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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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CIRCULATORY SYSTEM DEVICES PANEL

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April 6, 2021
9:00 a.m.

Via Microsoft Teams Videoconference

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Heart Transplant Recipient with OCS Heart in DCD Trial

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Heart Transplant Recipient with OCS Heart in DCD Trial

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M E E T I N G

(9:03 a.m.)

DR. LANGE: Good morning. I would like to call this meeting of the Circulatory Devices Panel to order.

I am Richard Lange, the chairperson of this Panel. I'm president of Texas Tech University Health Sciences Center in El Paso, where I'm also dean of the Paul L. Foster School of Medicine. I'm a general cardiologist now, but spent most of my formative years as an interventional cardiologist.

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

For today's agenda, the Panel will discuss, make recommendations, and vote on information regarding the premarket approval application, that is the PMA, for the TransMedics Organ Care System (OCS) Heart by TransMedics, Inc.

Before we begin, I would like to ask our distinguished Committee members and FDA attending virtually to introduce themselves. Committee members, please turn on your video monitors if you've not done so already and unmute your phone before you speak. I will call your name. At that time please state your area of expertise, your position, and your affiliation. I'll start with Dr. Vetrovec.

DR. VETROVEC: Hi, I'm Dr. George Vetrovec, Professor Emeritus, Virginia Commonwealth University, an interventional cardiologist by career.

DR. LANGE: Great. Thank you, George.

Dr. Blankenship.

DR. BLANKENSHIP: Good morning, I'm an interventional cardiologist and currently Professor of Medicine and interim director of cardiology at the University of New Mexico.

DR. LANGE: Good morning, Jim.

Dr. Connor.

DR. O'CONNOR: Good morning, I'm Chris O'Connor. I'm an affiliate physician by training and currently, I'm the president of the Inova Heart and Vascular Institute, which is an independent academic health system in Northern Virginia.

DR. LANGE: Good morning, Chris.

And now Dr. Jason Connor.

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

DR. LANGE: Thanks for joining us, Jason.

Dr. Brindis.

DR. BRINDIS: Hi, I'm Ralph Brindis. I'm a Clinical Professor of Medicine at UCSF, a career in general cardiology and interventional cardiology, and also have a role with the National Cardiovascular Data Registry of the American College of Cardiology.

DR. LANGE: Thank you, Ralph, for joining us.

Dr. Allen.

DR. ALLEN: Hi, there. I'm Keith Allen. I'm a cardiac and vascular surgeon, director of surgical research and the surgical director of the structural heart program at the Mid America Heart Institute in Kansas City, Missouri.

DR. LANGE: Great. Thank you, Keith.

Dr. Kwon.

DR. KWON: Hi, my name is Murray Kwon, cardiothoracic surgery, UCLA, associate professor.

DR. LANGE: Murray, thank you for joining us.

Dr. Bonde.

DR. BONDE: I'm a cardiac surgeon specializing in adult cardiac surgery with an emphasis on therapies for heart failure.

DR. LANGE: Thank you, Pramod.

Dr. Gallagher.

DR. GALLAGHER: Good morning. Colleen Gallagher. And I am an executive director for clinical ethics as well as a professor in the Department of Critical Care at the University of Texas MD Anderson Cancer Center.

DR. LANGE: Thank you, Colleen.

Mr. Stanum (ph.). Mr. Stammers, I'm sorry.

MR. STAMMERS: Good morning. I'm a certified clinical perfusionist emeritus and the vice president of clinical quality and outcomes research at Specialty Care in Brentwood, Tennessee.

DR. LANGE: Thank you, Al.

Dr. Yuh.

DR. YUH: Good morning, I'm David Yuh. I'm the chairman of surgery at the Stamford Health System in Stamford, Connecticut. I'm an active cardiothoracic surgeon and have about 10 years of prior experience in surgical therapies for heart failure.

DR. LANGE: Thank you, David.

Dr. Yeh.

DR. YEH: Robert Yeh. I'm an interventional cardiologist at Beth Israel Deaconess Medical Center, where I also direct the Smith Center for Outcomes Research in Cardiology, and Associate Professor of Medicine at Harvard Medical School.

DR. LANGE: Thank you, Robert.

Dr. Selzman.

DR. SELZMAN: Hi, I'm Craig Selzman. I'm one of the surgeons at the University of

Utah and so do some of this transplant stuff every once in a while.

DR. LANGE: Thank you, Craig.

Dr. Katz.

DR. KATZ: I'm Mark Katz. I'm a cardiac surgeon and professor, and chief of the Division of Cardiothoracic Surgery at the Medical University of South Carolina.

DR. LANGE: Thank you, Mark, for joining us.

Dr. Cigarroa.

DR. CIGARROA: Morning, I'm Joaquin Cigarroa. I'm Professor of Medicine at Oregon Health & Sciences University, a general cardiologist with added qualifications in interventional cardiology, and clinical chief of the Knight Cardiovascular Institute.

DR. LANGE: Great.

Dr. Hirshfeld.

Thank you, Joaquin.

DR. HIRSHFELD: Good morning, I'm John Hirshfeld. I'm a Professor Emeritus of Medicine at the University of Pennsylvania, and my clinical career was all in interventional cardiology.

DR. LANGE: Thank you, John, for joining us.

Dr. Burke.

DR. BURKE: Hi, I'm Allen Burke. I'm a Professor of Pathology at the University of Maryland. I specialize in cardiovascular and pulmonary pathology.

DR. LANGE: Great. Allen, thank you.

Dr. Nuszkowski.

DR. NUSZKOWSKI: Hi, my name is Mark Nuszkowski. I'm chief perfusionist at Children's National Medical Center in Washington, D.C.

DR. LANGE: Thank you very much.

Dr. Borer.

(No response.)

DR. LANGE: Jeff, you're on mute. I don't see him on right now. We'll circle back around.

Dr. Moon.

DR. MOON: Yeah, good morning. I'm Marc Moon. I'm the chief of cardiac surgery and professor at Washington University in St. Louis, and I do adult cardiac surgery.

DR. LANGE: Great. Thank you, Mark.

Normally, Jacqueline Alikhaani would be participating on the Panel as our Consumer Representative. I'm sorry to report that she's had a death in the family and will be unable to join us today.

Debra Dunn.

MS. DUNN: Hi, good morning. Can you hear me?

DR. LANGE: Yes, ma'am.

MS. DUNN: Yes. I'm an 18-year heart failure patient. I just received my ninth biventricular ICD device. I've been over the meadow and through the woods with infection, lead extraction, and my third lead was just extracted January 15th and I was not able to get a replacement, so I have the HIS procedure right now for the third lead. So I'm very interested in this Panel.

DR. LANGE: Debra, thanks for joining us as our Patient Representative, I appreciate it.

Mr. Jarvis.

MR. JARVIS: Yeah, hi. Gary Jarvis. I'm the Industry Representative to the Panel.

DR. LANGE: Perfect. Gary, thank you for joining us.

I'm going to once again extend -- Dr. Borer, can you hear and are you able to

introduce yourself?

(No response.)

DR. LANGE: When he's able to join us, Jeff is a distinguished professor at SUNY Downstate Health Sciences University in Brooklyn, New York. We look forward to him joining us.

Dr. Zuckerman.

DR. ZUCKERMAN: Good morning. Bram Zuckerman, Director, FDA Office of Cardiovascular Devices. Thank you, Dr. Lange.

DR. LANGE: Great, thank you. I'm going to be handing it over to Aden Asefa in just a second, she's our Designated Federal Officer for today's Circulatory Devices Panel and she will now have the opportunity to make some introductory remarks.

Take it away, Aden.

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

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

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

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has

authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential 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 regarding the premarket application (PMA) for the TransMedics Organ Care System Heart by TransMedics, Incorporated. The OCS Heart, a portable extracorporeal heart perfusion and monitoring system, is indicated for the resuscitation, preservation, and assessment of donor hearts in a near-physiologic, normothermic, and beating state intended for a potential transplant recipient.

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

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

For the duration of the Circulatory System Devices Panel meeting on April 6th, 2021, Drs. Marc Moon and Christopher O'Connor have been appointed to serve as a Temporary Voting Member, and Ms. Jacqueline Alikahaani has been appointed to serve as a Temporary Non-Voting Consumer Representative. For the record, Dr. O'Connor serves as a consultant

and Ms. Alikahaani serves a consumer representative of the Cardiovascular and Renal Drugs Advisory Committee at the Center for Drug Evaluation and Research. Dr. Moon serves a consultant on the Pediatric Advisory Committee in the Office of Pediatric Therapeutics. These individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be consider at this meeting.

The appointment was authorized by Russell Fortney, Director of the Advisory Committee Oversight and Management Staff, on March 25th, 2021.

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

FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue.

A copy of this statement will be available for review and included as part of the official transcript.

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

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

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

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

Thank you very much. And back over to Dr. Lange.

DR. LANGE: Aden, thanks for your comments.

I want to acknowledge the FDA for really assembling a very distinguished panel with

a wide breadth of experience and knowledge, so thank you very much. And for the panelists for participating in today's important event, as well.

We'll now proceed with the Sponsor's presentation. I would like to invite the Sponsor to begin.

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

The Sponsor will have 90 minutes to present and, Sponsor, at this time you may now begin your presentation. Thank you.

DR. HASSANEIN: Good morning. My name is Waleed Hassanein, I'm the president and chief executive officer of TransMedics. Prior to TransMedics, I was a cardiac surgery research fellow at Brigham and Women's Hospital here in Boston, and prior to that I was a general surgery resident at Georgetown University Medical Center. I want to start today by thanking Chairman Lange, members of the Panel, Dr. Zuckerman, and the FDA review team for the opportunity to discuss the data supporting the approval of the Organ Care System Heart in the United States. Let me start with some background on TransMedics.

TransMedics was founded in 1998 to develop the Organ Care System, or OCS technology, to increase donor organ utilization for transplant and improve post-transplant clinical outcomes. TransMedics is a clinically driven organization that pioneered the concept of extracorporeal perfusion of donor hearts, lungs, and livers for transplants. To date, we have sponsored and successfully completed eight FDA pivotal trials involving all three organs. The OCS was invented, developed, and manufactured here in the United States.

The OCS Lung is FDA approved for two clinical indications, and the OCS Liver is currently under review by the FDA. Today we are here to discuss the approval of the OCS

Heart, which is approved internationally and has been used in more than 1,000 heart transplants worldwide.

For the last decade, the number of organ donors have doubled in the United States. Yet heart transplantation has remained limited to only 30% utilization of the donor pool. This leaves thousands of donor hearts unused every year. Importantly, it limits the access of patients with heart failure to lifesaving heart transplant procedures. And even patients who may get to the heart transplant waiting list are not guaranteed a new heart and many patients die while waiting for a heart transplant.

This is because the underutilization of donor hearts leads to long wait times and the longer a patient is on the waiting list for a heart transplant, the higher the risk for mortality. For patients with the highest urgency status, Status 1A, mortality is nearly 25% in the first year.

For the past four decades we have made significant innovations in all aspects of heart transplant therapy with one exception, donor heart preservation. Our only option has been limited to cold storage. Simply, an Igloo cooler and ice.

Cold storage has three major limitations that significantly restrict donor heart utilization. First, every minute the heart is on ice, it is being subjected to a time-dependent ischemic injury. Second, there is no way to optimize the donor heart while it's being preserved. And third, there's no way to assess the viability of the donor heart on ice before transplanting it into a recipient.

For these reasons, today we only transplant the healthiest hearts from the healthiest donors or so-called standard criteria hearts. This is why only three out of every 10 available donor hearts are used for transplant annually.

The amount of time a heart is subjected to ischemic injury on cold storage is also directly correlated to the rate of primary graft dysfunction, or PGD, in the immediate post-

transplant period. PGD has been reported to occur anywhere between 15 and 31%.

The OCS is an integrated portable platform that was designed to address the limitations of cold storage and increase donor heart utilization for transplants. It is composed of three major components, the OCS Heart console on the left, the Heart perfusion set in the middle, and the Heart solution set on the right. Let me show you how the system works.

The Organ Care System is designed to be a compact, lightweight, fully integrated system to facilitate portability during organ retrieval. The perfusion module is designed to fit right into the portable console.

The system is primed with donor blood. In addition to the blood prime, we add key additives like antibiotics, substrate, and hormones. Two simple cannulations of the aorta and pulmonary artery are all that's required to establish perfusion of the donor heart on the OCS.

Once the heart is ready to be instrumented into the OCS System, the organ chamber is opened and the recirculating line is removed. The first portion of the instrumentation is to de-air the aorta and the cannula. Once the aorta is de-aired, the cannula is secured in place. The heart is adjusted and the PA cannula is secure once the heart regains sinus rhythm.

As you can see, organ preservation becomes a more dynamic process where the clinical user can optimize perfusion, substrate, and oxygen delivery and monitor organ function, rhythm, and contractility. For metabolic assessment, we collect perfusate sample to monitor lactate trends and other blood chemistries.

Once all is checked, the organ is now ready to be transported to the recipient hospital. The OCS is designed to fit in all modes of air and ground transport for donor retrieval.

To date, we have completed three clinical trials to evaluate the OCS Heart System for three different heart transplant indications. Our pivotal trial, the OCS Heart EXPAND and continued access protocol, or CAP, were designed to support the proposed indication we are discussing today for extended criteria donor hearts. We will be presenting data on 116 patients with at least 30-day post-transplant outcomes. Of these, 75 were EXPAND and 41 were in CAP.

An earlier generation of the OCS Heart device and use model was studied more than a decade ago in the PROCEED II trial. It was a smaller trial that included 62 standard criteria donor hearts preserved on the OCS System. Post-transplant outcomes were compared to patients with heart preserved using cold storage. PROCEED met its primary effectiveness and safety endpoints and the results were published in the *Lancet* in 2015.

However, it is important to note that PROCEED was conducted for a completely different clinical indication that no one proposed in this PMA. I will review the high-level findings of this trial and the significant differences between EXPAND and PROCEED later in our presentation today.

Finally, we have completed enrollment in a 90-patient trial to support a DCD heart indication in the United States, and we're rapidly enrolling in the CAP for the same trial.

Given that EXPAND and CAP trial inclusion criteria are identical to the proposed indications in the current PMA, we strongly believe that the results from EXPAND and CAP represent the primary dataset supporting the current PMA and indication being discussed today.

Prior to the initiation of EXPAND, TransMedics consulted with leading U.S. academic heart failure cardiologists and transplant surgeons to help define the specific types of donor hearts that are considered extended criteria for heart transplants in the United States. Their collective recommendations were reflected in the donor eligibility criteria for this

trial, which are also identical to our proposed indications in this PMA. These represent donor hearts that are seldomly used for heart transplants using cold storage in the U.S. today.

TransMedics is proposing the following indication: TransMedics Organ Care System Heart System is a portable extracorporeal organ perfusion and monitoring system indicated for the resuscitation, preservation, and assessment of donor hearts intended for transplantation with one or more of the following clinical criteria: first, expected cross-clamp or ischemic time of 4 hours or more due to donor or recipient characteristics, or expected cross-clamp or ischemic time of 2 hours or more with at least one of the additional risk factors shown on the slide.

It is important that the data clearly and unequivocally demonstrate that donor hearts we enrolled in EXPAND and CAP trial had a significantly higher risk profile than the standard criteria hearts included in the earlier PROCEED II study, as well as the U.S. national heart transplant population in the UNOS database.

Now let me highlight the overall EXPAND and CAP clinical results. The EXPAND trial met its primary effectiveness endpoint. It showed that OCS Heart System is effective for the resuscitation, perseveration, and assessment of extended criteria donor hearts that are seldom used for transplants in the United States.

The donor heart in EXPAND and CAP were refused by other centers an average of 60 times prior to being accepted into the trial. With the OCS, we were able to successfully transplant 84% of these hearts. Simply stated, we took 10 hearts that had been refused for transplantation due to a variety of clinical reasons or risk factors. The use of the OCS resulted in eight of these hearts being successfully transplanted and with excellent post-transplant clinical outcomes. There were no unexpected safety findings and the 8% rate of severe PGD observed is well below the rates reported in the literature. In EXPAND and CAP,

patient survival at 30-day post-transplant was 97%, which is comparable to the U.S. standard heart transplant outcomes. All-cause survival was 92% at 6 months and 87% at 12 months. Importantly, when looking at cardiac-related survival, which is related to the heart allograft, survival was 96% at both 6 and 12 months.

We believe these results demonstrate ample assurances of safety, effectiveness, and significant clinical benefits to support the approval of the OCS Heart System for extended criteria donor hearts.

Here's our agenda for the rest of the presentation. Dr. Farr will discuss the clinical need to increase donor heart utilization. Dr. Schroder will review the results of the EXPAND and CAP. I will return to provide a summary of our earlier PROCEED II study and the key differences between PROCEED and EXPAND. Chris Mullin, our independent statistical expert, will then provide his perspectives on the FDA's extrapolated long-term survival modeling. I will return to present our positions on the FDA discussion questions and review our training and post-approval programs. Finally, Dr. Shah will close our presentation with his clinical perspective and benefit-risk assessment of the OCS Heart System. We will then be happy to address all of your questions.

We also have several additional experts to help answer any of your questions.

Regarding financial disclosures, Chris Mullin has been compensated for his time as an independent statistical consultant to TransMedics. All other speakers have not received any compensation and none have any equity interests in TransMedics.

Thank you for your attention. I will now turn the presentation to Dr. Farr.

DR. FARR: Good morning, my name is Maryjane Farr. I am the medical director of the adult heart transplant program at Columbia University, one of the oldest and highest volume heart transplant centers in the world. I'm here today to discuss the urgent unmet need to extend the utilization of donor hearts for patients with end-stage heart failure.

Heart failure is the major public health issue affecting approximately 6.5 million adults in the U.S. alone. Due to the aging of the population, the American Heart Association estimates that the prevalence of heart failure will increase by 40 to 50% in just the next 10 years to nearly 8.5 million patients, of those with heart failure, about 5 to 10% of end-stage heart failure, many of whom are candidates for heart transplantation or durable mechanical assist device therapy. This represents at least 300,000 patients in the United States.

The most recent literature suggests that the 1-year mortality rate for patients with end-stage heart failure is approximately 40 to 60% without advanced therapies.

