKERMAN: Thank you.

DR. KATO: Yes.

DR. PAGE: And I'm seeing heads nod, and Dr. Good.

DR. GOOD: I would continue the same quality of life measures they already have, just following through. We've already got three.

DR. PAGE: Yes, they're including those. Okay, good.

So now let's move on to the second protocol and discuss that.

And there's been comment about the number of centers. Thrown into this is number of centers and the issue of trying to evaluate the learning curve with the first 10 to 20 patients at each site, and it's also brought up how many physicians in each group should be included.

Comments from the Panel. Dr. Somberg.

DR. SOMBERG: I think it's -- in a postapproval study, it's kind of late to try to evaluate learning curve. By the time we have this all evaluated, almost everybody, you know, who's out there who is waiting is going to be evaluated, is a limited, small population. So I think you have to -- I mean, what are we doing here? We're asking about durability, quality of life, any new things we determine, and we should try to capture as many centers as we can, so I wouldn't put a limit on it.

So I think the number of centers in a postapproval study is different than how fast are you going to roll this out, which I think is an issue for the FDA and the Sponsor to deal with in their potential liabilities. So I think we're asking, maybe, too many questions late on, which we shouldn't, and I think we should focus more on different pharmacologic therapies in the late situation as opposed to a learning curve at that point.

DR. PAGE: Thank you.

Dr. Lange.

DR. LANGE: I applaud the Sponsor for wanting to do the studies with the -- first, number of procedures done because I think that goes to their training and how well they're doing and what they can do to improve it, so I applaud that.

I would defer regarding the boundaries for non-inferiority to my statistician sitting at the end of the table, but I would like to see some analysis of whether it's 750 patients as proposed by the Sponsor or 1,000 patients that are required.

My last comment is I'm surprised that vascular complication isn't one of the major composite safety endpoints.

DR. ZUCKERMAN: Okay. So, Dr. Lange, could we have you and the Panel look at the Sponsor's slide, C-124, because I think that outlines some of the proposed parameters and points of disagreement between FDA and the Sponsor.

And I would like you to appreciate that it's not the onus of the statistician to figure out what the delta has to be for each of the important hypotheses; it actually needs to be done by the clinician, and then we can run the numbers because, you know, as pointed out here, the FDA has asked for a relatively tight hypothesis-driven postapproval study for each of these key parameters.

Whether it comes out to 750 or 1,000 depends on what power is assumed by the Sponsor and so forth, so I wouldn't necessarily worry about

those numbers as opposed to what is clinically relevant such that we can have a good assurance that in a postapproval setting, we will know that this technology is being used appropriately in the United States.

DR. PAGE: Dr. Borer.

DR. BORER: I think that the tighter the better because this is the only -- yeah, the study that's just been done is probably the last time we're going to be comparing this kind of device without this kind of device, and so everything else is going to be compared with this device. Unless the new device replaces it, in which case we'll have a little bit of creep in the other direction.

I think we ought to make the delta as tight as possible. You're talking about a 20 percent upper bound of the confidence interval, I believe. That's very tight, but I would certainly -- I would agree with that, and I would agree with all the events and endpoints that you are -- that you've listed here in 124.

DR. PAGE: So is everybody on the Panel looking at Slide C-124?

Dr. Jeevanandam.

DR. JEEVANANDAM: I think those events are fine. I think there are a couple of points. First of all, is this just a voluntary registry or is this actually going to be a study because -- are we going to have a tally of all the devices that are actually implanted and are we going to assign that to each patient and then follow each patient? Is this going to be an auditable study?

Is this just going to be something that they voluntarily report? That's one question.

I think that this is transformative technology enough that we need more information, and it would be nice that if it was a tight study with -- that's auditable, potentially auditable.

I think the other thing is the importance of making sure that they stay within the definition of the inoperable patient who is getting this device, and it would be a nice way to see if there has been some creep. So I think collecting the data on the exact patient population this is going into is going to be important as well.

DR. PAGE: Dr. Zuckerman, do you want to answer his questions to the nature of this study as proposed?

DR. ZUCKERMAN: Yes. This needs to be a well done postapproval study where we believe the data, the data are auditable and we can answer important questions. Perhaps Dr. Ritchey wants to come back to the microphone to add something.

DR. RITCHEY: While we would like to see data that is collected at intervals annually, the proposal is as stated on page 5 of 6 there to have a non-randomized, prospective, consecutively enrolled registry. It's going to be consecutive enrollment at a certain number of sites, as proposed.

DR. PAGE: So my understanding is this is going to be 75 sites with a rigorous data collection, and I'm hearing from the Panel comfort with

these endpoints as seen on Slide C-124.

The other question that was asked of us is the issue of the 30 days for safety and one year for composite effectiveness. Is the Panel comfortable with those numbers, or should safety be continued beyond 30 days in terms of analysis?

Dr. Naftel.

DR. NAFTEL: Let me just back up for a second. The consecutive patients, I'm assuming this is with informed consent, so that's -- you know, so it's not like a registry with no informed consent. I mean, it's a big point. They've got to get past that informed consent, so you will not get some of those early, unhappy patients for whatever reason, so that's one thing.

As far as the follow-up, given that I'm guessing it would take a while for these patients to all get enrolled, for me, I'd be happy enough with the 30 day and one year, but certainly I think we'd want to track the major events and show those wonderful Kaplan-Meier curves to go as long as we had follow-up for the patients because I'd want to see that because we've all said in a lot of this, we wish we knew more about what happened after two years.

We'll get a lot of that from the continuation of the premarket patients, but that's a fairly small number, and that data in the 1,000 patients, I think we can get that, so I'm lobbying that we have a continuous -- certainly look at the major events, like death.

DR. PAGE: So to answer the question, you would extend the safety analysis to a year, as well, or stay with 30 days?

DR. NAFTEL: Oh, for certainly 30 days and one year for both, but I would like an estimate, a time-related estimate, of death to go for as long as the follow-up time for these patients.

DR. PAGE: So as is proposed, the safety is a 30-day analysis, but you're saying you want safety issues being followed through a year as well?

DR. NAFTEL: I do, yes.

DR. PAGE: Yeah.

Dr. Kato.

DR. KATO: I guess -- well. If you're going to follow this thing out for five years, you're going to be looking at, you know, maybe this will be device failure at five years. So I think that 30 days and one year is fine, but I think it's going to be an ongoing safety and effectiveness measure until, you know, the end, which is five years or death.

DR. PAGE: Dr. Good.

DR. GOOD: Well, I read this a couple times, and I was a little bit confused about exactly how they're going to enroll the number of patients per site and how they're really going to roll out the sites. I read through it and I thought do I understand it and I didn't very much. I don't think -- it sounds like there's going to be a maximum of 20 patients per site. They're

going to cut it off at some point. And as they get closer to the intended sample size, all sites would be notified to stop consenting. So there may be some variability in the number of patients who enroll per site. I guess that's okay. That's not a big deal.

But I was also a little bit confused about the rollout. It seemed kind of fast to me, and that was kind of discussed here earlier; Dr. Lange kind of mentioned that. And I'm wondering if we really ought to be quite so aggressive in rollout considering some of the safety issues here.

And then one last thing. I'll have to put my neurologist hat on here. There's no neurologist on the data safety monitoring board, and considering stroke is a major complication rate, there's thoracic surgeon, et cetera, et cetera, but I would recommend that a neurologist be on the data safety monitoring board as well.

DR. PAGE: So noted.

Other comments?

(No response.)

DR. PAGE: Dr. Zuckerman, is it appropriate for us to further consider the rollout? The FDA and the Sponsor have discussed a rollout that includes 200 centers, 75 of which, as I understand it, are going to be study centers for Post-Approval Study 2. Is that correct?

DR. ZUCKERMAN: That's my understanding, yeah.

DR. PAGE: And has that already been established and

negotiated, or is that something that you're asking this Panel to comment on and potentially mitigate?

DR. ZUCKERMAN: Everything is still up for negotiation, so we really would like Panel input on how this technology could be safely and effectively rolled out.

DR. PAGE: So -- yes, Ms. Patrick-Lake.

MS. PATRICK-LANE: So I do have a comment on that. When we saw the Sponsor slide earlier this morning about the clinical trial sites, there was a swath going across the western United States that had no trial sites and no patients in my geographic area, in particular, did not have access. So I'm highly concerned that the East Coast definitely has centers that have higher volume.

And I'm also concerned about integrity such as if the Sponsor has somebody who is their valve customer and they want access to a technology, are they going to be chosen over a site that might be a Center of Excellence with a lower volume? And I think we want to make sure that patients have access to the best care.

I'm also not certain that enrolling 10 patients per site best serves patients, and I know that we have to be financially realistic in the postmarket studies, but I just didn't -- I wasn't moved and I'm not a statistician, but it didn't seem very convincing.

DR. PAGE: Your question is 10 is too many or too few?

MS. PATRICK-LANE: Too few.

DR. PAGE: Okay. My understanding is 10 is -- 75 centers, 10 each, but they won't stop at 10. They're just going to be enrolling in this trial through 10, the 75 centers, to reach the 750 to 1,000, if I'm interpreting the data correctly.

MS. PATRICK-LANE: I also wasn't moved by 20.

DR. PAGE: Okay, but is there concern that the overall population in this trial should be more than 1,000?

MS. PATRICK-LANE: I'm concerned about operator experience. I'm not sure what we're going to learn from 10 patients or 20 divided by four interventionalists.

DR. PAGE: Okay.

Dr. Lange.

DR. LANGE: And so I think the point's very well taken by Ms. Patrick-Lake and is that what I would encourage the FDA to consider is, in this rollout phase, especially if you're going to go to 1,000 patients, is to have some centers enroll 20 or 30 or 40. If everybody enrolls 10 to 20, you're never going to answer the learning curve.

DR. PAGE: Dr. Borer.

DR. BORER: Defining a learning curve may be very difficult in any event. And as someone who ran a cath lab for many years and did interventions, I have to say I don't think that the number has to be very large,

whatever that is, you know, more than 20, more than 10, in order to have a reasonable sense of how to do these procedures.

The point was made earlier that there's some cross-talk that goes on that was made in the presentation of the data, and there is. People who are familiar with putting catheters into the heart and crossing the aortic valve don't need a tremendous amount of additional experience to be able to use new implements there. So I'm not so worried about that.

There's one other thing here, though, that we haven't commented about and that's (d). How should a postmarket cohort be followed for comparison to the premarket cohort? Well, we talked about timing and the types of studies that should be done. I think our only recourse there is to be as rigorous as we can about the inclusion criteria to make sure, to the best extent we can, that patients who are included in this postmarket survey are selected according to the same criteria as were in the PARTNER trial because that's all we know about.

DR. PAGE: Dr. Kato.

DR. KATO: Not to dig up that famous slide that we saw before, but I think you start to roll out -- okay, so on the post -- you know, after the study was done, five new centers come online and all of a sudden the signal is lost, okay. We now multiply that by, you know, we take it up to 75 sites. Without rigorous criteria, the signal may really be lost or swing the other way, and that's a concern. Again, for -- we don't know what's going to happen but

they lost the signal on five new sites. That's a problem.

DR. PAGE: Although our statisticians would tell us that it was too small a sample to define a different signal, but one can't argue with the data as they were shown.

Dr. Somberg.

DR. SOMBERG: I think the most important thing is not to have a concentration of experience from a few centers. What we want to do is broaden the registry so we know how the real world experience will be and what can go wrong. So if we let centers keep on -- you have up to 75 centers, but each center has one and one center has 40, 50, 60, it doesn't give you what you really want to know, so I think it's important that there be 75 centers, that there be about 10 patients per center, and that is what's encouraged to get an overall view of how this is done.

Now, if you want to evaluate a learning effect, then you have to do a very small number of centers and follow them for a very long time. You can't find both data points in one large study.

DR. PAGE: Thank you.

Dr. Brindis.