Patients with end-stage heart failure with recurrent hospitalizations really have just two treatment options to survive. They can either get a mechanical heart pump or they can get a heart transplant.

A mechanical heart pump, also known as a VAD or a ventricular assist device, requires open chest surgery and can be beneficial as a therapy in itself or as a bridge to transplant for patients with a long waiting time. Importantly, the 2-year survival of patients with the newest durable LVAD, which is the HeartMate 3, is 79%.

However, there are many heart failure patients who are not suitable for an LVAD either because they have biventricular heart failure or they have such surgical complexity that going straight to heart transplant is a better strategy for long-term survival. In addition, while on an LVAD there can be many complications such as bleeding, infection, and worst of all, stroke. Many patients find it very difficult to be on a machine in which the batteries and drive lines sit outside the body. These patients can't even take a shower.

Heart failure clinicians and major societies in the United States and worldwide recognize heart transplantation as the gold standard and the only definitive replacement therapy for end-stage heart failure.

Given the medical advances over the past decade, clinical outcomes for a heart

transplant are excellent. While there are many factors that can affect survival, the 1-year survival rate after transplant is 88 to 90% and about 72% after 5 years. It's important to note that these survival statistics are as high as they are because we must be very selective about which hearts we use, given the limitations of cold storage that I'll discuss shortly.

Heart transplant has also been shown to substantially improve patients' functional status and health-related quality of life.

Unfortunately, one of the major problems with heart transplant is the supply. In 2020 there were 12,500 deceased organ donors in the United States. Yet, there were just 3,600 heart transplants performed. This means that only three of every 10 hearts potentially eligible for transplant from DBD or donation after brain death donors are currently utilized. To give you an example, from that same pool of deceased donors, almost 8,400 livers in the United States were transplanted. This leads to an oversold transplant waiting list, meaning that there are more people on the waiting list than who will ever be transplanted.

Data from the United Network for Organ Sharing, shown here, indicate that over the span of a year there are nearly 7,000 heart candidates listed, but less than half get transplanted every year. The reality is that many people die waiting every year, which is devastating for patients and their families and all of us who take care of them.

So why can't we get these patients transplanted? Because despite all the advances in modern medicine over the past 40 years, the best we still have is hypothermic preservation, or cold storage, to transplant a donor heart to a recipient. This is problematic because there are many limitations to cold storage.

Cold storage is an ongoing race against the clock. Hearts can only be preserved safely on ice for approximately 4 hours. Time-dependent ischemic injury is a risk when preserving a heart and increases the longer the heart is outside the body. Therefore, a

recipient's location oftentimes limits them from getting a donor heart that is a good match for them. Additionally, cold storage does not allow for therapeutic intervention through replenishing oxygen and nutrients to ensure optimal preservation. And lastly, preserving the heart in a cooler on ice doesn't allow us to assess the heart's function and viability before transplanting the heart into the recipient.

This means that we can only safely transplant the most health standard criteria hearts. Hearts that are too far away from the intended recipient or from older donors or donors with any risk factors preclude those hearts from being transplanted using cold storage. So every year the vast majority of potential donor hearts go unutilized.

Previously, donor hearts were allocated based on proximity to the recipient, which generally meant that those in rural communities or without the means to travel didn't receive hearts. But recent important changes in heart allocation now underscore that the organs are a national resource and that organs should be allocated to the sickest patients first, starting at 500 miles.

As of January 2020, UNOS, under guidance from the United States Department of Health and Human Services, determined that local allocation was not consistent with federal mandates of fair access. What this means for transplant programs is that we are now able to transplant the sickest patients first, but it also means longer travel times, often in planes, and longer ischemic times. But we can't consistently meet this federal mandate with cold storage.

New technologies to mitigate the adverse effects of long ischemic times are needed now more than ever. And not only can a new technology allow us to reach more patients, but it can help expand the donor pool, especially from community hospitals that are not very close to airports.

Currently, standard criteria of donation after brain death or DBD donors are used for

heart transplant recipients by and large. However, donation after circulatory death or DCD is a growing pool of donors being used for other failing organs, but these hearts have never been used for heart transplantation until the OCS was used in Europe and Australia.

In 2019, there were 1,543 DCD donors who were in what we would consider an ideal age range. At least one organ, the liver, kidney, or lung, was transplanted from these donors. But only seven hearts were able to be used and this was possible only through the use of OCS in a clinical trial. The ability to utilize as many hearts from this donor pool would be a significant advance in moving patients off the heart transplant waiting list.

To summarize, heart transplant is the gold standard therapy and only definitive replacement therapy for patients with end-stage heart failure. Without intervention, approximately half of these patients die within the first year of diagnosis.

Despite significant progress in most aspects of heart transplantation, the technique for donor heart preservation has remained cold storage for more than 40 years. The limitations of cold storage typically restrict utilization to the healthiest and youngest standard criteria donor hearts in close proximity to intended recipients, ultimately restricting the number of lifesaving heart transplants that can be performed.

Thus, there is a significant unmet need for new heart preservation technologies to address the limitations of cold storage and increase the number of lifesaving heart transplants that can be performed.

Thank you for your attention. I will now turn the presentation over to my transplant colleague, Dr. Schroder.

DR. SCHRODER: Good morning, my name is Jacob Schroder. I'm the surgical director of the heart transplant program at Duke University. I also serve as the national principal investigator of the Heart EXPAND trial, which I'm pleased to discuss today.

EXPAND was designed to evaluate the ability of the OCS to increase utilization of

donor hearts that are rarely used today due to the limitations of cold storage. The enrollment of donors and recipients reflect the proposed indication, extended criteria donor hearts, and typical heart recipients.

EXPAND was designed as a single-arm, multicenter study conducted at centers in the United States. Let me take a moment to discuss this further.

While a randomized controlled trial would've been preferred, after much discussion, a panel of heart transplant experts felt it would have been unethical to randomize extended criteria hearts to cold storage and that many investigators would lack equipoise, thus limiting enrollment. Additionally, we felt that a concurrent control arm of standard criteria cold storage donor hearts would have been of limited clinical use, essentially comparing apples to oranges. This is a different donor heart population.

The donor risk factors that constituted the inclusion criteria for EXPAND were defined by a panel of expert heart failure cardiologists and surgeons. For a donor heart to be eligible for EXPAND, the expected total cross-clamp time had to be at least 4 hours or at least 2 hours plus one or more of the additional risk factors shown here.

The protocol included several acceptance criteria to guide the transplant surgeon in determining the transplantability of the donor heart. First, the arterial lactate level should be less than five at the end of the OCS perfusion period with a stable lactate trend.

Second, the OCS heart perfusion parameters should also be stable within following recommended ranges: coronary flow within 400 to 900 mL/min and aortic pressure between 40 to 100 mm/Hg.

Lastly, the transplanting surgeon or heart failure cardiologist had to be clinically satisfied with the overall donor heart condition on the OCS.

Importantly, the protocol instructed that the recipient's surgical procedure should not be started until the donor heart was accepted on OCS.

Heart transplantation is a complicated and dynamic process. The FDA has identified concerns regarding the use of lactates on OCS and the use of clinical judgment in determining the transplantability of donor hearts. Let me address this concern.

Lactate levels are an important biomarker for hypoperfusion and myocardial ischemia. If the heart is not getting enough oxygen, the lactate level will rise.

In 2009, TransMedics presented data from the first 49 transplanted patients with the OCS using standard criteria hearts. This analysis found that the lactate trend, rate of lactate change, and the final lactate were significant predicators of graft dysfunction. A limit of 5 mmol/L was established for subsequent use of the OCS in clinical studies and commercial use outside the U.S. However, it's important to note that the baseline lactate in this sample was 1 mmol or less, so ending up at a level of five represented a substantial increase.

In EXPAND, a qualifier for stable lactate trend was added to accommodate extended criteria hearts where the starting lactate might be as high as three or four. In the study, investigators turned down some hearts because the lactate trend was increasing despite attempts to maximize perfusion and aortic pressure. In some cases, this clinical judgment was made when the absolute lactate level was below five because the clinician was convinced that all efforts to make the heart viable for transplant had been exhausted. Naturally, no surgeon in the study wanted to transplant a poorly functioning heart into a recipient and risk primary graft dysfunction and poor patient outcome.

It's also important to note that lactate is not the only parameter used to determine transplantability. The stability of coronary flow and aortic pressure are also critically important. The use of clinical judgment, which is all we have with standard of care cold storage donor hearts, was also an important consideration in deciding whether to accept a heart on OCS.

The ability of OCS to provide additional data to inform clinical judgment about the

organ's viability is one of its greatest benefits. We don't have this opportunity with cold storage donor hearts where the heart is procured and packed in ice and then the surgical team rushes to minimize ischemic time. The outcome, as related to preservation method, is already predetermined but unknown. Having done this hundreds of times, there is always a "hold your breath and hope the heart works" moment. With significant unknowns, most centers are not willing to accept this risk with extended criteria hearts and thus, many go unutilized. The OCS gives us additional information to assist clinical judgment and ensure, to the best of our ability, a good patient outcome.

The recipient inclusion criteria reflect typical adult heart transplant candidates. The trial excluded patients who had a prior solid organ or bone marrow transplant, those with chronic use of hemodialysis or with a diagnosis of chronic renal insufficiency, or patients requiring multi-organ transplantation.

The primary effectiveness endpoint was a composite of patient survival at Day 30 and the absence of severe PGD in the first 24 hours after transplant. The safety endpoint was the incidence of heart graft-related SAEs in the first 30 days.

Let me provide some background on the rationale for performance goals in EXPAND. For the primary endpoint, there is no published data on the rate of PGD in extended criteria donor heart transplants. Therefore, the higher range of published PGD of 30% was added to the 5% rate of 30-day mortality for standard criteria hearts to derive a performance goal of 65%. Given the sample size of 75 patients, the observed success rate had to be at least 80% in order to meet the 65% performance goal, which is based on the lower bound of the confidence interval.

The trial did not have a formal hypothesis test for the safety endpoint because there was no prior data on moderate and severe ISHLT PGD through 30 days post-transplant in this donor population. Furthermore, the primary effectiveness endpoint includes safety

components for survival and PGD.

There were three secondary endpoints. The first two were individual components of the composite primary endpoint. The third was the rate of donor heart utilization, the percentage of donor hearts that were successfully transplanted after instrumentation on the OCS.

Moderate or severe primary graft dysfunction was defined in the protocol according to the ISHLT consensus recommendations. Clinical events were independently adjudicated by the independent medical monitor, Dr. John Wallwork. Dr. Wallwork has extensive experience in transplantation and is a past president of the ISHLT. The medical monitor adjudicated PGD consistently according to the ISHLT consensus statement across all study patients.

This slide shows the breakdown of the heart risk factors for the 93 donor hearts included in the study. Forty-eight percent of the donor hearts met one criteria and 52 met more than one inclusion criteria with overlapping risk factors. This illustrates the complex nature of the donor hearts used in this trial and why many of these hearts, especially those with multiple risk factors, would be rarely used for transplantation with cold storage.

In one of the discussion questions for the Panel, the FDA raised a concern about revisions to donor heart inclusion criteria. Let me clarify this for you.

Several investigative sites only entered one inclusion criteria and did not enter additional criteria that were present in the donor. This was done because some investigators felt that only one inclusion criterion was needed to qualify a donor heart in the trial and thus entered only the first, but not additional risk factors that were present at the time of donor heart evaluation.

During their review of the PMA, additional donor inclusion criteria were identified by the FDA during review of the source documents. This led to a thorough source document

review and verification. Donor risk factors were re-tabulated to include all risk factors present, reflecting the true donor complexity. This information was then provided to the FDA. There was no change of the inclusion criteria at any point during the trial enrollment or afterwards.

To validate that donor hearts used in EXPAND are seldomly utilized for transplant, we obtained data from the UNOS SRTR database on all 10,426 heart transplants between 2015 and 2018, the same period of enrollment in EXPAND. The prevalence of risk factors was much higher in the donor hearts in EXPAND compared to the donor hearts transplanted with cold storage. We also compared UNOS to EXPAND looking at two or more risk factors. Again, the prevalence of donor hearts with multiple risk factors in EXPAND was significantly higher than the national transplant population.

Another way to characterize the donor hearts is to evaluate how many times a donor heart was rejected by other transplant centers before being accepted into the trial. EXPAND donor hearts were rejected by other centers an average of 66 times and a median of 29 times prior to acceptance. For a comparison, from 2007 to 2014, the median number of donor heart refusals in the United States prior to acceptance was two.

Seventy-five of 93 donor hearts that were preserved and assessed on OCS were transplanted in EXPAND for a utilization rate of 81%. Eighteen hearts did not meet the acceptance criteria on the OCS. All these hearts had continuously rising lactates despite attempts to optimize flow parameters. Additional reasons for exclusion include a final lactate above the threshold limit, RV dysfunction, or an inability to wean off pacing.

This chart of the mean arterial lactates over time illustrates that point. For the 18 hearts that were turned down, there is a continuous upward trend in arterial lactate. In contrast, the 75 hearts that were ultimately transplanted had a stable average trend. This difference between the lactate trends of accepted and rejected hearts reflects the

importance of using OCS lactate levels to augment clinical decision making.

Among the 75 recipients, the average age of patients was 55; most were male, and the average BMI was approximately 28. Nearly a quarter of the transplant recipients were older than 65. Two-thirds had a history of mechanical support with LVAD or BIVADs, a known risk factor for PGD. Sixteen percent had a female donor to male recipient mismatch, also a risk factor for PGD. Fifteen percent had renal dysfunction. More than two-thirds of patients were Status 1A, requiring intensive care hospitalization, cardiac-supporting IV medications, or a non-dischargeable mechanical assist device. In general, these were sicker recipients when compared to the UNOS registry based on their age, percentage of VAD use, and urgency status.

Next let's review the donor heart preservation characteristics. The average total cross-clamp or out-of-body time in EXPAND was more than 6 hours. Yet the OCS reduced the amount of actual ischemic time to only 1.7 hours. For reference, we looked at the SRTR database and found that 85% of hearts transplanted in the United States were transplanted with less than 4 hours of ischemic time on cold storage.

The OCS met the primary effectiveness endpoint with 88% of patients surviving to Day 30 without experiencing severe PGD in the first 24 hours. The lower confidence bound of 78% was well above the pre-specified performance goal of 65% with an associated p-value of less than 0.0001.

This slide shows the two components of the composite primary endpoint. First, 94.6% of patients survived through Day 30 post-transplant. This is consistent with the national average of 95.7% with standard criteria donors.

Second, the incidence of severe PGD in the first 24 hours was 10.7%. There was one patient who needed a retransplant and was transplanted off study with a second heart. This patient survived through 30 days, but failed the primary endpoint due to having severe

PGD.

To put these results in context, this slide shows the rates of severe and moderate or severe PGD within 24 hours from EXPAND, along with the rates from other studies published in the literature. The fourth line down is the single institution data from my center, pre-EXPAND, 31.2%. Despite the extended criteria nature of the donor hearts, PGD rates in EXPAND were similar to or lower than those in other published studies looking at lower-risk standard criteria donor hearts.

Before reviewing the survival results in the EXPAND trial, it's important to understand how we look at long-term mortality. Most of the patients undergoing transplantation are not healthy. The majority are on VADs, which adds another layer of complexity to their risk factors. Once they undergo a heart transplant, they are on immunosuppressive therapy for the rest of their lives.

Mortality in the immediate post-transplant period for the first 30 to 90 days is very likely related either to the invasive and extensive transplant surgery or the cardiac graft itself.

Preservation technologies have the greatest impact on the early post-transplant course, so the rate of early survival and PGD are the most useful measures.

However, after the initial post-transplant period, heart transplant recipients are subjected to competing risk factors for non-cardiac causes of death. Therefore, in order to assess long-term outcomes for a preservation technology, cardiac-related survival is a clinically appropriate endpoint. With that background, let's discuss survival results in EXPAND.

This Kaplan-Meier analysis shows all-cause and cardiac-related survival for Heart EXPAND patients through 24 months. At 6 months, all-cause survival was 88%. At 12 months, 84%. The 1-year cardiac graft-related survival rate in EXPAND was 95%. As I

mentioned, cardiac graft-related survival directly assesses mortality that could be related to the heart preservation itself. Let me explain.

Of the deaths that occurred in EXPAND, four were reported and adjudicated as cardiac graft related. Four others, representing 5% of the absolute mortality, were due to recipient factors not related to the transplanted heart, in general, or the use of the OCS System. One patient died on Day 29 due to preexisting advanced liver cirrhosis. One patient died on Day 80 likely due to undiagnosed parenchymal lung disease leading to postoperative respiratory failure. One patient died on Day 212 due to reoccurring extracardiac amyloidosis with refractory GI bleeding. And one patient died from a car accident 14 months after transplant.

The primary safety endpoint was the number of heart graft-related SAEs through 30 days. PGD was adjudicated by the independent medical monitor based on pre-specified ISHLT definitions. The incidence moderate or severe PGD was 14.7%, and one patient had primary graft failure requiring retransplantation. The mean number of primary endpoint events per patient was 0.2. The full list of all SAEs was provided in the Sponsor's briefing document and reflect the type of events that commonly occur following transplantation.

The FDA approved a continued access protocol for the EXPAND trial. The CAP used an identical clinical protocol to the one used in EXPAND. These results provide further support for the safety and effectiveness of the OCS Heart System for extended criteria donors.

The EXPAND CAP study is still enrolling. Forty-one patients had at least 30-day follow-up and 6-month data was available for 26 patients. Ninety-one percent of donor hearts were utilized for transplantation with a hundred percent 30-day survival. And with similar demographics and risk factors to patients in EXPAND, there's been only one case of severe PGD in the CAP.

A poolability analysis of EXPAND and the CAP data was completed and determined that the data could be pooled in order to evaluate the totality of the results. The pooled EXPAND and CAP data were excellent from both safety and effectiveness perspectives. The utilization rate of extended criteria hearts was 84% with a 97% 30-day all-cause survival and an 8% incidence of severe PGD.

In the combined analysis, overall survival was high at 6 and 12 months at 92 and 87%, respectively. These are comparable to transplant outcomes in the United States with standard criteria hearts. Cardiac-related survival was even higher at 96% through 12 months.

To conclude, the data from EXPAND and CAP provide substantial evidence of the safety and effectiveness of the OCS Heart System.

The primary effectiveness endpoint in EXPAND was met.