DR. BRINDIS: Well, one of the issues that we have is the tension between the cost of a postapproval study and the markedly less cost of a registry. And so, you know, in deference to the Sponsor, they can't -- we can't ask them or I wouldn't ask them to be able to do a postapproval study

for all of the patients, for example, that are having the valve implanted. So the cost would be incredibly prohibitive.

But we are -- there is synergy in collecting data in the registry that will answer a lot of these questions for us in terms of responsible diffusion and rollout of this innovative technology across the nation with the added value of the postapproval study in a more select group where Bram and his colleagues at the FDA and the clinical community are going to be more comfortable with the robustness of that particular data.

So the tension that we have is trying to figure out we can get both, particularly if we are fortunate enough to get both, but what we should be able to ask in a more modest group, and that's my own challenge in terms of the number of patients per center or whatever.

DR. PAGE: Okay.

Dr. Zuckerman, are you starting to get input that's going to be useful to you?

DR. ZUCKERMAN: Yeah. If I were to summarize regarding Panel comments on Slide C-124 and the other components, I would suggest that, Number 1, the Panel is looking for a variety of volume sites, which I think is a component of the postapproval study; a relatively tight delta for each of the major safety and effectiveness endpoints; data at 30 days and one year, clinical follow-up years 2, 3, 4, and 5, as well as valve durability data, the echocardiography. It does appear that there's a need to be some good

monitoring of the results so that we can detect early signals of adverse problems.

Is that it in a nutshell, Dr. Page?

DR. PAGE: Yeah, I think that's the case. There is concern from the Panel that this be monitored very carefully and early on, whether it were every site. There's some dichotomy as to concentrating on a smaller number of sites or doing is, I think is fairly reasonable, 75 sites. But really looking carefully at these sites, and it's in everyone's best interest here.

These need to be study patients that are similar to PARTNER Cohort B, or there's concern, at least from the Panel, that they may not look as good as the data do in terms of the randomized pivotal trial that we've reviewed today.

Dr. Good.

DR. GOOD: Can I ask one question? There's going to be a lot of sites that don't participate in PAS 2; is that correct? Seventy-five sites participate in PAS 2. This will be rolled out to quite a few more sites.

DR. PAGE: That is what has been proposed.

DR. GOOD: Yeah, right. Right.

DR. PAGE: And likewise it's been proposed that every patient be enrolled in a registry, which, I'm hearing consistently from the Panel, is a requirement.

DR. GOOD: One last thing, just the emphasis, I think we've

covered this but, you know, bullet point 2 on Slide 124 that these be hypothesis-driven, not inferiority side, prespecified, individually powered endpoints. And I just kind of want to read that into the record again. I think everybody agrees. Is that -- or they don't agree?

DR. PAGE: I'm seeing agreement from the Panel that this needs to be rigorously examined.

DR. SOMBERG: I don't think if you individually power it, that 1,000 would be an adequate sample, if you took all, what is it, five or six endpoints. So be careful what you read into the record.

DR. PAGE: Dr. Naftel.

DR. NAFTEL: So just a philosophical question. In the postmarket study -- so there will be tight hypotheses, and it will really look just like a premarket study. So the question, and I ask this at every Panel meeting, is when the study is concluded, the postapproval study, is there a point where you say okay, we've met the endpoints, and the company and FDA shakes hands and says good, we've done it, or if you don't meet them, does the device get de-approved?

Or is this really a quality assurance process where you're watching along the way closely and you look, oh, there does seem to be a learning curve, let's get together with the company and work on that? Like, is this quality control, or is it really a postmarket study where you might take some action?

DR. ZUCKERMAN: It's a real postapproval study, and one option is if results are not looking as favorable as the IDE study, the FDA can bring the results back to this advisory panel or make an internal decision, et cetera. But I think where you and Dr. Brindis were going is that hopefully this initial postapproval study will be one component of an eventual strategic plan where there will be development of a national registry and things will continue to be followed so that everyone will benefit.

I do want to get back to Dr. Somberg's point. He indicated that with 1,000 patients, it may not be possible to drill down on each of these component endpoints. What the FDA would like to hear, then, is there's nothing magical about 1,000 patients. Certainly other postapproval studies have been larger, others have been smaller. What is critical to hear is should each of these component endpoints be examined with a relevant hypothesis? Slide C-124.

DR. PAGE: Comments from the Panel. So what Dr. Zuckerman is trying to get us pinned down is balancing size of this postapproval study with what's really important, and I'll throw out there, just for discussion, are major vascular events as important an endpoint to drive the size of the study? Is that as important as neurological events?

Dr. Somberg.

DR. SOMBERG: I would say not. I would power the study on neurologic events, what the signal we saw from the preliminary data we're

most concerned about and the others, we will tally. And, you know, most studies, you don't power for every possible adversity; otherwise you'd have to have the whole universe take part.

DR. PAGE: That sounds very reasonable to me. I'm looking at heads nodding, and they're not falling asleep, so I'd say you're in agreement.

So, Bram, I think that's the answer. You're hearing mortality and neurologic events as being what we're really focusing on here. Quality of life relates to the patients, but as -- and we're going to be getting information, just valve durability at five years, quality of life to five years, those aren't endpoints that are compared to the previous trial because we don't have those data. So the trial ought to be powered according to getting meaningful data regarding neurologic and death.

DR. ZUCKERMAN: Good.

DR. PAGE: Okay, moving on.

MR. BARRETT: I just want to seek clarification from you on one comment you made earlier about the registry. We went back and forth several times about the registry, and you said something to the effect that every patient should be put in a registry and I just want to clarify that what you meant is a society-sponsored registry and you weren't implying that that was a company's --

DR. PAGE: That was a personal statement, perhaps, and as chair, that may not represent the Panel, but I think there has been put

forward, certainly, the fact that STS and ACC have registries that get the vast majority. And I've seen a consensus, so far, that that would be important; if not a vast majority, than perhaps 100 percent. But I'll defer to other comments from the Panel. Thank you for bringing that up.

Dr. Borer.

DR. BORER: Yeah. I think it's sort of in the too-hard box where the registry should be, but I will say that I believe that every patient who receives this valve should be registered. I said it before in the context of mechanisms that are available to the FDA, to assure that the valve is used for the indication that has been presented in the population for whom it's considered to be indicated and to try to avoid slippage.

And I believe that having to register each patient and having to provide some information in that registration document about why you're doing this procedure will be a useful safeguard against slippage. So I think it has to be done in every patient. I'm not suggesting that the company has to pay for that. I don't know what the mechanism is, and I don't think we can come to a consensus here about that today. That's something for the FDA to talk about with the company and whoever, and the societies. But I think that that has to be done. I would suggest that.

DR. PAGE: Thank you.

Dr. Naftel.

DR. NAFTEL: I would say that a registry will not prevent

slippage. I think it will document slippage.

DR. PAGE: Fair enough.

Any -- Dr. Lange.

DR. LANGE: As a non-chair, I'll take the prerogative of being very specific. Since the NCC, ACC-NCDR, and STS are working on a joint database, the company would mandate before they'll offer this, is they have to participate in that registry.

DR. PAGE: Do I have any disagreement from the Panel?

(No response.)

DR. PAGE: And now I can comment that I agree with that as well. Again, I'm not implying who will pay for that. That's a bigger issue than we're going to tackle right now. So thank you for bringing that up, though.

So if I may, let's move on to overall safety and effectiveness. Let me remind the Panel that we will take one vote. This is not the time of the vote, but this is the time where you can say whether you consider safety and effectiveness to be demonstrated here.

To read the question: Based on the study results that included a significant reduction in mortality but increase in neurological events and vascular complications for the TAVI group, please discuss whether you believe the overall data demonstrate a reasonable assurance of safety and effectiveness for the SAPIEN THV in the intended patient population. Please also discuss all the key factors that influence your assessment.

And this question is open to comment from any and all of the Panelists. Go ahead, please.

MS. PATRICK-LANE: I just want to say that patient reported outcomes are quality -- as quality of life data are efficacy outcomes, and patients don't want to undergo a therapy that's not going to improve their quality of life. So I think that we saw some really, really strong data, and I appreciate the Sponsor actually collected it in the manner that they did.

And I think I'll close by saying that we are concerned about strokes, and I think that absolutely we need to do some work in this area. But it's also really, really hard to have a stroke if you're dead, so I'll leave it at that.

DR. PAGE: Well stated.

Dr. Good.

DR. GOOD: Well, I think that this is probably effective in significantly reducing mortality. I had, except for the little hiccup with the continued access patients that we saw, I was really convinced. I guess I'm still convinced. We have to go with the study as it was proposed, I agree with that. But I do think it's probably effective in decreasing mortality.

I have some questions about the safety, and I'm not sure. I understand there's always a balance, but we need to know much, much more about the strokes.

DR. PAGE: Thank you. And Mr. Swink will define safety again

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for us, I think, before our vote.

Other comments?

Dr. Jeevanandam.

DR. JEEVANANDAM: Yeah, I agree. I mean, I think in terms of effectiveness, it increases COA, decreases the gradient, solves the problem with aortic stenosis. Is there certainly a safety marker in terms of neurological events? I think, you know, we tackled that a couple ways. I mean, first of all, we have to let the patient know that yes, you can get this therapy, but there is a higher chance of stroke. I think that's an important thing that we need to let the patients be educated.

I think the physicians need to know as well, and whether it's put in as a warning or a black box warning or something, until we can demonstrate that those strokes start going away, maybe because of technique or new size of valves, et cetera, I think it is a major concern that people need to know. You know, they can say fine, I'll take the aortic valve with realizing that there's a higher chance of stroke, but we need to educate the consumer that there is such a risk.

DR. PAGE: Thank you.

Dr. Somberg.

DR. SOMBERG: I was impressed by the PARTNER trial, and I thought it was very dramatic and I was willing to forgive the -- of necessity, the part and parcel to the process, the higher incidence of stroke.

When I saw the continuous access data and realized it was not included in the single effectiveness study, the PARTNER trial, Part B, I'm concerned that the results, when you put it all together, is less dramatic and therefore you have a very thin benefit. And I think that has to be conveyed to the physician and to the patient who has to make this decision because we've heard today, many times, that people really don't understand what they're getting. We have a question of durability for long term; we don't have that question with the surgical approach to the situation.

So I think if we have such a dramatic difference in outcome, then we can forgive some of these other problems, but if we cut that down markedly, I think we have to be extra cautious, and we have to ask the FDA to be more proactive in prescribing really who should get this because it may be very marginal indeed.

DR. PAGE: Thank you.

Mr. Dubbs, and then I saw Dr. Borer and Dr. Brindis.

MR. DUBBS: I'm not sure where the word assurance comes from, whether that's mandated language by the FDA or language that's been put in here for purposes of our discussion. But I'm concerned that assurance may be the wrong word.

What we've seen is the potential, we've seen the possibility, but we also have seen a fair number of adverse events and risks related to neurological issues related to corrosion versus mitigation and other things.

And so using the word assurance carries with it a much more significant thrust than using a word other than assurance. So I'd suggest we think about that.

DR. PAGE: Dr. Zuckerman, do you want to comment as to whether that's standard, reasonable assurance is a standard phrase?

DR. ZUCKERMAN: For a PMA device, reasonable assurance of safety and effectiveness is our regulatory bar.

DR. PAGE: Great. Thank you.

Dr. Borer and then Dr. Brindis and then Dr. Naftel.

DR. BORER: Okay. In summary, I believe that the overall data demonstrate a reasonable assurance of safety and effectiveness for this device in the intended patient population. I'm not so concerned about whether the mortality benefit is large or small. I think that no matter how you slice it, it's not terribly large, and I don't think in this patient population it's the primary concern.

I think the primary concern is quality of life, and you bet I'm concerned about strokes, as I've said, but I think the preponderance of data that the Sponsor has developed suggest that quality of life is more likely to be improved for a patient who undergoes this procedure than not. So as long as we stick to the intended population, as it says here, then I think that the benefit/risk relationship is acceptable.

DR. PAGE: Great, thank you.