In EXPAND and CAP, 84% of the donor hearts were utilized and transplanted. These hearts were refused for transplant an average of 60 times before being accepted for transplant with the OCS.

Reassuringly, the rate of severe PGD in EXPAND and CAP was 8%, which is well below the rates reported in the literature, with no unexpected safety findings.

All-cause survival outcomes were similar to the national average with cold storage, and cardiac-related survival was high.

I would like to take a few minutes to speak more personally about what the OCS means for our patients. For decades we've talked about heart transplant being supply limited, that there just aren't enough good donors. But we need to retrain ourselves. What EXPAND shows us is that there are plenty of good donors. We just need to use the technology available to expand the donor pool for each of our recipients. With the use of OCS for extended criteria donors now, and with DCD donors in the future, we will have

access to a significantly greater suitable donor pool. Thus, we could not only transplant everyone on the wait list, but also expand the wait list to include many patients who have never had access to transplant.

Thank you. And I'll now turn the presentation over to Dr. Hassanein.

DR. HASSANEIN: Thank you, Dr. Schroder.

I will now review the high-level data from our old PROCEED II trial, specifically focusing on the issues raised by the FDA and why these issues are less relevant to this PMA and indications before you today.

By way of background, PROCEED II was the first trial of any ex vivo organ perfusion technology in the United States. FDA strongly advised TransMedics to model the PROCEED II trial on the 2001 Celsior heart perseveration solution study. PROCEED was designed to demonstrate that OCS Heart System was non-inferior to cold storage for preservation of standard criteria donor hearts. Patients were followed for 30 days post-transplant, which was the same follow-up period for the Celsior trial.

The PROCEED trial met its primary effectiveness and safety endpoints, and the results were published in the *Lancet* in 2015.

Nearly 2 years after the trial was concluded, an unplanned post hoc analysis of long-term survival data obtained from the UNOS registry revealed increased overall mortality in the OCS arm compared to control. We took this finding very seriously and performed several analyses to better understand this data. We will share with you the findings in the upcoming slides.

We are proud of the PROCEED trial and stand by the results achieved. However, we do not think PROCEED results play a major role in assessing the OCS for the PMA indication being discussed today, and here is why. This was an older, smaller sample size trial designed for a completely different indication. Importantly, there are substantial

differences in the donor populations as well as the device design and the clinical use model between PROCEED II and EXPAND trials. Let me summarize the key differences.

EXPAND and CAP study donor hearts with one or more risk factors make them seldom utilized for heart transplants in the United States. This was clearly demonstrated by the UNOS match run refusal data on this slide. EXPAND and CAP had a significantly higher number of match run refusals compared to PROCEED, which had the same median number of match run refusals to the UNOS national database for standard criteria heart transplants. In addition, EXPAND used a second-generation OCS device that had two major changes to the device design, as well as the incorporation of a unified myocardial protection technique during implantation post-OCS use.

Therefore, the results from EXPAND and CAP directly support the proposed indication for extended criteria donor hearts and are the pivotal data for consideration in this PMA, not the PROCEED II.

Now let me address the long-term survival findings highlighted by FDA. The unplanned post hoc long-term survival analysis of the U.S. subset of the patients in PROCEED II through 5 years shows lower overall survival for the OCS group compared to the control arm. TransMedics took this observation very seriously and we carefully performed a cause-of-death analysis to investigate the cause of this apparent survival difference. The rates of cardiac-related survival between the two groups were similar through 5 years. This indicated that the differences in all-cause mortality between the groups were unlikely related to the transplanted hearts or the preservation method.

Second, we used all causes of death that were provided in the UNOS database, combined with the adjudicated causes of death during the initial post-transplant period, to discern any meaningful correlation.

In the first 60 days post-transplant there were eight deaths, six in the OCS group and

two in control. There was one death in each group due to primary graft dysfunction. All other deaths in the OCS and control groups were not related to the preservation method. In fact, three of the five non-preservation related deaths in the OCS group had reported excellent cardiac function post-transplant, as shown on the slide. The other two non-preservation related deaths in the OCS group were related to hyperacute rejection and disseminated intravascular coagulopathy due to severe protamine reaction in an already sensitized patient. There was one additional non-preservation related death in the control group that was due to subarachnoid hemorrhage.

The early causes of death unequivocally refute any suggestion that the OCS may have been the direct cause of these deaths. Importantly, cardiac-related mortality that could be possibly related to the preservation was balanced between the two groups.

Beyond 60 days, excess mortality in the OCS group was generally related to late infections that occurred between 6 months and 2 years after transplant. These are highly unlikely to be attributed to the OCS preservation. We reached this conclusion because we went back and reviewed the immediate post-transplant data on these specific patients. None of these patients had any infection adverse event or serious adverse event throughout the 30-day post-transplant period.

Moreover, since the OCS is approved and has been used broadly outside of the United States, we also conducted a systematic review of the published literature to put the results of PROCEED II in the context of the global clinical experience with the OCS Heart System. We specifically assessed published short- and long-term heart transplant outcome data from the OCS that was compared to cold storage. To date, published peer-reviewed data from several different centers in different countries show consistently favorable and short- and long-term outcomes up to 5 years post-transplant, regardless of whether the OCS System was used to preserve standard criteria, extended criteria, or DCD donor hearts.

In summary, we strongly believe that the fact that cardiac graft-related mortality in PROCEED II was similar between the groups, and these published data on the OCS long-term survival provide additional support for the long-term safety of the OCS Heart System for donor heart preservation.

The imbalance in long-term survival seen in PROCEED was due to non-preservation related causes.

Now I would like to invite Chris Mullin, our independent biostatistical expert, to provide insights into the FDA's post hoc statistical models, which attempted to extrapolate long-term survival in PROCEED and EXPAND.

MR. MULLIN: Thank you, Dr. Hassanein.

My name is Chris Mullin, I'm a statistician with NAMSA, currently serving as director of product development strategy. Today I'd like to go over a few concerns we have regarding FDA's model for long-term survival.

First, just a quick review of the modeling FDA provided in their Executive Summary. FDA's model was developed based on data from 2015 from the PROCEED II trial. This was first used to extrapolate longer-term survival results for PROCEED II and second, to extrapolate longer-term survival results for EXPAND.

I'd like to review some concerns about the underlying assumptions of the model, as well as the empirical results, both of which call into question the validity of the extrapolation.

The model FDA used requires assumptions, and it's not clear if those assumptions are appropriate. In particular, parametric models used by FDA have very strong assumptions regarding the underlying hazard rates.

We have some specific concerns with regards to the piecewise exponential model for long-term survival because the model itself, and the particular cut points were all chosen in

a post hoc fashion. This is a concern because data-driven model choices, including piecewise exponential model cut points, can lead to bias or an inflation of a Type I or a Type II error. The FDA asserts that the cut points in their post hoc model were not data driven. However, they have provided no clinical justification for the cut points they selected, which calls into question the validity of the model.

Finally, if we actually look at how FDA's model fits the data, we find concerns there, as well. This table outlines the differences in estimates between the Kaplan-Meier nonparametric method and FDA's parametric piecewise exponential model. In other words, these differences represent the measure of the inaccuracy of the FDA's model prediction.

Results are shown by row for years post-transplant. The first column of numbers we see is for the OCS Heart group from PROCEED II, where differences between Kaplan-Meier and model estimates at 4 and 5 years are 1.4 and 3.5 percentage points. In the standard of care group, we see even larger discrepancies between Kaplan-Meier estimates and the prediction from the FDA's model, where survival is underestimated by more than eight percentage points at 5 years. This calls into question extrapolations out to 4 or 5 years, the applicability of the model to the EXPAND OCS Heart data at these time points, and of course, extrapolations to later time points.

As Dr. Hassanein will review in a minute substantial significant differences between the trial populations that also call into question the validity of FDA's extrapolations and application of the model to the EXPAND trial.

So in conclusion, the assumptions of FDA's particular choice of model are questionable, and the model does not fit the observed data at late time points. Therefore, this model appears neither valid nor reliable for extrapolation of long-term data in heart transplantation.

Thank you. And I will now turn the presentation back to Dr. Hassanein.

DR. HASSANEIN: Thank you, Chris.

As you have seen from reading the panel briefing materials, and you will see from the FDA's presentation today, TransMedics and the FDA have several meaningful differences of opinion on key aspects of the clinical data. We are concerned that many of the discussion topics posed by the FDA are predicated on incorrect interpretations or significant mischaracterizations of the results and conduct in our trial.

In this section, I will provide TransMedics' positions and data supporting our conclusions on each of the FDA discussion questions posed to the Panel. I'll start with discussion Question 1 on the design and conduct of the EXPAND trial.

Regarding study design, we could not ethically randomize patients to receive extended criteria donor hearts preserved from cold storage, given that the damage caused by cold storage is the primary reason why these hearts are not used today.

Additionally, a concurrent control arm of standard criteria donor hearts preserved with cold storage would be of limited clinical value because heart transplant outcomes have been stable for the past decade, and all outcome data are prospectively collected in the UNOS registry. The UNOS registry data can be used to provide a point of reference for the EXPAND results, as we have done.

We derived our performance goal of 65% for the primary effectiveness endpoint based on published literature rates of primary graft dysfunction and mortality with standard criteria hearts available at the time EXPAND was designed. This was thought to be a reasonable clinical threshold because with the sample size of 75 patients, the actual success rate had to be at least 80%, which is a clinically high bar to meet given the high-risk nature of these donor hearts.

The donor heart inclusion criteria represented risk factors that were defined by U.S. academic clinical experts and not just by TransMedics. Importantly, the comparative

analysis to the UNOS registry strongly and unequivocally supports the fact that EXPAND and CAP donor hearts had significantly more risk factors than hearts transplanted in the United States using cold storage.

In summary, the EXPAND trial is a well-designed, clinically and statistically robust clinical trial. UNOS registry data analysis validated the inclusion criteria used in EXPAND and CAP to be the representative of extended criteria donor hearts in the United States.

Next, let me address the study conduct points. We are very proud of the conduct of the EXPAND trial and have complete confidence in its findings. Unfortunately, we must correct several inaccurate statements that were made by the FDA in their briefing material and in their slides.

The FDA asserts that donor heart inclusion criteria were modified. This is an incorrect characterization. All risk factors for inclusion were listed in the original source documents and were available to investigators at the time of acceptance. Some centers merely listed one criterion in the case report form despite the fact that some donors met multiple criteria because only one was sufficient to enroll a donor in EXPAND. Once this was discovered, TransMedics reviewed the source documents and re-tabulated the criteria for EXPAND donor hearts to provide the complete and accurate picture of the risk factors that were considered by investigators before accepting the donor heart in the EXPAND trial. The FDA is incorrect to assert that eligibility criteria were changed.

The FDA also asserts that site-identified PGDs were changed or reclassified during the adjudication process. Again, this is an incorrect characterization of the adjudication process in EXPAND and the entire purpose of adjudication in clinical trials, in general. By definition, adjudication in clinical trials enables certain site-reported data points to be upgraded or downgraded to ensure consistency across all centers and patients in the trial. The medical monitor, Dr. John Wallwork, who is present on our call today, strictly adhered

to the ISHLT definitions of severe and moderate PGDs, as defined in the trial protocol, and we applied them consistently across all trial patients. He ultimately downgraded two site-reported cases of PGD on the basis of not meeting the ISHLT PGD guidelines. But he also upgraded seven site-reported cases from no PGD to moderate PGD. So in fact, more cases of PGD were actually upgraded by the medical monitor than downgraded.

Importantly, we performed a sensitivity analysis that was included in our panel briefing material which found that there was no impact on the primary effectiveness or safety endpoints regardless of whether the site-determined or adjudicated PGD assessments were used.

In summary, the EXPAND and CAP trials were conducted according to the highest clinical standards, and the adjudication process strictly adhered to the trial protocol.

The second discussion question focuses on the EXPAND inclusion criteria and that they potentially overlap with standard criteria hearts transplanted in the United States and as studied in the old PROCEED II trial.

Analysis of the UNOS registry data unequivocally demonstrates that EXPAND and CAP donor hearts were significantly different from donor hearts transplanted routinely in the United States. For example, EXPAND donors were older, had higher rates of left ventricular hypertrophy, extended cross-clamp times, low ejection fractions, and downtimes of 20 minutes or greater.

Importantly, more than half of the donor hearts in EXPAND had multiple risk factors, which further adds to the complex nature of these donors. And as you see in this slide, there are very few of these donors with multiple risk factors that are transplanted in the United States today on cold storage.

In conclusion, the data clearly show that EXPAND and CAP enrolled donor hearts that are seldom used for transplant in the United States on cold storage.

This conclusion was further validated by the substantial difference in match run refusals for donor hearts used in EXPAND and CAP compared to PROCEED and the UNOS national database. The median number of refusals in PROCEED was identical to the national average of two. EXPAND donor hearts were refused for transplant at 10 times the rate in the national database.

The third discussion question focuses on whether lactate levels are an accurate and reliable measure for assessing the transplantability of donor hearts on the Organ Care System.

As discussed earlier by Dr. Schroder, prior clinical data with standard criteria hearts demonstrated that the OCS lactate levels are sensitive and highly specific biomarkers for graft dysfunction post-transplant. The FDA asserts that lactate is the principal determinant for transplantability on the OCS. This is another complete mischaracterization of the OCS use model, and an oversimplification of the complex decision-making process of accepting a heart for transplant in general.

While the lactate level and overall trend are important guides to manage OCS heart perfusion, they are not the only parameters to determine transplantability. The EXPAND protocol defined three criteria for transplanting an EXPAND donor heart: lactate level and stable lactate trend over time, stable OCS perfusion parameters of aortic pressure and coronary flow, and the clinical judgment of the transplanting surgeon on the overall clinical condition of the donor heart. It is not as simple as saying that any donor heart with a lactate under a particular threshold is transplantable and those above a threshold should be thrown away.

The overall clinical assessment of all variables, as well as the medical status of the recipient, are also critical factors. Importantly, the OCS heart use model for expanding CAP studies have been successfully used internationally with excellent clinical outcomes with

both DBD and DCD donor hearts with more than 1,000 hearts transplanted using OCS worldwide. Our position is that lactate level and lactate trends are useful guides to managing perfusion of donor hearts on the OCS, but lactate must be interpreted in conjunction with other OCS perfusion parameters, as well as clinical judgment, to determine transplantability.

Question 4a focuses on the clinical implications of the survival results in PROCEED II and its impact on EXPAND's results. Chris Mullin has already reviewed the major statistical flaws with the FDA's extrapolated modeling of long-term survival, so I will restrict my discussion to the observed clinical data from the two trials.

In EXPAND and CAP, we observed favorable all-cause and cardiac-related survival through 12 months. As the primary data for this PMA, EXPAND results support the use of the OCS for extended criteria donor hearts. In PROCEED II, we observed an imbalance in non-cardiac related mortality due to late infection and malignancy. However, the cardiac-related mortality was comparable between the OCS and the control groups. Thus, we considered the PROCEED II results to be supportive.

In Question 4b, the FDA asks whether the results of EXPAND indicate a probable benefit of shorter wait times for patients on the waiting list. The goal of the OCS with this PMA and with our ongoing DCD program is to increase the utilization of donor hearts that would likely otherwise be discarded due to limitations of cold storage, thereby allowing more patients to receive a lifesaving heart transplant. Of course, with an increase of donor heart availability, the wait time could be shorter, which would be a greater outcome for patients in need of a heart transplant.

In summary, the favorable long-term overall and cardiac related survival in EXPAND and CAP trials, as well as the significant clinical and public health benefits of increasing the number of transplantable hearts in the United States, support the approval of the OCS

Heart System.

In Question 4c, the FDA suggests that OCS provides suboptimal survival for donor hearts for the only criterion is an anticipated cross-clamp time of 4 hours or more. The data do not support this assessment. We performed a Kaplan-Meier analysis of the 33 patients from EXPAND and CAP who were transplanted with donor hearts meeting that specific criteria. The data clearly show that the overall survival results are comparable to the overall trial results. And importantly, cardiac related survival was a hundred percent. All four deaths were due to non-cardiac causes such as car accident and preexisting liver cirrhosis.

These data clearly show that the OCS Heart System has demonstrated safety and effectiveness for donor hearts with anticipated cross-clamp time of 4 hours or more. This analysis also shows that the OCS offers the significant clinical benefit of enabling long-distance donor heart retrieval and transplantation, which is one of the most significant limitations we face today with cold storage. In fact, UNOS data show that only 16% of hearts transplanted in the U.S. today have a cross-clamp time of more than 4 hours. In contrast, 97% of donor hearts transplanted in EXPAND and CAP had a cross-clamp time of greater than 4 hours.

In Question 5, the FDA will ask you to discuss the potential of preservation related injury that led to donor hearts turned down on OCS. We have observed no clinical evidence of OCS-related injury. The FDA did not consider several important clinical factors when evaluating the pathology results of a donor heart that had been subjected to several clinical conditions that will result in histological findings.

First, the donor hearts studied in EXPAND and CAP were hearts with significant risk factors that made them highly unlikely to be used for transplant or cold storage. Many of these risk factors could contribute to histological findings of the donor hearts. For example,

donor hearts with downtime of greater than or equal to 20 minutes, which represents 31% of the EXPAND and CAP donor population, would have pathological evidence of ischemia reperfusion injury regardless of the OCS use. This happens because of warm ischemic injury during cardiac arrest and the reperfusion injury that occurs after CPR.

Second, brain death, in and of itself, is associated with significant physiological changes that could show as pathological findings that are confounding and would be independent of OCS use.

Third, to our knowledge, there has never been any published or presented clinical or preclinical reports directly or indirectly linking the OCS Heart System to myocardial injury during perfusion.

And finally, the ability of the OCS Heart System to turn down potentially bad extended criteria donor hearts is actually a significant benefit compared to the flying blind cold storage. Specifically, having 84% of these extended criteria hearts that were perfused in OCS successfully transplanted is a significant benefit and advancement in heart transplantation.

Based on the above and the independent pathology reports, we assert that there is no definitive clinical evidence of OCS-related injury of the donor hearts turned down on OCS. The core pathologist of the EXPAND trial, Dr. Jake Demetris, is the Starzl Professor of Transplantation Pathology at the University of Pittsburgh, and he's a world-renowned expert in solid organ transplant pathology. He's here and available should the Panel have any questions on the pathology reports or the FDA's interpretations of the findings.