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Dr. Brindis.

DR. BRINDIS: To be succinct, I agree totally, and those were my comments.

DR. PAGE: Beautifully stated.

Dr. Naftel.

DR. NAFTEL: I agree totally, too.

Just one point. Informed consent these days is supposed to include a total discussion of risk and benefits for all the possible treatments. And so right now, if I were going to write that very quickly, I'd say okay, if you go with this new treatment, instead of having a 50/50 chance of being alive for one year, you have a 50/50 chance of being alive at two years and with the stroke rate, it would be roughly doubled. I think that's good, and I think that meets every bar we want; it's really good.

And I want to commend the Sponsor, though, that you have not used the words that the professional societies use, the transformational technology and life-saving technology; you know, that's not where we are at all. We're not even close to that. We're at a very good beginning for new technology and a good improvement and a wonderful step, but I appreciate you avoiding those words, and I hope if approval is recommended, I hope I don't read those words in the *Wall Street Journal*.

DR. PAGE: Dr. Lange.

DR. LANGE: Agree with the comments. I think it is reasonable

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assurance, and I would echo what Ms. Patrick-Lake said, is that we have a patient brochure that's woefully inadequate for patients giving informed consent about the procedure. And what I'd urge the Sponsor to do is you have the data and that is -- and I would lay it all before the patient in a way that they can understand, perhaps like Dr. Naftel said or some other way. But the way it's currently presented now is inadequate.

DR. PAGE: Thank you, Dr. Lange.

Dr. Slotwiner.

DR. SLOTWINER: And I just want to echo what everybody has said. I think they've done a very nice job of showing effectiveness. I think the control group emphasizes what a sick population this is and with no good alternatives, and so I think that this offers hope to the study population described.

DR. PAGE: Thank you.

Dr. Kato.

DR. KATO: The one thing that I was impressed with just a few minutes ago, the comment that, you know, yes, these people are very sick and despite being very sick -- and they know they're sick -- they still -- you know, a group still went for the device and they took their chances and they said we're going to for it.

And so you have to give them -- you know, you have to give them the credit that at least, you know, under the rules of guidelines and

informed consent, despite the fact that there is a risk -- and we can argue about whether it's safe or not, and despite the fact that there is some double-digit mortality, which we still have yet to define with -- even with the device, this group of people, you know, went ahead and got the device despite all that.

I think that's really admirable, you know, that they did that. It's going to help out a lot. I think I agree with the entire -- of the discussion. Everybody -- you know, we still don't know all the answers, but it gets us to the next step.

DR. PAGE: Great, thank you.

Dr. Ferguson, do you have any other comments? We didn't get that for the record.

DR. FERGUSON: I concur with Dr. Borer.

DR. PAGE: Great, thank you.

Well, we have come to the time, then, for summations, comments, or clarifications, first from the FDA. Are there any --

DR. ZUCKERMAN: No additional comments at this time.

DR. PAGE: Thank you very much.

Are there any summations, comments, or clarifications from the Sponsor? You have 10 minutes available.

DR. SMITH: Yes. Just to remind you, I'm Craig Smith. I'm the Chairman of Surgery at Columbia, the surgical principal investigator of the

trial. And I have the distinct privilege of speaking for everybody on the bride side of the aisle here in our summary.

So first, I must thank the Sponsor, the FDA, and all the my co-investigators who let me get up here and talk on their behalf and, of course, the Panel, not least. There are many things we agree about and you've just heard about several of them. I think, starting with the biggest ones as far as the benefits, I think it's easy to say, I would argue that we agree that there is a substantial mortality benefit, an equally substantial hemodynamic benefit. And if you move down the softness gradient, there is an impressive quality of life benefit, a somewhat less impressive or more nebulous, perhaps, exercise benefit in the six-minute walks. So there are benefits.

I think you also could not get through this day without understanding that there are concerns, complications. There are bleeding and vascular complications that are quite clearly increased in frequency with the device. I think one of the easiest things to say about this device, partly because of the nature of it, is that it's easy to speculate that improved technology and experience will have a lot to do with minimizing those particular problems.

We just heard a long discussion, all day, really, about stroke. That is clearly a concern. The causality is much less clear, so a little harder to speculate today that experience alone or techniques alone will mitigate that.

Nonetheless, it's a concern. I think it's probably pointless, especially this time of the day, to argue whether it's a concern that's diminishing or a concern that's being exaggerated by Luddites or being minimized by zealots. It's a concern. And you cannot sit through this day or spend five years working on this trial and not understand that it's a concern.

A couple of less well-understood issues, aortic regurgitation, valve durability, remain out there. I think it would be wrong, frankly, based on what we know today, to assume that this means we're headed down the primrose path of the CYPHER stent story we heard from one of the commentators. I think we just have to wait and see on those issues.

So because we know there are great benefits but there are also some residual concerns, I think we would also all agree that dispersion has to be done thoughtfully, you know, in some measured way with adequate training in place at every step and there has to be some kind of appropriate data monitoring. So I would argue another area of substantial agreement.

As far as indications are concerned, the discussion makes it clear, very good point, for patients for whom aggressive treatment of the aortic valve has utility, in other words, for whom it's not futile; some are inoperable. And in that inoperable group, even though inoperable, many of them or some of them, at least, will do -- will live longer and do better. Unfortunately, there are also some who will do better but not live much longer, and there are some who will live longer and do no better. And we do

have to work at refining that process, and that will happen as we all work together.

Indication creep has been discussed, important issue, no question about it. I think that both these issues, the indication creep and the issue I just discussed about indications going forward pivot on preservation of the heart valve team concept, which may be one of the most contributions this trial makes. And it's just as important that the surgeons be in there or I should say -- yes, the surgeons need to be there. It's just as important that the general cardiologist and interventional cardiologist and other team members be part of this team as to have the surgeons there.

As I pointed out this morning, surgeons have kind of enjoyed 20 years of complaining about how the interventionalists manipulate indications for PCI. We've been outside the tent all this time. Well, now we're inside the tent. And if there are shifts and boundaries, we're going to be wearing it along with everybody else. And preserving that collegiality, I think, is what's going to preserve the indications and prevent indication creep.

So I think I've said just about enough. I want to bring you back to the two patient advocates you heard from this morning. They're always compelling. I'll just point out the miracle they describe is replacement of the aortic valve. That's been around for 50 years and has become one of the most highly refined, highly reproducible, relatively low-risk procedures we do for patients. It treats a lethal debilitating condition very effectively. It is as

close to being something miraculous as anything surgeons do. It's replacement of the aortic valve.

TAVR is a very effective replacement of the aortic valve. So what this Panel can do on this particular hot summer day is make that very effective treatment available to inoperable patients. And I think there is time aplenty ahead of us to have experience and evolution of technique file off the remaining rough edges.

I'll stop there. Thank you all again.

DR. PAGE: Thank you very much.

Before we proceed to a vote, I'd like to ask Robert Dubbs, our Consumer Representative; Mr. Barrett, our Industry Representative; and Ms. Patrick-Lake, our Patient Representative, if they have any additional final comments.

Mr. Dubbs.

MR. DUBBS: I do not.

MR. BARRETT: I have just a couple of very brief comments, first to sort of start by stating the obvious. The Sponsors conducted a well-controlled clinical study that met the prespecified primary efficacy endpoint. And as I sit back and reflect on today and many other prior panel meeting experiences, I think it's interesting to comment on what we didn't talk about today.

We didn't talk about the lack of a control group, we didn't talk

about the change in the primary efficacy endpoint. We didn't talk about the quality of the data or missing data, or the quality of the clinical monitoring. We didn't talk about the significant discrepancies in the analysis of the FDA and the Sponsor. And so I really think that all of the stakeholders have conducted -- that designed and conducted and analyzed and presented the study, including the Sponsor, the principal investigators, the study sites and the Agency, really are to be complimented because at least some of us have been in many meetings where a lot of discussion was devoted to things that we didn't talk about today. It really was a high-quality study.

Having said that, whenever you do a complex study, you can learn things, and I think the FDA clinical review, in particular, was very helpful for me, and there were a lot of lessons learned, and I was encouraged to hear, and I think it was from Dr. Swain, that a white paper is being put together. And if it hasn't been already, I hope that you will release that as soon as possible so that other sponsors and researchers in this field can have access to those lessons learned.

Thank you.

DR. PAGE: Thank you very much.

Ms. Patrick-Lake.

MS. PATRICK-LANE: I would just say that it was clear that the benefits outweighed the risks for the intended population, and I also was really encouraged to see the quality of life data be part of the randomized

clinical trial, and I hope to see more of that in the future.

DR. PAGE: Thank you.

And let me just recognize all three of you as being terrific representatives on this Panel. You've been active, you've been engaged, and we really appreciate the insights you provided.

We're now ready to vote on the Panel's recommendation to FDA for this PMA. The voting procedure has changed to an automated system. The Panel is expected to respond to three questions regarding first, safety; then effectiveness; and then risk versus benefit.

Mr. Swink will now read these three definitions to assist in the premarket approval application voting process. Mr. Swink will also read the indication statement for this product. I should also mention that I will not be voting unless there's a case of a tie.

Mr. Swink.

MR. SWINK: The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert Advisory Panel on designated medical device premarket approval applications that are filed with the Agency. The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable, publicly available information.

The definitions of safety, effectiveness, and valid scientific evidence are as follows:

Safety is defined at 21 C.F.R. Section 860.7 - There is a reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risk.

Effectiveness as defined in 21 C.F.R. Section 860.7(e)(1) - There is a reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Valid Scientific Evidence as defined in 21 C.F.R. Section 860.7(c)(2) - Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and reasonably be concluded by qualified experts that there is reasonable assurance of safety and effectiveness of a device under its conditions of use. Isolated case reports,

random experience reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

The Sponsor has proposed the following indications for use:

The Edwards SAPIEN Transcatheter Heart Valve, model 9000TFX, sizes 23 mm and 26 mm, and RetroFlex 3 Delivery System are indicated for transfemoral delivery in patients with severe aortic stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing co-morbidities would not preclude the expected benefit from the correction of aortic stenosis.

The RetroFlex Balloon Catheter is indicated for pre-dilatation of a stenotic cardiac valve prior to implantation of a transcatheter heart valve.

The Crimper is indicated for preparing the Edwards SAPIEN Transcatheter Heart Valve for implantation.

The following questions relate to the approvability of the Edwards SAPIEN THV. Please answer these questions based on your expertise, the information you reviewed in preparation for this meeting, and the information presented today.

You have a handheld remote that will capture the vote for each question in front of you.

DR. PAGE: And before we proceed with that, Mr. Swink, I believe we modified this to include symptomatic and native, so that should

be read into the indication for use.

Is that acceptable? I'm sorry?

MR. DUBBS: Can you read it with the changes?

DR. PAGE: Shall I go ahead? The Edwards SAPIEN

Transcatheter Heart Valve, model 9000TFX, sizes 23 mm and 26 mm, and RetroFlex 3 Delivery System are indicated for transfemoral delivery in patients with severe symptomatic native valve aortic stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis.

And the remainder is the same. Thanks.

Mr. Swink.

MR. SWINK: All right, so we'll take out your handheld remotes.

For the next three questions, please press 1 to vote yes; 2 to vote no; and 3 to abstain. Please be certain of your response before you select your answer as once the selection is made, there will be no opportunity to change your vote.

So before we begin, we'll take a test vote to verify the voting devices are working properly. So the question is now up on --

DR. PAGE: Is it hot outside today?

MR. SWINK: Press 1 for yes; 2 for no; and 3 to abstain. And as you press your answer, your name should disappear from the screen.

Give us a second.

DR. PAGE: Bear with us.

(Pause.)

DR. JEEVANANDAM: Dr. Page, I got a question.

DR. PAGE: Yes, sir.

DR. JEEVANANDAM: Is there any opportunity to be able to change -- I mean, if I wanted to vote on "determined by two cardiac surgeons," for instance, is there an opportunity to do that or to bring it up to a vote? Or how does one do that?