Question 6 asked whether the donor hearts' inclusion criteria used in EXPAND identify a reasonable set of extended criteria that define hearts not routinely used for transplantation after cold static storage. As we have shown previously, based on UNOS data analysis and match run refusals, we are confident that the EXPAND and CAP trial

enrolled donor hearts that are seldomly used for transplantation in the United States with cold storage.

FDA Question 7 asks about the overall benefit-risk of the OCS Heart System. Dr. Shah will be addressing this more fully in his presentation, but I want to discuss one specific point in the FDA's question.

FDA asserts that the turndown rate for hearts preserved in the OCS is high. TransMedics, and now our clinical expert, have arrived at the complete opposite conclusion. In EXPAND and CAP, the utilization rate of extended criteria hearts was 84%. We think this is a remarkable result given that these hearts were rejected for transplant an average of 60 times prior to transplant in our studies, and the vast majority would likely have gone unused if it was not for the use of the OCS.

And when we look at the profile of the 22 extended criteria hearts that were turned down after OCS assessment, the average number of 72 refusals was even higher than the overall trial population and more than half had multiple risk factors indicating that they may have been unsuitable for transplant altogether. The 84% utilization rate from extended criteria donor hearts achieved in EXPAND and CAP is a significant clinical and public health benefit of the OCS to increase heart transplant procedures in the United States.

I will address Question 8 in the next section on our post-approval study. Now, I would like to take a few moments to review our OCS Heart training and post-approval programs.

As a clinically driven organization, training and support for our clinical users is paramount. TransMedics has a dedicated clinical training facility equipped with the latest surgical and diagnostic equipment to replicate the organ retrieval environment. To date, we have conducted training in our facility for more than 90 global transplant centers with more than 400 healthcare professionals trained on our three OCS products.

Our training program is multifaceted. It includes both classroom style as well as wet lab training sessions to provide hands-on surgical training on OCS Heart simulation, management, and troubleshooting. Our clinical training program has three key components that have been refined throughout the years based on our large and growing clinical experience worldwide.

First, every new clinical center must undergo a 2-day hands-on clinical training program at our training facility. This includes full surgical wet lab training on instrumentation, management, and assessment of the donor organ on the Organ Care System. In addition, it covers troubleshooting scenarios and clinical lessons learned from real OCS clinical cases in the field.

Second, we also have a 24 by 7 phone and text messaging hotline to assist and address questions from users as needed during the use of the OCS System.

Finally, we have developed a proprietary OCS support software application that contains step-by-step instructions and training videos to serve as an additional reference to our clinical users.

Now let me summarize our post-approval program and directly address FDA's Question 8 related to the selection of the performance goal. We are planning for a two-part post-approval program that is clinically driven and statistically sound.

First, a new enrollment patient registry to collect additional data on the use of the OCS Heart System in a real-world setting. We are planning to enroll 175 new patients in a prospective heart transplant registry. The primary endpoint is 12-month cardiac related survival to minimize the confounding clinical variables on the clinical outcome. Our proposed performance goal is 86%. The FDA has noted a concern with this performance goal because the observed cardiac related survival in EXPAND was 95%.

However, it is important to emphasize that the statistical test is based on the lower

bound of the confidence interval, not on the point estimate. To meet this performance goal we have to assume an observed 93% cardiac related survival in the study at 1 year. Therefore, our proposed performance goal is clinically and statistically justified. We will follow all patients up to 5 years through UNOS registry data for patients and graft survival.

The second component of our post-approval program will involve follow-up of EXPAND patients for up to 5 years using the UNOS database.

Thank you. And now let me turn to Dr. Shah to conclude our presentation.

DR. SHAH: Well, thank you. I'm Ashish Shah, Professor of Cardiac Surgery at Vanderbilt University Medical Center. I served as a principal investigator in the EXPAND trial and I'm pleased to share my clinical perspectives on the OCS Heart System.

We've witnessed significant clinical advancements in heart failure management over the last two decades. On the other hand we've essentially relied on cold storage techniques over the last 40 years and as you've heard, this has significantly limited the number of transplants that can be performed.

As we discussed today, TransMedics is proposing the following indication for the OCS Heart System. The current proposal focuses on extended criteria hearts, the same types of donor hearts studied in EXPAND and CAP. These are donor hearts that are seldomly used for transplant using cold storage due to clinical concerns about ischemic injury, the need for additional optimization, and ultimately, primary graft dysfunction.

As was previously reviewed by other presenters, these are hearts that are not typically used today. Donor hearts in the EXPAND and CAP trial had significantly more risk factors than standard criteria donor hearts used nationally, and were rejected 60 times on average before being accepted by an EXPAND or CAP trial center.

Combining EXPAND and CAP, 84% of donor hearts were utilized. Therefore, it follows that by allowing for greater use of extended criteria donor hearts we could

potentially double the number of heart transplants performed in the U.S. each year. Frankly, there is no other plausible mechanism to increase heart transplantation this significantly. Not only is this exciting for the field and for surgeons like myself, but it is life saving for these desperate patients whose only real option is transplant. I sincerely believe this is the future of heart transplantation.

With OCS we no longer need to fly blind with a heart sitting in an ice cooler. With OCS we now have the ability to continuously monitor the health of the heart the entire way, from the donor to the recipient. With OCS we can optimize hearts ex vivo with additional clinical assessment tools that facilitate clinical decision making. And with OCS we can now utilize hearts that would likely not be used today.

The FDA is asking the Panel to discuss the clinical implications of the EXPAND results. The all-cause survival through the first year in EXPAND and CAP trials was comparable to the national average with standard criteria donors. And cardiac-related survival was very high.

Another way to contextualize these results is to compare survival in EXPAND to the survival of patients on the heart transplant waiting list. And as you can see here, survival at 9 months in EXPAND, as shown in red, was associated with an absolute improvement of 10 percentage points as compared to wait list survival, shown in blue. These data clearly show the OCS would provide patients with a meaningful long-term survival benefit, not only for those currently on the waiting list, but those who aren't able to get on.

The OCS heart technology is the advancement we need in organ preservation, it resulted in distant procurement of donor hearts that couldn't be achieved with cold storage. The mean cross-clamp time for distant procurements in the EXPAND trial was a little over 7 hours compared to 3.2 hours with cold storage. And with the OCS these same donor hearts could be transported on average more than 900 miles to reach the recipient.

This distance is not possible with cold storage. According to UNOS, 94% of hearts on cold storage were limited to a range of less than 500 miles.

For the first time the OCS technology may enable national sharing of donor hearts, allowing for a patient in need of a transplant in Seattle to receive a heart from a donor in Anchorage or even crossing the ocean from Hawaii to Los Angeles. In fact, the distances you see on this map have already been achieved with the OCS Heart System.

For example, one heart from a 38-year-old donor who died of a cerebrovascular hemorrhage was more than a thousand miles away from the recipient hospital. This donor heart was turned down 327 times by other transplant centers before being accepted by an EXPAND site. The heart was resuscitated, preserved, and transported on the OCS to a Tall (ph.) recipient, blood type O with non-ischemic cardiomyopathy. This was a Status 1A patient on an LVAD waiting for nearly 1 year prior to receiving a heart in the EXPAND study. This patient was transplanted successfully, discharged within 2 weeks, and is doing well 4 years after the transplant. If not for the OCS, the heart that saved this patient's life would almost certainly have been discarded and the recipient may not be alive today.

Today we perform about 3,600 heart transplants a year with standard criteria donors using cold storage. Using the data from EXPAND, I would like to show you what approval of the OCS could mean for the field of heart transplantation and importantly, for patients.

Approval of the OCS Heart for extended criteria donors could significantly increase the total number of heart transplants performed in the U.S. This would offer the possibility of lifesaving heart transplants to thousands of patients on the waiting list, as well as patients who may not be considered for transplant today due to the severe scarcity of donor hearts.

This technology has a potential we didn't even consider possible a few years ago, the ability to transplant donor hearts after circulatory death, or DCD hearts. The Sponsor's

pivotal U.S. study is ongoing, but more than 230 DCD hearts have already been transplanted on this device globally. This is why approval of this technology is so important. Our own experience at Vanderbilt with the OCS System, both in EXPAND and the DCD trial, has affirmed my belief that this is the future of heart transplantation.

Thank you for your attention. Now let me turn the podium back to Dr. Hassanein for questions.

DR. LANGE: Great. I'd like to thank the Sponsor's representatives for their presentation, and at this particular time this gives the Panel the opportunity to ask clarifying questions to the Sponsor. And this portion will end no later than 11:15 Central Time.

So with that, let me open it up to the Panel for clarifying questions. If you'll raise your hand, I'll acknowledge you. Dr. Yuh, Dr. Allen, Dr. Connor, Dr. Blakenship, and Dr. Moon.

DR. YUH: Thank you very much, that was a very well-organized presentation. I have two questions relatively straightforward. One, was the duration of OCS support looked at as a parameter towards impact on, a possible impact on primary endpoints?

And secondly, I noticed -- and if I'm incorrect, please correct me -- that del Nido solution was used as the cardioplegia agent in your study, and was there any consideration given that that might have a positive confounding impact on your results?

DR. HASSANEIN: Thank you, Dr. Yuh. Waleed Hassanein, TransMedics.

Relating to the first question, we've looked at the total cross-clamp time as a potential factor for the primary effectiveness endpoint and we did not see significant difference all the way up to greater than 7 hours, but we did not look specifically at just the OCS perfusion portion of that. We just looked at the total cross-clamp time.

Related to the second question, which is the del Nido, the del Nido was nothing but

to standardize the cardioplegia for this trial. We learned from the PROCEED trial that there was heterogeneous cardioplegia used and we wanted to just standardize this to something that is readily available here in the United States, but we did not look at the cardioplegia as a factor in the outcome for this trial.

DR. YUH: Thank you.

DR. LANGE: Great. Dr. Connor, Dr. Jason Connor.

DR. CONNOR: Jason Connor here.

So you had said multiple times and throughout how your KOL (ph.) said it was unethical to run a randomized trial for EXPAND. So I was wondering (a) like if you have the names of the people who said that and (b) did you have anyone on your steering committee, or however that worked, that was encouraging you to run an RCT and what fraction it was? You just said "they," but you didn't say was it five to four or was it 10 to 1.

And then given that you didn't run an RCT, did you consider doing a decent size animal trial where maybe you could look at cold storage for 7-8 hours versus your device in cows, pigs, dogs, so that we could get reliable RCT data that way for long-term viability?

DR. HASSANEIN: Thank you, Dr. Connor. Waleed Hassanein, TransMedics.

So the names of the esteemed heart transplant and heart failure cardiology experts that literally defined that criteria, as well as the direction of the trial design, were Dr. John Kobashigawa, Dr. Donna Mancini, Dr. Abbas Ardehali, Dr. Yoshifumi Naka, Dr. Frank Pagani, Dr. Joseph Rogers, Dr. Ed Soltesz, Dr. Randy Starling, Dr. Jake Schroder, Dr. Carmelo Milano, Dr. Pete Hansen, Fardad Esmailian, all leading heart failure cardiologists and transplant surgeons.

You know, I don't have the exact count, but remembering out of memory it was almost unanimous that everybody said we could not randomize, and some actually were more vocal to say even if they clinically would welcome the randomization process they

were very concerned about the conduct of the trial related to knowing that a donor that is going to be 5 or 6 hours away to be randomized to ice. And some even brought up the issue that the IRB in their institution will not support it.

Related to the second question, unfortunately, we did not study this particular question in animals because at this time, Dr. Connor, we already are using the OCS outside of the -- I'm sorry, we're using the OCS Heart outside of the U.S. in clinical transplants, transplanting extended criteria hearts for at least at a couple of years, and the outcomes were great, the early reports were fantastic, some even were published. So we did not look at trying to do that with cold storage.

The reason why we didn't do that is our clinical belief that the primary reason why these hearts are not transplanted is the fact of the cold storage limitation, whether it's ischemic injury, the lack of assessment, the lack of resuscitative capabilities that don't exist in cold storage. That's why we didn't want to do that in animal, because we felt that it wouldn't provide us any meaningful data to do that.

DR. LANGE: Great. Dr. Connor, did that answer your question, before I move on?

DR. CONNOR: Yes, thank you.

DR. LANGE: So I've got -- if I've not called your name and you did raise your hand, but I've got Dr. Allen, Dr. Blankenship, Dr. Moon, Dr. O'Connor, and Dr. Cigarroa. And then Dr. Jarvis and then Dr. Katz.

So Dr. Allen.

DR. ALLEN: Yeah. And I want to congratulate TransMedics, that was a very nice and concise presentation. I really have just one question. It was either slide 51 or 52 looking at cardiac survival versus overall survival between EXPAND and CAP, and while between those trials the cardiac survival was very similar, but your overall survival was quite a bit better in your later CAP trial compared to EXPAND. What happened there, and I never saw any -- you

hypothesize something was done different, was it just a learning curve of how to manage these patients? But what were you doing different that -- or was it just dumb luck?

DR. HASSANEIN: Thank you, Dr. Allen. Waleed Hassanein, TransMedics.

We haven't done anything different in the CAP trial compared to EXPAND. It's the same sites. Yes, there was one center that contributed to that, but we've done poolability analysis and the data was proven statistically that it's poolable. One can attribute that to experience. The sites that were enrolling in EXPAND have enrolled quite a bit of cases in -- I'm sorry, in the CAP -- have been experienced sites, one of the most experienced centers of heart transplantation in the U.S.

Can I please get the poolability analysis for EXPAND and CAP, please? Slide.

So that's the only thing we can attribute that to. But again, we looked at poolability. We made sure that poolability is appropriate, it's poolable. And for some reason the slides are not showing yet, but it's in the panel briefing. Here it is.

DR. LANGE: And so yeah, if you can't get it now, Dr. Hassanein, when it comes up we'll show it back up, okay?

DR. HASSANEIN: Great, thank you. Thank you. These are the results of the poolability analysis to make sure that the data is poolable between EXPAND and CAP.

DR. ALLEN: Thank you.

DR. HASSANEIN: Thank you, Dr. Allen.

DR. LANGE: Dr. Blankenship.

DR. BLANKENSHIP: Thank you for the presentation. One of the most convincing arguments that the hearts in EXPAND were different than, say, standard of care hearts were the turndowns, and Dr. Shah mentioned one heart was turned down 327 times, so I think that's more than the number of heart transplant centers. So for those of us not in the heart transplant world, could you tell us what constitutes a turndown and what does it mean

when a heart is turned down 60 times? Is that 60 transplant centers are offered that heart and turn it down?

DR. HASSANEIN: Thank you, Dr. Blankenship. Waleed Hassanein, TransMedics.

A match run turndown is not necessarily based on the number of centers, it's a combination of number of centers and number of patients listed at that institution. So for example, Center A would turn down a heart for their entire list and that may be 10 patients, maybe three patients, it could be one patient that matches, so that's the aggregate match run refusals is what is represented here.

DR. LANGE: Great. Dr. Blankenship, did that answer your question?

DR. BLANKENSHIP: Yes, thank you very much.

DR. HASSANEIN: Thank you.

DR. LANGE: Dr. Moon.

DR. MOON: Yeah, I just wanted a little clarification. In the presentation they said the donor hearts were refused by other centers 60 times. In Dr. Shah's case report he said it was 327 centers. That's more centers than there are overall. How did you guys come up with these numbers?

DR. HASSANEIN: Sure. Again, Dr. Moon, thank you for the question. Waleed Hassanein, TransMedics.

The match run data is not the number of centers' refusal, it's a combination of number of centers and number of patients listed on their transplant waiting list at these institutions. So the combination of both, that's what represents the match run refusal.

DR. MOON: Okay.

DR. HASSANEIN: Again, the similar example that -- the one that I gave to Dr. Blankenship. A center may have five or six or one patient that matches that potential donor and if they turn it down for all their waiting list patients, it would count for each

patient that's listed on their waiting list as a refusal. So that's what aggregates up to 300-plus refusals.

DR. MOON: Okay, because --

(Cross-talk.)

DR. HASSANEIN: I'm sorry to interrupt, Dr. Moon, but the one point I want to show in the upcoming slide is regardless of was it patients, is it center, we looked at the match run refusals, and in this slide it shows it for all of our heart trials that we're reporting on today. EXPAND clearly shows significant match run refusals for those donor hearts compared to both PROCEED and the national average, and you can see that PROCEED and the national average, based on the UNOS database, is identical. So regardless if it's number of centers, number of patients, which we know they're aggregate, it shows a tenfold increase in the refusals, match run refusals, for these donor hearts.

DR. LANGE: So Dr. Hassanein, perhaps at the break someone can actually provide that by the number of centers that refused --

(Cross-talk.)

DR. HASSANEIN: Sure. We'll try to do that absolutely after the break.

DR. LANGE: Terrific.

Dr. O'Connor.

DR. O'CONNOR: Yes, thank you. And thank you for the clear presentation.

Dr. Hassanein, is it your belief that OCS offers no advantage versus cold storage in standard criteria hearts?

DR. HASSANEIN: Dr. O'Connor, thank you for the question. Waleed Hassanein, TransMedics.

Dr. O'Connor, our belief -- I'll give you an answer that is half data driven, half belief driven. Our belief is the OCS would significantly benefit heart transplantation on any type

of donor hearts that is preserved in the OCS. However, I have to -- you know, I'm a cardiac surgeon in training before TransMedics, so I have to look at the data. What the data shows, that clearly we demonstrated that benefit in the EXPAND and CAP population. There is a question about long-term survival in PROCEED, we take full -- you know, we stand by the results. However, this is an older trial, smaller sample size, the indication and the selection were very different 11-12 years ago, and it's a completely different device and completely different use model. That may be the nucleus of your question, but what we are proposing is an indication that matches our results from EXPAND and it is agnostic of what type of heart it shows. It is matching the results that we've proven in EXPAND and CAP.

DR. O'CONNOR: And along those lines, in the EXPAND, the patients who had cross-clamp times greater than 4 hours and a risk factor, I think, which comprises about 17% had similar outcomes to the overall population or the population that was not in that subset.

DR. HASSANEIN: Dr. O'Connor, can you please clarify the question?

DR. O'CONNOR: The patients that had a cross-clamp time of greater than 4 hours and a risk factor.

DR. HASSANEIN: Right.