MR. SWINK: What would you do -- we're voting on as it's written, as the question's written, so if you don't agree with it, vote no, and afterwards you will be given an opportunity to explain why.

DR. JEEVANANDAM: Okay.

DR. PAGE: But would there be another vote after that, or is this a one-vote time?

DR. ZUCKERMAN: No. But individuals will have a chance, after the votes, to explain why they voted and perhaps what would make them change a certain vote. And they should take ample opportunity.

DR. PAGE: Okay.

DR. ZUCKERMAN: But there's one vote right now.

DR. PAGE: One vote now, but if this did not pass, would there be an option for a second vote with more surgeons, or is this one time?

DR. ZUCKERMAN: No. There will only be an option for comments.

(Pause.)

DR. PAGE: So let's try it again?

MR. SWINK: Yeah, try it again.

So 1 for yes; 2 for no; 3 to abstain.

(Pause.)

DR. PAGE: I shouldn't be up there in the first place. I don't have a clicker.

MR. SWINK: Michael, did you vote?

All right, we'll go to Plan B. If you'll open your folders, we have a paper ballot. So everybody open your blue folders, in the back of the right. All right, so you look for -- there's a paper in their blue folders that looks like this on the right side.

DR. PAGE: Do you want them to put their names on this?

MR. SWINK: Yeah.

So on the top you'll see, it says Panelist's name, write your name on top, and then we'll just go through each question. You can vote after we read each one.

All right, does everybody have the paper out? Ralph Brindis, do you have your paper? Okay. All right, so here we go.

Voting Question 1: Is there reasonable assurance that the

Edwards SAPIEN Transcatheter Heart Valve is safe for use in patients with severe aortic stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis?

MR. DUBBS: Don't you have to amend that question to comply with the way you changed the indication?

MR. SWINK: Yes. We will state that to meet the criteria specified in the proposed indication as discussed today.

All right, the voting is now closed.

Voting Question 2: Is there reasonable assurance that the Edwards SAPIEN Transcatheter Heart Valve is effective for use in patients with severe aortic stenosis who meet the criteria specified in the proposed indication?

All right. And 3: Do the benefits of the Edwards SAPIEN Transcatheter Heart Valve for use in patients with severe aortic stenosis who meet the criteria specified in the proposed indication outweigh the risks of the Edwards SAPIEN Transcatheter Heart Valve for use in patients with severe aortic stenosis who meet the criteria specified in the proposed indication?

Okay. So what I'll do is, if you could pass your papers toward me from both sides, we'll take a two-minute break to tally the votes.

(Off the record.)

(On the record.)

MR. SWINK: All right, what I'll do first is I'll have to read into the record what each doctor voted on each question.

So Dr. Brindis voted yes for Question 1, yes for 2, and yes for 3.

Dr. Lange voted yes for 1, yes for 2, yes for 3.

Dr. Borer voted yes for 1, yes for 2, yes for 3.

Dr. Ferguson voted yes for 1, yes for 2, yes for 3.

Dr. Good voted no for 1, yes for 2, yes for 3.

Dr. Slotwiner voted yes for 1, yes for 2, yes for 3.

Dr. Somberg voted yes for 1, no for 2, abstain from 3.

Dr. Kato voted no for 1, yes for 2, yes for 3.

Dr. Jeevanandam voted no for 1, yes for 2, yes for 3.

And Dr. Naftel voted yes for 1, yes for 2, and yes for 3.

So we'll just read into the record.

On Question 1, the Panel voted 7 to 3 that the data shows that there is reasonable assurance that the Edwards SAPIEN Transcatheter Heart Valve is safe for use in patients with severe aortic stenosis who meet the criteria specified in the proposed indication.

On Question 2, the Panel voted 9 to 2 that there is reasonable assurance that the Edwards SAPIEN Transcatheter Heart Valve is effective for use in patients with severe aortic stenosis who meet the criteria specified in the proposed indication.

And for Question 3, the Panel voted 9 to 0 to 1 that the benefits of the Edwards SAPIEN Transcatheter Heart Valve for use in prescribed patient populations do outweigh the risk of the Edwards SAPIEN Transcatheter Heart Valve for use in the prescribed patient population.

The three voting questions are now complete. We now need to collect the non-working voting devices.

(Laughter.)

MR. SWINK: So if you could pass those to the center.

DR. PAGE: And the next step is for the Panel members each to discuss their votes. I'll start around on the left here with Dr. Ferguson and just go through each of the voting members to just comment, to the duration you wish, on your vote and why you voted that way.

Dr. Ferguson.

DR. FERGUSON: I no longer have the questions in front of me, but the -- in regards to safety, I thought that there were clearly increased risks for stroke and vascular complications, but I think with an adequate training program and improved patient education and informed consent, that the benefits of survival and quality of life would outweigh the complications that we're seeing.

And in regards to the third question, could you just remind me?

DR. PAGE: Balance of safety and effectiveness.

DR. FERGUSON: Right. I think it's, you know, clearly the

demonstrated benefits and survival and quality of life outweigh the adverse effects.

DR. PAGE: Thank you.

Dr. Good.

DR. GOOD: Well, I'm hopeful that the safety risks could be mitigated in the future with better training, better understanding of stroke and probably prevention of stroke, but I had to vote no because I didn't think it really was safe at this time. On the other hand, I voted yes for effectiveness. I think it is effective in reducing mortality and quality of life. And overall I voted yes. I thought that the benefits outweigh the risks.

MR. SWINK: Just for the record, I think I read Question 2 wrong. It was 9 to 1 for effectiveness.

DR. PAGE: Thank you.

Dr. Borer.

DR. BORER: Yeah, I thought that the preponderance of the data overall favored the procedure as being -- as conferring benefits that outweigh the risks for the stated population. And I would have to say that if the reasons that Dr. Jeevanandam and Dr. Kato voted as they did have to do with one surgeon versus two surgeons, I agree with them. I think it would be better to have two surgeons. So that should be on the record.

DR. PAGE: Thank you.

Dr. Brindis.