DR. O'CONNOR: The 17% of your population. Were their outcomes the same as those that did not meet that specific --

(Cross-talk.)

DR. HASSANEIN: Yes. The outcomes were the same and as we showed in the presentation, when we only focused on the cross-clamp of 4 hours or more, which is a single criterion, the outcomes were presented in the presentation and showed clearly that cardiac related survival was a hundred percent and all the mortality that occurred in that subgroup was all non-cardiac related.

DR. O'CONNOR: Thank you.

DR. HASSANEIN: Thank you.

DR. O'CONNOR: Thank you, Dr. Lange.

DR. LANGE: Yeah. So Dr. Hassanein, I think if I could expand on what Dr. O'Connor is saying, those are the 33 of the 116 patients, and if you could show the similar data for those, for the other patients, as well.

DR. HASSANEIN: Yes. Dr. Lange, can we show that after the break?

DR. LANGE: Yes, sir.

DR. HASSANEIN: Data for all the other patients that had a cross-clamp of 4 hours or more.

DR. LANGE: Yeah, with the risk factors. Yes.

DR. HASSANEIN: We'll do that. Thank you.

DR. LANGE: I've got Dr. Cigarroa, Mr. Jarvis, and Dr. Katz.

Is there anybody else that I've missed so far? And then Dr. Selzman and Bonde and Bram, Dr. Zuckerman.

Okay, so Dr. Cigarroa.

DR. CIGARROA: Good morning and thank you for the presentation. This is Joaquin Cigarroa.

I'd like some clarification on the process for adjudication. Was there a single individual reviewing and adjudicating or did you have a committee?

DR. HASSANEIN: Dr. Cigarroa, thank you for the question. Waleed Hassanein, TransMedics.

For this particular trial we had a single medical monitor, which is Professor John Wallwork. But for other, you know, the newer trials, we always now have a CEC committee of a minimum of three people. But for EXPAND and CAP, it was a single medical monitor that adjudicated all the adverse events in a blinded fashion.

DR. CIGARROA: Thank you for that clarification.

DR. LANGE: Mr. Jarvis.

MR. JARVIS: Yeah, hi. Gary Jarvis.

Well, I'd like to thank the company for their excellent presentation, but what I was wondering, all this data that's up there, did you happen to compare any of this data to any of the national databases that are out there, as well?

DR. HASSANEIN: You mean UNOS database or SRTR database?

MR. JARVIS: Yes, the SRTR and others.

DR. HASSANEIN: Thank you, Mr. Jarvis. Waleed Hassanein, TransMedics.

So for the longest time we actually approached UNOS formally and asked them to perform a propensity match analysis because we were focusing on how different our risk factors are compared to the national average. UNOS came back and said they're unable to do that because of the significant high-risk factors in EXPAND.

More recently, when we saw the draft FDA questions, we were concerned that FDA is raising the issue that there may be a reduction in the outcome of survival with the OCS. So we went back and we compared un-risk adjusted, no risk adjustment whatsoever for the same period of the trial with the UNOS database. We've always presented to FDA the analysis or, I apologize, the benchmarking on an annual basis, but this time we did a formal Kaplan-Meier analysis comparing the outcome of EXPAND and CAP to the SRTR national database of 10,800 patients that were transplanted in the U.S. using standard criteria hearts in the same time window of EXPAND and CAP.

And I want to disclose that this analysis is a recent analysis that we have not submitted to FDA for their review. However, we felt it is important to be prepared with that analysis to address panel questions.

As you can see here, EXPAND and CAP had similar survival outcomes to the national

standard heart transplant database. Simply stated, we took hearts that had been refused on average 60 times or more and made them successfully transplanted at a rate of 84% with an excellent survival, long-term survival, and excellent primary graft dysfunction rate at 8%, which is one-third the reported average.

We also went back and we said let's look even further and see if we can look at the SRTR data from the centers that actually contributed to the EXPAND and CAP, which is the closest we could get to a concurrent control, and the results were similar. Again, that is a recent analysis that we only conducted after we saw the draft FDA question and we have not had the opportunity to share with the FDA for their review. And as you can see here, that is the same site data comparing outcome from EXPAND and CAP to the SRTR database from heart transplanted, standard criteria hearts at the same trial sites.

DR. LANGE: Thank you, Dr. Hassanein.

I've got Dr. Katz, Dr. Selzman, Dr. Bonde, and Dr. Zuckerman.

So Dr. Katz.

DR. KATZ: So just two brief things, so to help with my understanding. I assume that what was labeled as the ischemic time, that included the time to prep the heart and put it on the system and then to decannulate the heart and do the standard prep for implant. What is about the average time for just preparing the heart to put on the system? Out of curiosity.

DR. HASSANEIN: Thank you, Dr. Katz. Waleed Hassanein, TransMedics.

It's approximately anywhere between 20 to 30 minutes depending on the expertise of the team. We haven't seen it anywhere above that in a very, very long time. That is in the front end, which is really the time from cross-clamp until you get the aorta cannulated and perfused in the OCS. On the back end, it's an average of anywhere between 60 to 90 minutes, which is really the reimplantation time. And in between is the perfusion,

perfusion time on OCS, which is not ischemic.

DR. KATZ: And then one more brief question, if that's okay. Any information about shorter times. So for example, and someone alluded to this a little bit earlier, if you just had a heart that was going to have a two or two and a half hour ischemic period used in the OCS versus cold perfusion, is there any information about that?

DR. HASSANEIN: If I can ask your permission to look into that specifically with the other question and report on it after the break, I would greatly appreciate it.

DR. KATZ: Again, without extra criteria. I'm interested --

(Cross-talk.)

DR. HASSANEIN: Just looking at the total cross-clamp time between 2 and 3 hours or something like that?

DR. KATZ: Correct.

DR. HASSANEIN: Will that work?

DR. KATZ: Exactly.

DR. HASSANEIN: So if I have your permission to do that and look into that and bring the data that I have after break, I would greatly appreciate it.

DR. LANGE: Great. Dr. Hassanein, I'm actually making -- the things that we'll need after the break, I'm making list of them so we can --

(Cross-talk.)

DR. HASSANEIN: Great, great. Thank you.

DR. LANGE: I've got Dr. Selzman, Dr. Bonde, Dr. Zuckerman, Dr. Cigarroa again.

DR. SELZMAN: Thank you. Craig Selzman.

So a number of questions, but three that are directly related to understanding EXPAND a little bit better. So the issue is the long cross-clamp and about 6 hours total out-of-body time. Not to make fun of our kidney transplant colleagues that want to do all their

stuff at 7:00 in the morning, if we -- do you have data that's not just time, but just actually travel distance, because is the time just related to people going a little bit slower or is it actually because we're traveling to Hawaii or Puerto Rico or other places? That's my first question.

DR. HASSANEIN: So yes, we actually looked into that and the first slide here represents the actual time, donor to recipient, but also distance, donor to recipient, and how do they match to the UNOS database. So it's not a matter of slowness, it's actually a matter of distance retrieval. And I think the slide that Dr. Shah demonstrated in his section, these are all really cases from EXPAND and CAP and again, for disclosure, there's one recent case in the CAP that occurred literally last week, which is the one from Honolulu to LA. But all of the rest of the distance here were presented in our analysis to the FDA through the EXPAND and CAP. So it's the former. It's the former, Dr. Selzman, not the latter.

DR. SELZMAN: It would be good to have a range, that's helpful.

DR. HASSANEIN: Sure.

DR. SELZMAN: A second question. You know, you mentioned that most of the turndowns is a multifactorial decision process, but actually your data is really all about lactate, I think eight of the nine were all about lactate, and then you referenced -- I tried to find this article and couldn't find it because I think it was just an abstract to the ISHLT, this Hamed reference. So there really is no science attached to the lactate, the best that we can tell. And this might be relevant to your post-approval study.

How are you going to more objectively assess heart function? You know, I think the one case that you said that didn't convert well back into a sinus rhythm, I think that's a very objective piece. But looking at a heart beating ex vivo and saying it looks better or not better, do you have plans to have more objective methods to assess function? And this is actually not recognizing that there could be other biomarkers that could be used, as well.

DR. HASSANEIN: Sure. Thank you, Dr. Selzman. Waleed Hassanein, TransMedics.

Actually, I want to clarify one important fact. In the OCS, the heart is perfused antegrade through the aortic root into the coronary sinus, so the heart us unloaded, so the only functional assessment we have in that is just the contractility of the beating heart in an empty state, so it's not a loaded condition. That's number one.

But the other parameters that would rely on is exactly what you highlighted, the return to sinus rhythm, the contractility of the RV, the contractility of the LV, and the lactate trend. So to your early point of the question, yes, lactate is a key indicator to -- as a sign of ischemia, as a sign of the anaerobic metabolism. So that's the first red flag. From there you need to assess that or interpret that based on perfusion parameters.

DR. SELZMAN: Okay.

DR. HASSANEIN: For example, you have to look at aortic pressure and coronary flow and then ultimately, the clinical judgment is in everything you highlighted and I reiterated.

DR. SELZMAN: Okay. I'm sorry, just because I want to get this one last question in.

DR. HASSANEIN: Please, please.

DR. SELZMAN: So if you were to take your PROCEED population --

DR. HASSANEIN: Um-hum.

DR. SELZMAN: -- and I understand the reluctance to use PROCEED to inform us too much about EXPAND, but if you were to identify patients in PROCEED that met the inclusion criteria for EXPAND, did you do that analysis? Do you have long-term data on those PROCEED patients? So were there patients in PROCEED that would have been exactly the patients of the EXPAND population? I understand that they're different.

DR. HASSANEIN: Yeah.

DR. SELZMAN: And if so, what were the outcomes of those patients?

DR. HASSANEIN: If you allow me to look into that specific question and report back

after lunch, I would greatly appreciate it. But from where I sit, I don't believe that we had anybody in PROCEED that would match the extended criteria nature of EXPAND except maybe for cross-clamp time, but please allow me the opportunity to review the data with the team and report back after lunch.

DR. SELZMAN: But that's the thing, right, that's your number one. That's your number one piece, right? There's no reason really for us to think that left ventricular hypertrophy is going to get better on a pump, right? So the key indication is still going to be the length of time, so having that additional data might be important.

DR. HASSANEIN: Sure, we'll look into that. But I want to highlight the LV point is our ability to protect the LVH better by minimizing ischemic damage on LVH heart. We're not saying that it will get better on the OCS. Just to clarify.

DR. LANGE: I've got Dr. Bonde, Dr. Zuckerman, and Dr. Cigarroa.

DR. BONDE: Thank you for your excellent presentation and certainly, a huge advance in the last five decades of heart transplantation. I have three questions, one is a general question and two are very specific.

The first question is how do you reconcile the new allocation policy now? Then you said that in your trial you had the sick patients, how many of those sick patients now will get downgraded not to be sick as Status 3 or Status 4 now?

The second question has to do with how many specific number of patients require a post-transplant mechanical circulatory support either in the form of ECMO, biventricular assist devices, or an intra-aortic balloon pump or a long duration of inotropes? And this is related to your post-transplant PGD.

DR. HASSANEIN: Um-hum.

DR. BONDE: The third question has to do with the system itself, or the machine itself. How many instances of hearts coming off the cannulas are the systems not working

appropriately? Again, notice so far any combined experience, either due to surgeon error or due to machine error or due to perfusion error, because this will be important when you're looking at 16% to 20% of the hearts being rejected and some of them will also include these because this has implications for the cost. If somebody's flying off, flying back, and then the heart being rejected, so that has got implication for the cost for the center as well as for the recipient.

DR. HASSANEIN: Thank you, Dr. Bonde. Let me address all three questions. Waleed Hassanein, TransMedics.

So relating to the new allocation and the status for the recipient, the EXPAND and CAP actually were conducted with the new allocation scheme, so we don't expect a significant change or shift in the interpretation of the data based on a new allocation. In fact, the long retrieval distances that we highlighted and the ability of the OCS to make these hearts available for transplant is another data-driven testament to that.

Related to the second question, the PGD assessment in the EXPAND and CAP trial followed the 2014 ISHLT guideline to the strict definition. So any PGD 3, which totaled 8%, were all related to mechanical circulatory support or ECMO or intra-aortic balloon pump. So 8% of PGD, as you know, is well below the reported rates of PGD in standard contemporary heart transplant in the United States.

Related to the third part of the question or the third question, to the best of my knowledge, and I will verify that during the break, there has never been a device malfunction or a cannulation failure or anything related to the device that led to a discard of a heart, but I will verify that.

The point about the -- I think you might be asking that question, and please correct me if I'm wrong, related to some references in the FDA material about the disconnection of the --

(Audio feedback.)

DR. HASSANEIN: -- that was primarily done by the retrieval team to unload the RV and that is another sign to Dr. Selzman's earlier question. When you see the RV distended, even in an empty heart, just pumping a liter of coronary flow or so, that's a negative or red flag. So they would unload the RV by disconnecting the cannula, but the heart is continuing to be perfused through the aortic root. But to the best of my knowledge, there has never been any device related or cannula related event that would lead to discarding of these hearts. But allow me 10 seconds to address the other point, the other side of this.

(Cross-talk.)

DR. HASSANEIN: Go ahead. Go ahead, Dr. Lange. I'm sorry.

DR. LANGE: I have two more questions I want to get in.

DR. HASSANEIN: Sure.

DR. LANGE: And so there will be adequate time later.

So Dr. Zuckerman.

DR. ZUCKERMAN: Yes. Thank you, Dr. Lange.

First, Dr. Hassanein, thank you and your team for a very nice presentation. My question is an extension of Dr. Allen's earlier question relating to the proposed PAS. The hundred seventy-five patients is a very large cohort. Can you clarify for the Panel, would all these patients come from new sites? Because Dr. Allen asked some key questions about how to extend this knowledge to new sites and so what percentage would be new sites?

And the second ask is perhaps after the lunch break you could allow Dr. Allen and other Panel members to talk with some of your principal investigators to better understand what are the tricks of the trade that would need to be generalized and studied at new sites. Thank you, if you could respond.

DR. HASSANEIN: Thank you, Dr. Zuckerman, and thank you for the opportunity to

present today. Waleed Hassanein, TransMedics.

Of course, the Panel is more than welcome to talk to our leaders that have done the work, to get their perspective that really determines discretion.

So let me address related to the new sites and the PAS. Let me address the question from one angle first and then I'll come specifically to the PAS. Over the past 4 years or maybe even more, our training program and certification program has been extremely robust and a testament to that -- it's not just my opinion, the fact that we moved from an eight to nine-center, in EXPAND and CAP, to 25-center DCD program, a significant number of new centers, all of which have been performing OCS completely solo, relying on our either 24 by 7 hotline or our training app, provide significant confidence that the training and the support model is mature enough to enable us to enter into the postmarket setting with a strong confidence that the learning curves are not going to be repeated. So that's number one.

Number two, relating to sort of the natural progression. Of course, naturally, we would start with centers that have experience with the OCS, for example, 25 centers already are engaged in the DCD program. There's additional centers from the CAP program that haven't been included yet in the -- or I'm sorry, in the EXPAND program that haven't been included in the DCD program, centers that had experience with PROCEED. So starting naturally with centers that have experience, that makes perfect sense.

But we feel very confident that any new center that has a dedicated heart transplant team that will go through our certification and they have to attend that program. I think our track record points that it's very solid and we were able to replicate that experience across 25 new U.S. heart transplant programs in the DCD trial. And again, our leaders can weigh in from their perspective at the Chairman's discretion.

DR. LANGE: Great. Dr. Zuckerman, does that tangentially answer your question?

DR. ZUCKERMAN: Yes. Perhaps after the lunch break Drs. Schroder and Shah may want to give comments and have back-and-forth with the Panel.

DR. LANGE: Sounds great.

Dr. Cigarroa, I think you probably have the last question before break.

DR. CIGARROA: Thank you. This is Joaquin Cigarroa.

One is a point of clarification and a second is a question. Going back several questions ago, there was a comment about ischemic and non-ischemic time relative to going on to the device and then coming off of the device and being implanted. Is it not true that the entire period involves thresholds of ischemia and just what you're classifying is ischemic or non-ischemic, because lactates are not normal in the graph that you provided for any, it's just threshold of either (a) a trend or (b) an absolute cutoff of five. So the way I see this is that the ischemic time is occurring inclusive of the cardioplegia, it's just a magnitude, so can you comment on that? And then I have one clarifying question.

DR. HASSANEIN: Thank you, Dr. Cigarroa. Waleed Hassanein, TransMedics.

We respectfully see it slightly different. When we talk about cold ischemic time, we talk about the absolute cold ischemic time that occurs pre-OCS perfusion and post-OCS perfusion, which is the instrumentation period and the reimplantation time. In between is the perfusion, OCS perfusion. We don't consider this ischemic time because there's active perfusion of oxygenated blood into the heart. Whether or not the lactate will rise, it could signify a preexisting injury and release of lactate from an injured myocardium. So it's not necessarily a new ischemic injury on OCS, and that's why I said the lactate has to be interpreted carefully, making sure that the aortic pressure and coronary flows are normalized before we really assess the lactate. So that's how we see that.

And when we talk about the total cross-clamp time, it includes all three windows, all three periods, from the minute the aortic cross-clamp is in the donor until aortic cross-

clamp is released in the recipient.

DR. CIGARROA: Okay, so you are assuming that effective coronary blood flow and aortic pressures are equivalent to no ongoing ischemia, as opposed to complete normalization of lactate, is that correct?

DR. HASSANEIN: I'm sorry, Dr. Cigarroa, can you repeat the question?

DR. CIGARROA: So your definition of an absence of ischemia during the period that the donor heart is on OCS is defined by the aortic pressure and coronary blood flow, not necessarily ongoing lactate production.

DR. HASSANEIN: Thank you for the question. In a simplistic fashion, yes. And as I described, however, your point about lactate rising is a valid clinical point. However, I'm addressing that by saying a rising lactate on the OCS may not necessarily mean an active ischemic injury that's occurring right at the moment. It could be a reflection of a previous ischemic damage and this is the reperfusion part of it, of releasing lactate. So yes, in a simplistic fashion, we are saying that given that aortic pressure and flows are adjusted and normalized to near-physiologic levels, that that should limit the ischemic injury on the donor heart.

DR. LANGE: Great. And so I'm going to -- Joaquin, I'm sorry.

Dr. Kwon, did I miss your hand, as well?

DR. KWON: Yes.

DR. LANGE: Okay. So Joaquin, one quick question. And Dr. Kwon, then to you and then we'll take a break. So a quick question.

DR. CIGARROA: Thank you, Dr. Lange.

One more question. Do you plan on utilizing any parameters of myocardial function such as strain, as opposed to ejection fraction in your post-approval study?

DR. HASSANEIN: For post-transplant, post-transplant assessment, we have not

looked into that in detail yet, Dr. Cigarroa, but I appreciate that feedback. We have not looked at other than the traditional heart post-transplant assessment, but we would look into that and we'll review it with our clinical leaders.

DR. LANGE: Thank you.

DR. CIGARROA: Thank you.

DR. LANGE: And I'm sorry. And the last question, Dr. Kwon.

DR. KWON: Thank you. Thank you, Dr. Hassanein and your colleagues, for a very nice presentation. I just want to ask a couple questions.

One is about the 16% non-utilization rate in your EXPAND plus CAP group and your quotation that many of these hearts may not "have been suitable for OHT." And I think just knowing the resource and cost of these, of a dry run and this technology in particular, what are you doing to kind of limit this group?

And I want to mirror the comment that was made previously, is that although you have things like aortic pressures and coronary flows, in a nonfunctional model the clinical assessment is going to be heavily skewed towards the one objective marker you have, which is the lactate, and so how are you going to limit this as you leave the confines of a trial to prevent sort of the indication creep we see in other technologies and just leading to a blowup of cost and resources in donor selection moving forward?

DR. HASSANEIN: Thank you, Dr. Kwon. Waleed Hassanein from TransMedics.

So the 16% turndown rate, our position on them is the reason why we made the conclusion that they probably would have not been transplanted is this even higher rate of match run refusals of 72 and the fact that they have multiple risk factors.

Let me address your question specifically about the dry run and the cost of dry run. We believe that an 84% utilization rate is a very high utilization rate from this donor cohort. It is not the topic of this PMA, but this utilization rate of DCD hearts at 90-91%, we believe

it's a huge win for cardiac transplantation. To defray the cost of the dry run, TransMedics has worked with our users to make sure that we are investing in the program right beside them to make sure that we're not escalating the cost of the procedure. But as you know, and many of the heart transplant experts in this esteemed panel know, dry runs are the nature -- are existing in organ transplant and they're covered by commercial and CMS payers, but I know this is not the purpose of this meeting, but --

DR. LANGE: Dr. Hassanein, I'm sorry. The question he asked is how are you -- are you doing anything currently to limit the group that isn't being used? A yes or no.

DR. HASSANEIN: We're obviously working hard and making sure that people are sticking to -- adhering to the criteria and that's the best we can do at the moment. But we're actually seeing utilization rates actually improving even when we go to the DCD, to -- you know, close to 90-91%. So we hope to continue to see that trend progress and I hope that the concern raised that as you increase the deployment of the OCS, it's not going to result in -- it's not going to backfire. A testament to that is the DCD, we're going to 25 institutions and the utilization rate is even higher from a much different, much more riskier donor pool of DCD. So we hope that that trend continues even in the postmarket setting with the OCS.

DR. LANGE: We'll have additional time in the future. Before we close, I've got six things again to check on, Dr. Hassanein. One is the outcome of individuals that had greater than 4-hour time to perfusion and also risk factors, how those individuals fared compared to others. How many centers actually refused hearts, not just an aggregate. Again, the total cross-clamp time and its relationship to outcome. Distances traveled for these individuals that received OCS. And the analysis of the PROCEED patients who would have met EXPAND criteria and their long-term outcome. And then you're going to see if there was any device malformation or issues related to cannulation failure.

DR. HASSANEIN: Um-hum.

DR. LANGE: So thank you very much for your --

DR. HASSANEIN: Thank you.

DR. LANGE: -- presentation, and your response to the question and the great questions. We're going to take a 10-minute break and we're going to convene promptly at 9:30.

DR. HASSANEIN: Thank you.

DR. LANGE: So if you want to turn your video off, feel free to do so and we'll reconvene in 10 minutes. Thank you.

(Off the record at 11:26 a.m.)

(On the record at 11:37 a.m.)

DR. LANGE: Good, I'll ask the Panel members to resume their video. It's now 11:30 and I'd like to call the meeting back to order.

The FDA will now give their presentation, and I would like to remind the public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except by specific request of the Panel Chair.

The FDA will also have 90 minutes to present and I'll ask the FDA to now begin their presentation. Thank you.

DR. WENTZ: Good morning, my name is Catherine Wentz and I will be starting off the FDA presentation of the TransMedics Organ Care Heart System.

I would like to recognize the team of FDA reviewers across several disciplines who helped with the review of this PMA.

The FDA presenters this morning will include myself, Dr. Xuan Ye, Dr. John Sapirstein, Dr. Andrew Farb, and Fernando Aguel. The material each will be presenting is shown on this slide.

TransMedics has already presented a detailed device description, so FDA will not present any additional device description information.

The proposed indications for use statement, as you see here, reflect a set of conditions that the Sponsor feels defines a donor heart that would generally not be accepted for transplant. FDA notes several challenges with this set of conditions, including inherent subjectivity in determining whether the heart meets several of the criteria -- examples are highlighted on this slide -- and FDA also believes that these characteristics define donor hearts that may significantly overlap with hearts that are currently accepted for standard of care preservation and transplant.

The clinical history of the OCS Heart System includes two clinical studies that will be discussed today. The PROCEED II clinical study was a randomized controlled clinical trial conducted between 2009 and 2013 using standard criteria donor hearts. Donor hearts were randomized 1:1 to preservation with the OCS Heart System or standard of care using cold static preservation. A reasonable assurance of safety and effectiveness for standard criteria donor hearts was not determined.

EXPAND was a single-arm study conducted between 2015 and 2018 with donor hearts that the Sponsor defined as not meeting standard heart criteria. The clinical study protocol for EXPAND was submitted to FDA 6 months prior to the submission of the PMA for PROCEED II, therefore with a presumption of approval for the PROCEED II PMA for standard hearts. The Sponsor designed the EXPAND clinical study to leverage the results of PROCEED II and allow for an expanded indication for use in nonstandard criteria donor hearts.

An EXPAND continued access protocol was approved in 2019 to permit continued use of the OCS Heart System while the PMA was under review. While the CAP study is intended to be an extension of the original EXPAND study, the Sponsor did modify some of

the recipient and donor heart inclusion criteria. Additionally, site selection for the CAP study included the high performing sites from EXPAND, and 59% of CAP subject enrollment was at a single site.

The original EXPAND IDE application included some device design modifications as compared to the device used in the PROCEED II clinical study, which the Sponsor stated reflected minor design changes. These design changes included changing the oxygenator to one with an integrated heat exchanger, and the addition of a second compliance chamber and one-way valve in the circuit tubing after animal studies suggested a more physiologic waveform and improved profusion and lactate uptake which appeared to also reduce heart weight gain. The second compliance chamber was later removed shortly after initial enrollment into EXPAND.

There were a few device design changes that occurred over the early course of the EXPAND clinical study. Before any subjects were enrolled, the Sponsor replaced an off-the-shelf infusion pump with a TransMedics designed solution delivery system to perform the solution delivery functions and support a new automatic aortic pressure mode. Following six OCS-supported hearts, the Sponsor removed the second compliance chamber. Following OCS support for 17 donor hearts, the Sponsor made a software change to increase the upper specification limit for aortic pressure from 80 to 100 mm/Hg. FDA does not believe these changes affected the poolability of the data submitted in support of the device proposed for marketing.

I would like to preface the next couple of slides related to clinical protocol changes and FDA study design considerations by stating that in 2012, Congress revised Section 520(g) of the Food, Drug, and Cosmetic Act as quoted on this slide. In effect, this revision indicated that grounds for disapproving a clinical study or protocol change would primarily need to be directly associated with patient safety. Clinical study design concerns not

directly related to patient safety are to be communicated to the Sponsor as study design considerations and future concerns, usually as an enclosure to the IDE letter.

While FDA strongly recommends that the study design considerations be addressed in a timely manner to improve the scientific validity of a dataset that will be utilized to support a marketing application, the revised Section 520(g) does not require the IDE sponsor to respond to the study design considerations, and the sponsor can complete their study without implementing any of the recommendations.

Over the course of the EXPAND study there were two important protocol changes that led to updated clinical protocol versions. Following nine transplanted subjects, protocol version 1.3 was implemented, which revised the upper specification limits for aortic pressure from 80 to 100 mm/Hg and coronary flow from 800 to 900 mL/min.

Forty-one more subjects were transplanted when protocol version 1.4 was approved. Protocol version 1.4 requested an increase in sample size of 20 subjects from 55 to 75, and also included statistical plan modifications and definition changes with some examples shown on this slide.

At the time that TransMedics submitted these protocol changes, 48 subjects had already been transplanted and a large percentage of the results were available. For example, 46 subjects had 30-day endpoint data. There were at least six deaths, three of them primary endpoint failures. There were at least seven subjects with severe primary graft dysfunction or PGD classification reported by the sites, which were also primary endpoint failures, and there was one subject who, on postoperative Day 6, suffered a loss of allograft with an OCS-supported heart and was therefore retransplanted off-study with a standard of care donor heart.

While FDA approved protocol 1.4, we remind you that FDA was unable to disapprove the proposed protocol changes due to the revisions made to Section 520(g) of the Act.

FDA would also like to note that shortly after the introduction of protocol version 1.4, Site Number 2, contributing seven transplanted subjects to the EXPAND study, wrote a letter to FDA stating that an iPad application which was used by investigators for organ management contained information not available in the clinical protocol or instructions for use. An example includes a contraindication present in the iPad but not in the other documents.

After almost a year of communication between the site and TransMedics in an attempt to reconcile the document discrepancies and have the Sponsor obtain FDA approval for the differences, Site Number 2 terminated IRB approval citing concerns over unresolved important study discrepancies that "impacted study merit." This raises questions as to whether the same set of inclusion/exclusion criteria are being used consistently at all sites.

This slide will touch on the some of the study design considerations mentioned on slide 9 that were communicated to TransMedics early and that the FDA believed would improve the scientific validity of a dataset that would be used to support a marketing application.

There were 27 study design considerations and two future concerns that the Agency communicated to TransMedics but that the Sponsor chose not to implement into their clinical protocol. Some of the major concerns FDA identified from the beginning of the study are included on this slide.

First, FDA recommended that EXPAND be carried out as a nonrandomized concurrent controlled investigation in order to provide a better understanding of device performance.

The Sponsor did not propose a statistically driven safety endpoint with a pre-specified definition of success for the EXPAND study. This is challenging, especially since FDA had not determined a reasonable assurance of safety from the PROCEED II, and

EXPAND had no control arm for comparison.

The primary effectiveness endpoint was based on a 24-hour assessment of severe primary graft dysfunction and primary graft survival at 30 days. FDA had recommended that both moderate and severe PGD be captured for the primary endpoint since capturing all PGD grades is relevant to the understanding of the OCS Heart device's effect on patients' short and long-term outcomes and therefore the overall benefit-risk analysis.

And lastly, FDA has been consistent in our recommendation of the use of the ITT or modified ITT patient population as the primary analysis population in both PROCEED II and EXPAND clinical studies. The transplanted recipient population, which TransMedics used as the primary analysis population in the EXPAND study, ultimately excluded 22 subjects from important analyses including short and long-term survival.

The Agency believes that the intent-to-treat population is the most appropriate evaluable population, as it is necessary to include all eligible donor hearts in an effectiveness analysis. This type of analysis is needed to understand the clinical impact of the use of the OCS Heart System. For example, donor hearts and the survival rates have steadily increased over time, as shown here, in the 2019 Scientific Registry of Transplant Recipients' annual report, just published a few weeks ago.

Acknowledging overlap between extended and standard criteria donor heart definitions for the PROCEED II and EXPAND studies, as well as the high turndown rate for donor hearts supported on the OCS Heart System, the public health concern in question is the effect the OCS Heart System will have on the pool of transplantable donor hearts and ultimately, the long-term survival for transplant recipients.

In vitro studies performed with OCS Heart System included testing in all of the categories identified on this slide. All testing was considered acceptable with the exception of cybersecurity, which the FDA and the Sponsor continue to work through.

The Sponsor did not perform comprehensive animal studies that evaluated the final device design in a clinically relevant setting. The animal studies submitted in this PMA to support the final design of the OCS Heart System provided limited information on a non-controlled, non-GLP study on N = 2 ex vivo porcine hearts. While physiologic parameters were monitored for these two hearts during the study, histologic evaluation or other assessments of tissue viability or injury were not provided. One of the notable findings from the study was an increase in heart weight of 20% or more as shown in the table on this slide, which is consistent with tissue edema. Had there been a control or had there been a histologic evaluation, we may have been able to compare and assess the possibility of tissue injury due to the device.

The Sponsor also performed several other small animal studies under the previous PROCEED II PMA and EXPAND IDE clinical study largely centered on evaluating device design changes. FDA does not believe that these previous animal studies are applicable to the current OCS Heart System design or function and they were not designed to address fundamental safety and effectiveness questions.

One study performed on two ex vivo hearts followed the removal of the second compliance chamber. If you remember, this compliance chamber was added to the OCS Heart System after animal studies suggested several advantages, including improved profusion and reduced heart weight gain. However, following this animal study evaluating the design change to remove the compliance chamber, results indicated heart weight gains of 19 and 21%. This finding may be important once our presentation turns to the pathology of the turned-down hearts and the edema noted in many of the pathology reports.

So to sum up the animal studies for the present PMA, animal studies were limited in scope and number and importantly, did not include myocardial histologic analysis. Due to these limitations and the concerns FDA has about the possibility of myocardial damage by

the OCS System, FDA believes that the animal testing leaves several important questions of safety and performance unanswered for the current PMA. Well-designed and executed animal studies evaluating hearts supported with the OCS System compared to a standard of care static cold storage heart could provide valuable insights into myocardial preservation and injury patterns between these two strategies.

As the presentation moves forward, I would like to recognize some key issues that FDA has identified during our review of the OCS Heart System. Specifically, the presentations that follow will cover issues related to concerns with the study designs in both the PROCEED II and EXPAND studies; study conduct issues, including late adjudicated changes to investigators' assigned primary endpoint classifications for primary graft dysfunction and modifications to the donor heart inclusion criteria met for the study which were revised after data lock and FDA review; the possibility of substantial overlap between the definitions for standard and extended criteria donor hearts enrolled in both studies; whether lactate can confidently be relied upon as a metric to determine the transplant-ability of a donor heart post perfusion; the survival curves, both short and long-term for the PROCEED II an d EXPAND studies; the possibility of organ or tissue injury by the OCS Heart device; and ultimately, the public health concern regarding the impact the OCS Heart System will have on the pool of transplantable donor hearts and long-term survival for transplant recipients.

With this, I would like to introduce Dr. Xuan Ye, who will be presenting the statistical analyses for both the PROCEED II and EXPAND clinical studies.

DR. YE: Good morning, my name is Xuan Ye. I'm a statistical reviewer for OCS Heart System submission. I will discuss the clinical data sources used in this PMA submission and the Agency's predictive analysis based on survival models.

There are three data sources used to support the PMA application: PROCEED II,

EXPAND, and EXPAND CAP.

PROCEED II was a prospective, multicenter, randomized controlled clinical trial. It compared OCS Heart devices in a test group versus the cold storage standard of care, which is the control group. The donor hearts were standard criteria donor hearts. The planned sample size was 128 recipient patients with 1:1 randomization. There were 12 enrolling sites. A reasonable assurance of safety and effectiveness for standard criteria donor hearts was not determined.

The PROCEED II primary effectiveness endpoint was defined as 30-day patient survival following transplantation with the originally transplanted donor heart and no mechanical circulatory assist device at Day 30. The hypothesis test for this endpoint was a non-inferiority test with non-inferiority margins set at 10%; πOCS and πSOC are the respective proportions of subjects surviving at Day 30, as defined above. The pre-specified statistical test method is a normal approximation test with a one-sided alpha level at 0.05.

The PROCEED II safety endpoint was the incidence of CEC-adjudicated cardiac related serious adverse events up to 30 days following transplantation. The hypothesis test for this endpoint was a non-inferiority test with non-inferiority margin set at 10%. The statistical test method is a normal approximation test with a one-sided alpha level at 0.05. PROCEED II met its 30-day primary effectiveness and safety endpoints.

Although both FDA and the Sponsor recognized the importance of 30-day outcomes, longer-term results are critical in the overall assessment of device effectiveness and the benefit-risk.

This figure shows Kaplan-Meier survival curves of the PROCEED II trial. The upper curve, estimated survival for standard of care group; the lower curve is the estimated survival for the OCS Heart group; and the shaded area represents 95% confidence intervals. The curves start to separate at the beginning of the trial and continue this pattern over the

long term with a survival difference in favor of the standard of care group. Further details of this analysis will be discussed by Dr. Sapirstein.

EXPAND is a prospective, multicenter, single-arm study evaluating extended criteria donor hearts perfused with the OCS Heart System. The planned sample size was 75 transplanted heart recipients with the OCS-preserved hearts. There were 12 activated sites.

The primary effectiveness endpoint is a composite of patient survival at the Day 30 post-transplant and freedom from severe PGD-LV or PGD-RV primary graft dysfunction. The hypothesis test is a single proportion test with a performance score of 65%, where π is the true proportion of all transplanted recipients' survival at Day 30, as defined above. The pre-specified statistical test method is exact binomial test with one-sided alpha level at 0.05.

The safety endpoint was incidence of heart graft-related serious adverse events in the first 30 days post-transplantation. Serious adverse events are defined as moderate or severe PGD-LV or PGD-RV or graft failure leading to retransplantation. Note that no hypothesis testing was pre-specified for this endpoint.

EXPAND CAP is a continued access protocol of EXPAND approved for up to 75 donor hearts in February of 2019, while the current PMA was under review. Donor heart enrollment aligned with extended heart criteria defined in EXPAND.

The PROCEED II trial raised concerns about long-term survival probabilities among patients receiving hearts preserved with the OCS Heart device. In the EXPAND study there are limited survival data available beyond 2 years. From Kaplan-Meier analysis, one can estimate the survival probabilities for up to 3 years to gain insights into longer terms of -- FDA built parametric models using available EXPAND data to predict the 4-year and 5-year survival post-transplantation.