DR. BRINDIS: Briefly, I think that this is an innovative technology that is going to meet unmet needs for a population that's clearly going to be helped, with the appreciation of challenges in terms of the technology and the skill sets as talked about today.

I am incredibly encouraged by the endorsement of the Advisory Panel to the concept of a national registry so that we will not have missed opportunities in understanding, one, how we can assure safety related to the utilization in the rollout of this device, but also new clinical information for its proper application in potential off-label use.

DR. PAGE: Thank you.

Dr. Lange.

DR. LANGE: I would agree with the comment about having two surgeons agree. I would also add I would encourage the FDA to define the patient population that you'd like to target, and that is, as this intended patient population, but specifically those that have a life expectancy of more than 12 months aside from this.

A couple of comments. A well done study by the Sponsor. The postapproval study, big pluses for that. The registry, my commendation, the STS and the ACC for working together working very closely for a national registry that includes all patients, and I think it's going to be very important.

DR. PAGE: Thank you.

Dr. Slotwiner.

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(410) 974-0947

DR. SLOTWINER: Yes. I think the control group, you know, really indicated how desperate and sick these patients are, and I think the Sponsor clearly demonstrated that in this population, the device is effective at providing a meaningful extension of quality of life.

I do think that two surgeons should be involved in the evaluation, and I'd like to put that on the record. And I think a postapproval study is going to be essential to better understand the mechanism of stroke, effective treatments to decrease the risk of stroke, and monitor the rollout and training and assure that there isn't indication creep and that patients who we know benefit from open chest procedures don't get them.

And I think it will be essential to carry over from the postapproval study to the registry as described by the societies today, and I hope that's a model moving forward that will work not only through this device but possibly others similar to it that may come to this Panel in the future.

Thank you.

DR. PAGE: Thank you.

Dr. Naftel.

DR. NAFTEL: I would also like to commend the Sponsor. I thought it was a very, very good study and well presented.

I'd like to make the point that the device is not safe and it's not effective for all patients. It is safer than the standard treatment and it's more

effective than the standard treatment. And those are obvious words that I said, but it just helps me to remember this is a high-risk population and nobody's immortal and nobody's free from risk. It's just this is an important increment step and I appreciate it.

Thank you.

DR. PAGE: Thank you.

Dr. Somberg.

DR. SOMBERG: I found aspects today very troubling. I didn't think we had an adequate compilation of the data with the continued access cohort and that concerned me, and therefore, I felt there was some assurance that the device, in this situation with a single non-blinded trial, might work, but I would've been more assured and been able to vote as I thought I was going to when I came here today, in favor of all three aspects, if that data had all been presented more coherently.

DR. PAGE: Dr. Jeevanandam.

DR. JEEVANANDAM: I really want to congratulate the Sponsor and the investigators for making this a very clean trial. I mean, there were no discrepancies in the trial, which was great. I do think that there is a safety concern with the incidence of strokes and I think it -- I voted that it was appropriate for this patient population. I think, you know, the FDA take our comments in terms of trying to make sure that it's the appropriate patient population that's treated with this device.

I think the way to do that is perhaps having two surgeons, like it was in the study, and to increase warnings on this device and accentuate the fact that stroke is higher incidence with this device and especially redo that patient brochure, which I thought was not appropriate.

DR. PAGE: Thank you.

Dr. Kato.

DR. KATO: I also would like to congratulate the Sponsor on taking the initiative to do a randomized controlled trial, as best you can, in the device world. Having participated in a number of panel meetings where there -- inferiority trials are one-sided trials and there's all these confounding problems, it was really actually refreshing to see some scientific rigor applied to this device.

I had to vote no on the safety issue because I am still concerned about the stroke rate. I am still concerned about the initial mortality associated with the device. And I think that, you know, yeah, is it better than dying or better than medical therapy? Yes. But, again, the survival curves don't change for about six months. And I think that I cannot personally give a vote of reasonable assurance of safety without better morbidity/mortality data on the procedure.

I mean, certainly, as a heart surgeon, I would not be considered to be a good heart surgeon if I had a mortality rate of, you know, 30 percent and a stroke rate of 8 percent. That said, I think this can be applied in a very

controlled fashion. I am strongly in favor of very tight controls on this as a rollout, not only to protect patients but also to ensure that this device has the highest likelihood of success.

Thank you.

DR. PAGE: Thank you.

Are there final comments from the remainder of the Panelists?

MR. DUBBS: I just wondered what the medical professionals think if two cardiologists disagree, one votes or one says yes and the other one says no. What do you do, go out and shop around until you find two? What's the answer to that?

DR. PAGE: I'll leave that hanging.

Any other comments?

MR. BARRETT: No. Thanks for doing a great job as chair.

DR. PAGE: Thank you.

I will state that I did not vote. If I had voted, I would have voted in the affirmative for all three. The issue of safety tripped up more people, and just remind you, the definition of safety is that it outweighs the probable risk. There is probable risk, there's no question there is risk to this procedure, but in my mind the benefits outweigh the risk.

And my own personal perspective is this is very important new therapy, and I think there were compelling statements from the patients and their representatives for the change that can be made in patients' lives. This

has to be implemented in the right patients and done very carefully with a true assessment by a surgeon. I personally would not favor two surgeons, but the surgeon that has to take his or her job very seriously.

I would like, personally and on behalf of the Panel, to thank the Sponsor and the investigators for the conduction of the trial and really a very nice presentation. I'd also like to thank the FDA, and I would like to thank the Panel.

And, Dr. Zuckerman, do you have any other comments?

DR. ZUCKERMAN: No. I would just like to thank Dr. Page and the rest of the Panel for doing some outstanding work today.

DR. PAGE: Well, we are 27 minutes past the hour of when we were going to adjourn. I apologize for that. On the other hand, we're not done until we get the job done. I feel like we accomplished important work here.

So with that, this meeting of the Circulatory System Devices Panel is adjourned. Thank you very much.

(Whereupon, at 6:48 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

CIRCULATORY SYSTEM DEVICES PANEL

July 20, 2011

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

Sussy Morehouse

Official Reporter

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947