This figure shows the EXPAND study Kaplan-Meier survival curve which was based on the most recent dataset from February 2020. The protocol sample size is 75 OCS Heart

recipients. From this analysis, we can estimate the survival probabilities up to 3 years. We may then apply parametric models to extrapolate longer-term survival probabilities.

To extrapolate longer-term survival estimates, we first looked at the estimated hazard function. As illustrated in this figure, the hazard function changes over the post-transplantation time. Specifically, the hazard function initially decreases and then increases. In addition, as the hazard function approaches the end of the time period, wider confidence limits are seen, meaning that there's greater uncertainty in hazard estimation to increased paucity of data points.

We applied two parametric models for extrapolation. The first is an exponential model which assumes a constant hazard rate. The second is a piecewise exponential model which assumes that the hazard rate is constant within specified time intervals and may be different across intervals. We estimated the hazard rate for each interval and utilized those to estimate longer-term survival rate.

Based on the fitted model, this figure shows the Kaplan-Meier survival curve and the remodel curves. The blue line is the EXPAND Kaplan-Meier curve. The orange line is exponential model curve and the red line is the piecewise exponential model curve. As expected, the piecewise exponential curve is a better -- constant hazard function. From the fitted models, we can predict longer-term survival probabilities and construct predicted intervals.

Please note that survival prediction for 4-year and 5-year has large uncertainty, which is reflected in the wide predictive intervals. The true uncertainty may go beyond the range if the model is not correct.

Please note that the survival prediction is limited by the strong model assumptions and data availability. The prediction for longer-term survival has large variabilities.

That concludes my presentation. I now give the podium to Dr. Sapirstein.

DR. SAPIRSTEIN: Good morning, I'm John Sapirstein. I'm a cardio-thoracic surgeon in the Office of Cardiovascular Devices and I'm going to present a summary of FDA's clinical review of the TransMedics Organ Care Heart System.

I'm going to begin by giving some background on why FDA will be focusing on both the PROCEED II and EXPAND clinical studies. PROCEED II was an evaluation of donor hearts broadly and FDA had comprehensively reviewed the data previously. However, that marketing application did not lead to our determination of a reasonable assurance of safety and effectiveness.

EXPAND evaluated donor hearts generally considered to be extended criteria, as defined by the Sponsor. This is the subject of the current PMA. FDA also received, in the latter part of 2020, supplemental data from a continued access protocol to EXPAND and we will be discussing those data, as well, and then review the IDE protocols and how the trials are executed, and discuss the limitations FDA identified in both the IDE process and during the PMA reviews. We'll then discuss the results of those trials, the effectiveness endpoints, key secondary endpoints and importantly, some adjunctive and post hoc analyses which FDA believes are crucial to evaluation of safety and effectiveness.

The primary objective for PROCEED II was to compare OCS preservation with the existing standard of care, cold static cardioplegia preservation. It was not explicitly limited to so-called "standard criteria" donor organs nor was it designed to show superiority of the OCS Heart System to the standard of care preservation technique.

EXPAND evaluated the safety and effectiveness of the system's ability to improve the utilization of donor hearts. It was limited to certain donor organs, specifically to extended or expanded criteria donor hearts, as defined by the Sponsor. It was not principally designed to assess the longer-term benefit-risk to patients after they received these donor organs.

The intended use of the OCS Heart System, as presented in the EXPAND IDE submission to FDA, was to assess certain hearts that do not meet standard acceptance criteria for transplantation. We believe that PROCEED II and EXPAND are both important to inform the assessment of the device's ability to do this.

So let's start with PROCEED II. PROCEED II was a randomized, multicenter study with 1:1 randomization of the device to standard of care. Because of the known and accepted complexities of organ procurement and transplantation, the study was necessarily unblinded. Importantly, randomization occurred prior to enrollment and enrollment occurred after the final in-chest acceptance of a donor organ. Thus, the randomization arm in this study was known prior to organ procurement. The study was testing for non-inferiority, not superiority, to the standard of care despite this being a first-of-a-kind device.

Effectiveness endpoints for PROCEED II are seen here. The primary study endpoint was a composite of patient and graft survival at 30 days in the absence of being on mechanical circulatory support, or MCS, at Day 30. The non-inferiority margin was 10%, secondary endpoints were moderate or severe acute rejection, as demonstrated by biopsy or clinical presentation, and the length of initial ICU stay after transplantation was also an endpoint.

There was a single secondary endpoint for safety, which was the incidence of clinical events committee adjudicated cardiac related serious adverse events occurring within 30 days of the transplantation. This, too, was a non-inferiority analysis. The cardiac event components of this composite are listed here. I will point out that this list was substantially wider at the beginning of the trial. The Sponsor, with its clinical events committee and steering committee, pared down the components of cardiac related serious adverse events during the trial without apprising FDA of that change.

FDA requested other effective measures for PROCEED II. We were interested in

longer-term survival and we will be showing those Kaplan-Meier analyses to you. These data were gotten from the Scientific Registry of Transplant Recipients, also called the SRTR, it's a government-funded database for all transplant recipients that is well established and recognized as being very robust.

We also asked for several post hoc analyses. We wanted to compare the survival of the PROCEED II subjects to the American transplantation experience as a whole based on the SRTR's annual data reports, the most recent of which was just published several weeks ago. This data report covers all waiting list subjects and transplant recipients in the United States. We also evaluated donor organs turned down after preservation, which we'll be discussing later. This included sensitivity analyses for the primary study endpoint, as well as a detailed pathologic review of the turned-down donor organs.

So here are the inclusion/exclusion criteria for the recipients in PROCEED II. I'll point out again that giving informed consent for participation was not the same as being enrolled. In red, those arrows, you see that two exclusion criteria were changed during the course of the trial; concurrent renal transplantation, which was changed to be allowed, and the number of prior sternotmies that a subject could have had prior to enrolling in the study, which was decreased.

On the donor side, the inclusion criteria are listed here and they're fairly uncontroversial for a potential donor heart. There were four analysis populations pre-specified for the recipients and one for the donor. The donor population is called OCS Heart, was all donor organs that were instrumented onto and then preserved and transported with the OCS Heart System. Recipients, I'll point out that the population the Sponsor chose for the primary analysis was per protocol. FDA, however, had recommended that the primary analysis be performed using the intention-to-treat protocol, or ITT.

The reason for this is that FDA believes the intention-to-treat analysis better

maintains the benefits from randomization of the trial. It accounts for screen failures that might occur after randomization, it accounts more fully for crossovers of preservation approach, and it more fully incorporates the possibility that one arm of the study, the treatment arm, would in all likelihood be more susceptible to clinician decisions not to proceed with the transplantation after preservation of the donor organ. This functionally, then, could work as an additional screening opportunity applied preferentially to the enrolled treatment arm subject donor organ after they had been included in intention-to-treat.

PROCEED II's intention-to-treat population is, in fact, perhaps better characterized as a modified intention-to-treat population with treatment best described as this full continuum from procurement followed by preservation, and then ultimately to execution of the transplant procedure.

In terms of enrollment in PROCEED II, there were 143 recipients that were enrolled and randomized between 2009 and 2013. There were 12 sites in total, eight of which were in the United States, and the U.S. sites contributed 91% of the study subjects overall. The highest enrolling centers each contributed approximately 30% of the overall population. FDA had recommended that no more than 20% of the population be enrolled at a single site.

There were post-enrollment screen failures and withdrawals, 12% of the OCS arm, 9% of the standard of care arm, with screen failures or withdrawals. There was crossover; 7% of the donor organs crossed over from the treatment arm to the control arm, 1% went from the control arm to the treatment arm. And then ultimately, 7% of the OCS Heart population was turned down by clinicians at the end of the preservation.

So let's walk through that a little bit more here. In dark blue are the defined analysis populations in the study, 74 subjects were enrolled into the treatment arm, OCS; 69 were

enrolled into the control arm of standard of care.

As we add in specific details of how patients navigated through the analysis populations, and this admittedly complicated slide is in FDA's Executive Summary, we can see that post-enrollment screen failures and withdrawals were more frequent in the OCS arm of the study, 9 of 74 subjects (12%) than in the control arm, 6 of 69 subjects (9%). Similarly, post-enrollment crossover was more frequent from the OCS arm, 5 of 74 or 7%, than it was from standard of care arm, which there was just one subject who crossed over. On the donor side we can see that there were 77 hearts accepted after in-chest assessment for device preservation versus 64 accepted for cold static preservation.

Post-enrollment preservation crossovers occurred in five of the 77 OCS-assigned hearts. Again, that's 7%. You can see highlighted on this slide the reasons for those crossovers. The one standard of care to OCS crossover was due to a misread of the randomization card. And while there were no turndowns, as is typical after standard of care preservation, 5 of the 67 OCS Heart donors (7%) were turned down after preservation with the device and not used for transplantation.

Demographics of the recipients are shown here. Overall, between the two arms, recipients were clinically similar. The standard of care of arm did, though, have a high proportion of female recipients and there was a high proportion of blood type O recipients in the OCS arm. Prior sensitization was low, as expected, in both arms of the study.

The use of mechanical circulatory support prior to receiving an organ in the trial was similar in both arms, approximately 30% of those subjects. And while the similarity held for the use of chronic mechanical support, such as a VAD as well, the duration of that pre-transplantation VAD use was longer in the standard of care arm. However, the use of more acute mechanical circulatory support, particularly intra-aortic balloon pumps, was higher in the control arm (standard of care) than in the OCS treatment arm, which had no subjects on

a balloon pump preoperatively. And so this does raise for FDA some uncertainty about the degree to which subjects in the two arms had equivalent clinical hemodynamic status prior to the transplantations.

In terms of the donor organ demographics in PROCEED, we can see that only one organ in the study had an ejection fraction less than 50%, this happened to have been in the standard of care arm. There were similar unexpected rates for cause of donor death in both arms, but I'll point out that 25% of all those deaths were associated with cardiac arrest. Data for downtime before resuscitation and return to circulation was not collected in PROCEED II, whereas in EXPAND, which we'll be discussing later, the presence of reported downtime greater than or equal to 20 minutes was a specific inclusion criterion for the donor organ into that study.

Looking at preservation times in the two arms, it's important to recognize that the use of this device does not obviate the need for cold ischemia, the average being approximately 1.9 hours in the treatment arm. But the overall cold ischemic time was substantially longer in standard of care hearts, nearly one and a half hours longer, than in OCS hearts, as one would expect.

The cross-clamp or a total so-called out-of-body time was about 2 hours longer for device-preserved donor organs, that's a 65% increase in out-of-body time in the treatment arm.

Now, since reperfusion ischemia required to instrument the donor organ onto the OCS device before perfusion was typically 30 minutes in length, it becomes fairly clear that the main driver for out-of-body times being so much longer in OCS than standard of care is that the time spent on device perfusion was rather extended comparatively. Indeed, perfusion time alone was roughly equivalent to the entire cross-clamp time of standard of care organs. This is somewhat surprising given that PROCEED II, this trial, was randomized

and preservation times should therefore have been similar in the two arms other than the time needed for instrumentation and then re-arrest with cardioplegia after device perfusion.

Let me discuss a little bit more about the cardioplegia. Because FDA has required for PROCEED II that no unapproved cardioplegia solutions be used with the device, most of the OCS hearts, 80% of them, achieved cardioplegic arrest with one specific so-called extracellular solution, histidine-tryptophan-ketoglutarate, HTK solution. In contrast, the majority of standard of care donor hearts did not use the HTK solution. Rather, these hearts were arrested with a variety of solutions, the most prevalent of which was the University of Wisconsin's solution, a so-called intracellular cardioplegia solution.

Because of this heterogeneity that we observed, FDA performed a post hoc covariate adjustment of the primary study endpoint and we found that the endpoint was, indeed, sensitive to cardioplegia type. The adjusted treatment difference went to 23% for the primary endpoint, greater than the non-inferiority margin of 10%. Cardioplegia may have an impact on the safety and effectiveness profile of the OCS Heart System. I will mention that with EXPAND, it was a single cardioplegia solution, del Nido solution, which is a crystalloid blood mixture, that was used in all instances.

So in terms of the primary study endpoint that I just mentioned, patient and graft survival absent mechanical circulatory support on Day 30. You can see that statistical non-inferiority was met in the per-protocol analysis. The treatment difference was 9.9%, just below the non-inferiority margin of 10%. All of the endpoint failures were on the basis of death. There were four treatment arm deaths within 30 days versus two deaths in the standard of care arm. FDA also noted that there were two non-endpoint deaths in the treatment arm shortly after this 30-day time point.

Therefore, this 10% non-inferiority margin was being applied to a 30-day mortality

comparison. And the point estimates of patient and graft survival actually favored standard of care, as you can see here, 97% versus 93%. And so superiority was not demonstrated in PROCEED II.

Non-inferiority was maintained in the modified intent-to-treat population that I mentioned before, as well as in the as-treated population. But because all of the endpoints were keyed to a fully completed transplantation, none of these analyses fully account for any impact that might've been caused by donor organs that were not utilized in the study. And so as you've already seen, 7% of the OCS Heart donor hearts which, of course, could have been randomized to standard of care, were turned down after device preservation. And so to estimate the potential effect on that primary endpoint with these turndowns, had they actually been transplanted, FDA performed a sensitivity analysis that serially added these donor organs to either the treatment or the control arm. And what we found, this is in the Executive Summary, was that the primary study endpoint was, in fact, very sensitive to clinicians' decisions about turning down the OCS Heart System organs after preservation.

Here's a secondary endpoint, initial intensive care unit stay in PROCEED II and non-inferiority was not demonstrated with the result, 47 hours, being greater than the margin of 12 hours. Overall, ICU stay did become more similar between the arms, though. And the use of mechanical circulatory support after transplantation was more frequent and it was of a longer duration in the treatment arm than in subjects who received standard of care donor hearts. And finally, the overall initial hospital stay was longer for recipients of the OCS donor organs. This longer hospitalization, we believe, is a clinically significant difference.

Now, secondary endpoints included episodes of acute rejection, non-inferiority was not demonstrated although the incidence of these events in both arms was fairly low. Cardiac graft-related serious adverse events, the safety endpoint for the trial, did

demonstrate non-inferiority.

Now, in part because of the 30-day mortality differences that we saw, FDA asked for a longer-term survival analysis for PROCEED II subjects drawing upon the SRTR database. These data are available only for U.S. subjects, not to the non-U.S. participants. So there were 118 of these U.S. subjects, and these U.S. subjects represented 91% of the PROCEED II modified intent-to-treat population overall. It was low censoring at 5 years, as you can see, which speaks to the robustness of the SRTR database. And what we saw was that using an as-treated analysis, the standard of care subjects had a survival point estimate that was greater than the OCS Heart recipients at all time points out to 5 years. And you can see a hazard ratio for mortality here of 1.9.

And seen graphically, these are the Kaplan-Meier survival curves shown to you by us previously. Standard of care is in red, the OCS Heart is in blue, with wider confidence intervals as censoring increases beyond 5 years.

Now, on the right panel is 1, 3, and 5-year aggregate all-cause mortality of U.S. heart transplant recipients stratified by the year in which the transplants took place. This is data from the most recent, just published SRTR annual report and it updates what we presented to you in our Executive Summary. Mortality has been gradually decreasing over time, as you can see.

This blue area I've added represents the time frame during which PROCEED II subjects received their transplantations. And understanding that this is a post hoc comparison, we see that recipient mortality among PROCEED II subjects who received OCS Heart donor organs has been substantially higher than the contemporaneous results demonstrated in the SRTR, while PROCEED II standard of care subjects have experienced mortality rates somewhat lower than what is showing in the SRTR.

And so based on these two comparators, in other words, the randomized standard of

care arm from PROCEED II and the contemporaneous SRTR data, we believe that there was, in fact, a clinically meaningful survival benefit for cold static preservation over use of the OCS Heart device, and we think that this finding needs to inform the benefit-risk assessment of the current PMA, the EXPAND PMA.

And so to summarize our review of PROCEED II, the study had a complex trial design, which was understandable given the inherent complexities of organ transplantation. However, the trial may have had some important selection bias involved despite its randomization.

Using the OCS Heart System was associated with longer preservation times than cold static preservation. The device decreases but does not eliminate cold ischemic time for donor organs.

PROCEED II showed non-inferiority to standard of care for the 30-day effectiveness endpoint, but the clinical value of non-inferiority in this case is somewhat uncertain.

After transplant, the need for mechanical circulatory support, the length of initial ICU time, and the duration of the index hospitalization, all favored standard of care preservation over the device.

And 30-day mortality was higher in the recipients of OCS Heart organs than in standard of care recipients, and the standard of care survival benefit has persisted throughout long-term follow-up.

So let's now turn to EXPAND. This, as you know, is a single-arm study, also unblinded, also with enrollment occurring after in-chest acceptance of the donor organ immediately prior to procurement. Testing for EXPAND was against a performance goal. The Sponsor justified a performance goal as the comparator by indicating that a randomized comparator was unavailable given the non-standard nature of donor organs that were being studied.

FDA recommended that a nonrandomized concurrent comparator, in other words, standard of care preservation of nonrandomized donor hearts, would be more appropriate for the EXPAND trial since the safety and effectiveness inferences for the OCS Heart System remained unknown to us as the PROCEED II data had not yet been submitted to FDA for review.

Nonetheless, a performance goal was adopted by the Sponsor, and FDA accepted the chosen performance goal metric; in other words, we accepted that patient survival at Day 30 in the absence of ISHLT severe left or right primary graft dysfunction was appropriate. However, FDA did have concerns about the appropriateness of the value the Sponsor assigned to the performance goal, which was 65%.

First, that's because the literature cited by the Sponsor had very heterogeneous definitions of what actually constituted extended criteria donor organs, and none was completely consistent with the Sponsor's definition for EXPAND.

Second, the literature the Sponsor cited had heterogeneous definitions of what constituted primary graft dysfunction and as the Sponsor correctly noted, each of the studies used a slightly different definition. Now, this is because the ISHLT definition used in EXPAND, which importantly is very specific in delineating the criteria of primary graft dysfunction, you can see some of the caveats there on the right.

This definition was not promulgated, put out until 2014, and so all of the PGD data, all the primary graft dysfunction data that the Sponsor used to support its primary graft dysfunction-based performance goal value, actually that value predated the ISHLT PGD rating scheme. The performance goal was defined despite there being no prior experience reporting rates of ISHLT-defined primary graft dysfunction.

As previously pointed out, there were no hypotheses for any of the secondary endpoints. These first two here were merely the components of the primary endpoint and

the third one, a utilization rate, was the proportion of OCS-preserved donor hearts that were not transplanted or they were turned down after being on the device.

There was a single safety endpoint, the incidence of medical monitor adjudicated heart graft-related serious adverse events. Again, there was no hypothesis testing for this, although FDA did request a hypothesis-tested safety endpoint be added to EXPAND, again since a reasonable assurance of safety and effectiveness had not yet been demonstrated for any use of the device.

Now, heart graft-related serious adverse events, as I mentioned, were adjudicated but by a single individual, the medical monitor, unlike the clinical events committee that was part of PROCEED II. Heart graft-related serious adverse events were defined to include primary graft dysfunction. And so the medical monitor also ended up adjudicating the study's primary endpoint, as well, since that endpoint depended, in part, on distinguishing moderate from severe primary graft dysfunction.

It was not FDA's expectation that the primary effectiveness and the safety endpoints for a pivotal clinical trial would ultimately be adjudicated by one individual only. Despite precise complication of primary graft dysfunction in the ISHLT consensus statements, investigators' classifications of primary graft dysfunction did not always align with the medical monitor's classifications and often this was on the basis of a time course of the ventricular dysfunction.

Here are some of the additional effectiveness measures that FDA requested and that we'll be discussing a little bit later.

Now, these are the recipient inclusion and exclusion criteria in EXPAND and if we compare them to PROCEED II there on the right, we see the selection criteria were actually quite similar between the two studies except that for PROCEED II, some prior transplants or concurrent transplantation was allowed, unlike in EXPAND; while conversely, EXPAND

allowed for recipient risk factors such as prior sternotomy, ventilator dependence, and substantial mechanical circulatory support experienced preoperatively that had been excluded from PROCEED II.

Donor qualifications for acceptance into EXPAND as being extended criteria donor hearts are listed here. The criteria are very numerous and they relate to multiple donor characteristics. And if we compare these criteria side by side to PROCEED II's, it might at first seem that the trials used donors that were substantially different from each other but, in fact, we can see that the criteria do allow for overlap between the two donor populations. For example, donor age between 45 and 60 was allowed in both and sufficient by itself for enrollment into EXPAND. Cardiac function based on echocardiography ejection fraction overlapped. The criterion of left ventricular hypertrophy as measured by left ventricular wall thickness, while not explicitly overlapping, were extremely close at the low end of EXPAND's inclusion rings. In fact, the precision of discriminating 1 mm dimensions on echo is prone to variability.

An exclusion based on coronary disease was present, appropriately, in both of the trials. But investigators in both were allowed to make judgment calls as to whether some donor organs with coronary artery disease could, in fact, be part of the studies nonetheless.

Reported downtime greater than 20 minutes, this allowed for acceptance into EXPAND. Although as I mentioned previously, the duration of downtime, the 25% of the donor organs in PROCEED II, was simply unknown.

And finally, the subjective expectation of cross-clamp time, the expectation of cross-clamp time being greater than or equal to 4 hours, which was the most frequently occurring criterion in EXPAND, was something that may have been associated with an unknown number of PROCEED II donor organs, as well. PROCEED II did not prospectively evaluate cross-clamp times, estimated or actual.

So here are the EXPAND analysis populations, there were two. The OCS Heart population was the same as for PROCEED II, the only recipient population in EXPAND, transplanted recipient, was essentially a per-protocol analysis population again.

Enrollment into EXPAND occurred at nine sites in the United States between 2015 and 2018. One site withdrew from participation. The highest enrolling site, Site Number 6 in EXPAND, enrolled 39% of the transplanted recipient subjects despite FDA's recommendation, again, that no single site enroll more than 20% of subjects. There are no outcome data for approximately one-quarter of the consented subjects in EXPAND. Six percent were withdrawn prior to preservation, one of whom was a crossover to standard of care preservation, and 16% were withdrawn after preservation once the donor organs to which they were matched were turned down for transplantation.

Looking at the patient/donor organ flows, the 100 accepted donor organs are on the left and on the right are the 96 consented subjects or the ITT population. Again, dark blue are the protocol-defined analysis populations. And this is also taken from FDA's Executive Summary and shows the reasons and timing for donor and recipient transitions in and out of the various analysis populations.

Six of 96 subjects (6%) were pre-preservation subject withdrawals. Within that is the one OCS to cold static preservation crossover subject. Fifteen of 96 subjects were withdrawn after preservation of the matched donor organ for the reasons that are listed in the box there. These subject withdrawals happened as a consequence of 18 OCS hearts; 19 of the group, as a whole, being turned down after preservation.

The key recipient and donor demographics, the majority of donors had normal cardiac function, not too dissimilar from what was present in PROCEED II. As compared to PROCEED II, recipients in EXPAND had higher panel reactive antibodies, although in most cases the subjects were not highly sensitized. There were more patients with diabetes in

EXPAND and there was a higher rate of preoperative mechanical circulatory support use among EXPAND's recipients as compared to PROCEED II.

Here's a breakdown of the OCS donor organs and specific combinations of inclusion criteria that they met. The ones in green represent counts of donor organs accepted on the basis of a single inclusion criterion. The column on the left is transplanted hearts, while on the right are hearts turned down after preservation. Expected cross-clamp time greater than or equal to 4 hours was the most frequently invoked criterion.

As we consider the makeup of the EXPAND organ population, I'll make two observations. First, the Sponsor did make modifications to 20 of the criteria designations after FDA had performed our initial review of the PMA. In all cases, the changes resulted in additional criteria being added to the donor organs and 17 of those 20 additions changed donor organs previously characterized as having a single criterion to organs having multiple criteria.

Now, acceptance of donor hearts into the study as being extended criteria was to have been based upon the investigators' interpretation of data that they were aware of at the time of procurement. And so it's just unknown if information uncovered through post hoc data audits but not identified by investigators on the case report forms, it's not known if this actually informed investigators' decisions as to consider or not a donor organ as extended criteria.

And then secondly, regarding the inclusion criteria, certain criteria which are highlighted here in pink, were used more frequently to label a donor as extended criteria and these criteria that were more common, can be seen as either being frankly fairly subjective like the expected cross-clamp time, or prone to considerable intra- and inter-observer variability, like ejection fraction calculations, or limited by reporting difficulties, as in the case of downtime estimations.

And so overall, we believe that there is, in fact, an uncertain degree of overlap between the nature of donor organs included in EXPAND and those that were included in PROCEED II.

Now, turning to the details of OCS device preservation, cold ischemic time was about 1.7 hours, the perfusion time was just over four and a half hours, which was about 1 hour longer than what was seen in PROCEED II. Transplanted and turned-down hearts had similar starting lactate levels and the device flow parameters throughout preservation were also fairly similar.

Lactate trended upwards during preservation, but turned-down donor organs showed a greater lactate rise with final mean lactate being 1 -- excuse me, 5.1 mmol/L.

Now, lactate is a key OCS Heart System parameter identified by the Sponsor. In PROCEED II data, which is shown here, rising perfusate lactate level was a reason for three of five of the OCS Heart turndowns, and in vivo lactate in one instance was the reason an investigator chose not to use the OCS Heart device as randomized and instead opted for standard of care preservation. The Sponsor's threshold lactate level, as you already know, is five.

When we looked at the lactate trends in EXPAND, in the top panel here, we noted similar trends in transplanted and turned-down donor organs, and by that I mean there was a rise in lactate of similar magnitude over the course of most of the perfusion, though in both studies turned-down donor organs, as you can see in these graphs, typically, but not always, but typically had higher final lactate levels than transplanted organs did.

FDA believes there are limited preclinical or clinical data that can validate lactate below five as a biomarker of clinical viability or transplantability after isolated heart perfusion. And of course, there are no comparable lactate data available for donor organs that use cold static preservation.

But there is one subgroup from EXPAND that we believe is quite informative about a relationship between lactate and the OCS Heart System, those organs that had an expectation for prolonged cross-clamp time as the only criterion for using the device. This subgroup accounted for 29% of all accepted donors in the combined EXPAND and EXPAND CAP studies. By definition, these hearts then had none of what I would call donor-specific characteristics rendering them extended criteria. It was only a concern of out-of-body time, a more logistics-focused issue, if you will, that allowed for them to be considered extended criteria. So stated another way, these were functionally, functionally, standard criteria donor hearts which we know have close to 100% transplantation rates following cold static preservation. The one OCS II standard of care crossover in EXPAND, that I mentioned earlier, illustrates this fact. That donor organ had been accepted into the study based on the cross-clamp criterion alone, but it was successfully transplanted after cold static preservation.

Conversely, 18% of this time-only, if you will, subgroup, 7 of 40, were turned down after OCS Heart preservation with all these decisions, based either wholly or mostly upon clinicians' interpretation of lactate levels.

Now, the Sponsor's inference is that the device unmasked preexisting pathology and/or poor tolerance for preservation. FDA's inference is somewhat different in that we do not believe the etiology or significance of the lactate level is certain at this point. While we agree that there could be a masking of preexisting pathology, it's also possible that the device is simply not adequately preventing one ischemia during perfusion as intended. The device could be causing some other de novo injury to the heart leading to downstream ischemia and lactate generation, or the device's lactate readings may be signaling donor pathology that ultimately would've been inconsequential for post-transplantation function had the organ been preserved with the standard of care. And Dr. Andrew Farb will be

discussing the pathology evaluations and lactate levels in just a little bit.

Here is the primary effectiveness endpoint for EXPAND, patient survival without severe PGD of left or right ventricle. As you can see, the performance goal was met, the lower bound of the confidence interval was 78, the performance goal was 65%. Nine effectiveness endpoint failures occurred and they all involved primary graft dysfunction, while one-third of the severe primary graft dysfunction occurrences caused death within 30 days. This mortality rate is consistent with literature reports of PGD-associated mortality.

A secondary safety endpoint accounts for three additional episodes of moderate primary graft dysfunction and moderate primary graft dysfunction is a clinically important finding also associated with clinical sequelae. The utilization rate we already discussed. These were turndowns of organs, 19%. The other two secondary endpoints are merely the components of the primary endpoint composite.

Here are the ICU and hospitalization stays in EXPAND, the initial ICU stay was several days longer than in PROCEED II, while the initial hospitalization was approaching a week longer than in PROCEED II. The postoperative use of acute mechanical circulatory support was twice as common in EXPAND.

Here are waiting list times for heart transplant recipients. On the left are the transplanted recipients in EXPAND and on the right are the U.S. SRTR data. Compared to aggregate data, the OCS Heart System was associated with a clinically significant decrease in waiting list time. And this is particularly evident for blood type O recipients, a group well known to experience prolonged wait list times. Once subjects agreed to participate in EXPAND, the remaining wait time was relatively brief, about a month, as you can see here.

Now, to put this in some context, it's important to understand the current dynamics of the U.S. donor heart waiting list. These are the most recent SRTR data representing the waiting list in 2019. At the top is a sort of competing risk outcomes for all subjects on the

list at any time during the year. Forty-five percent remained on the waiting list at the end of the year, 3% died, 4% were removed from the list because they were too sick to receive a transplant. Forty-one percent, though, did receive a donor organ within the year and if you look at the donor wait list times for the subjects who did, who did get transplanted during the year, that's shown here on the bottom. You can see that nearly half received their transplant within 1 month of getting on the waiting list.

Here are the survival estimates and confidence intervals for EXPAND subjects after they were transplanted. It includes the parametric modeling that Dr. Ye just explained to you. Also shown are Kaplan-Meier curves for the two arms of PROCEED II. One-year survival estimate in EXPAND, 84%, is essentially equivalent to the treatment arm of PROCEED II, which is less than the survival in PROCEED II's cold static preservation arm.

Because the donor population in EXPAND was very heterogeneous, we performed several post hoc analyses to better explore the survival findings.

Our first post hoc analysis looked at the primary effectiveness endpoint which contains a 30-day perioperative survival metric stratified by the donor inclusion criteria and what we saw was that point estimates of survival among recipients of single criterion donor organs was somewhat surprisingly worse than the estimate of survival among those who received donor organs with multiple criteria.

So next we looked at longer-term survival estimates out to 2 years and again saw a trend of lower survival among donor organs having just one extended criterion. When we looked at the donors that had expected cross-clamp time as a criterion, either alone or in concert with others, point estimates of 2-year survival were paradoxically lower when the expected time was the only reason for being preserved with the device. Cross-clamp time in conjunction with one or more other criteria had a higher 2-year survival rate. And then if we look at the actual cross-clamp times experienced, those used for a shorter period of

time also had lower estimates of survival.

Now, any inferences from these analyses are certainly limited by their post hoc nature, their relatively small sample sizes, and their wide confidence intervals. But it is interesting to note that the survival estimates of these presumably lower-risk donor organs are consistent with the survival probability seen in the OCS arm of PROCEED, 75%.

We also have the adjunctive dataset from EXPAND CAP and this was a recently conducted expansion of the EXPAND IDE, they had minor modifications from the EXPAND IDE protocol. Forty-five subjects were enrolled, 41 had reached the 30-day primary effectiveness endpoint by the time the Sponsor presented these data to us in the latter part of 2020. Four of the 49 donor organs were turned down, that's 8%. In CAP, 59% of the enrolled subjects occurred at one site, which was also the high enrolling site in EXPAND. Recipient and donor demographics were generally consistent with EXPAND except for some aspects that I've highlighted here. Preservation parameters were likewise similar to what was seen in EXPAND.

Finally, secondary endpoint results, while not tested, appeared to be consistent with what EXPAND had demonstrated. CAP, however, reported and proved 6 and 12-month survival as compared to the IDE cohort. But there was substantial censoring, more than 50% of the data, since this was a very recently conducted study, and many subjects had not yet reached their 6 and 12-month time points, as the tick marks on the right curve demonstrate.

So we pooled the data from EXPAND and CAP, and you can see the pooled survival estimates here, including again piecewise modeling we viewed before. Although there again is increasing uncertainty with the model at longer time points, 2-year survival estimates for the pooled cohorts is 85%. And when we compare that to both the EXPAND population results alone, which is in blue on this slide, and PROCEED II device arm, which is

in purple, we see that pooling of EXPAND and EXPAND CAP datasets does shift the expected model survival curve upwards, somewhat closer to the standard of care survival curve in PROCEED II, which is shown in green.

These findings need to be looked at with appropriate caution because while perhaps meaningful, the data pooling was post hoc, there is that increasing uncertainty with the model as time points move farther out and there is a very substantial site effect, which you can see here.

One site enrolled nearly half of the pooled cohort subjects at 46%. We compared the 1-year survival, 1-year survival, from that high enrolling site to the aggregate survival from all the remaining pooled EXPAND and CAP sites. The survival probabilities and 95% confidence intervals are shown here, 93% versus 82%. And this, accordingly, may substantially affect the generalizability of the pooled EXPAND plus CAP survival results.

So in summary, then. The OCS Heart System is a first-of-a-kind organ preservation device that has an intuitive appeal because of its presumed reduction in ischemia reperfusion injury, and a presumed increase in procurement flexibility leading to more procurements taking place.

PROCEED II and EXPAND were conducted in series over a 10-year time span. The trials had complex designs that were necessary given the nature of organ transplantation and there likely was some selection bias in both.

EXPAND was to evaluate extended criteria donor hearts that were not ostensibly a part of PROCEED II. The most common reason to use the device in EXPAND was a priori expectation by investigators that there would be prolonged cross-clamp time after procurement. We do believe that there was overlap between the study's donor heart characteristics.

EXPAND did meet a performance goal of 30-day effectiveness, but the

appropriateness of that pre-specified performance goal is uncertain to us.

Midterm survival of EXPAND's extended criteria donor organs is higher than the PROCEED II device experience, but survival in hearts selected only on the basis of expected cross-clamp time being greater than or equal to 4 hours remains similar to the survival seen with the device arm from PROCEED II.

The OCS Heart System was associated with shorter waiting list times as compared to U.S. averages, and longer preservation times were seen as compared to cold static preservation. The OCS Heart System does decrease cold ischemic time for donor organs, but it does not eliminate the cold ischemia.

And 13% of accepted donors were subsequently turned down after preservation with the OCS Heart System. Reported lactate level was the main reason for clinician decisions to turn down those organs. We believe the validity of lactate as a determinant for transplantability after OCS Heart preservation is unclear.

And finally, ischemic injury was observed in turned-down donor hearts, but the precise correlation of that ischemia with device preservation remains uncertain to us, which Dr. Farb will now discuss. Thank you very much.

DR. FARB: Good morning, I'm Andrew Farb, Chief Medical Officer in the Office of Cardiovascular Devices. By background, I'm a cardiologist with additional training and experience in cardiovascular pathology. I'll be presenting FDA'S clinicopathologic analysis of hearts perfused with the OCS Heart System but turned down for transplant.

Our methods were as follows: EXPAND, EXPAND CAP, and PROCEED II donor hearts that were perfused on the OCS Heart System but turned down for transplant were identified. Pathology reports, gross cardiac specimen photos, and photomicrographs from the two core pathology labs were reviewed.

We compiled demographic data, medical history leading to brain death, and hospital

course information including vital signs, laboratories, and key cardiac assessments, including echocardiograms and cardiac cath reports.

From available records, we also collected study enrollment criteria, brain death to cross-clamp time, OCS Heart perfusion time, mean aortic pressure, mean coronary flow, lactate level assessments, and the reason the donor heart was turned down for transplant.

Starting first with the EXPAND study, the Sponsor provided cardiac pathology reports for 17 of 18 OCS-perfused donor hearts that were turned down for transplant. One report was not available. Evidence of acute diffuse or multifocal ventricular myocardial damage was seen in 16 of 17 hearts characterized by contraction band necrosis, coagulation necrosis, myocyte wavy fiber change, and interstitial edema. None of these hearts had other significant cardiac findings except for one heart with LVH and severe three-vessel coronary disease. The remaining heart showed healing subendocardial infarcts, consistent with myocardial injury prior to perfusion with the OCS Heart device.

Here are the cardiac pathologic findings in the four EXPAND CAP study hearts that were turned down for transplant. There was acute diffused ventricular myocardial damage in all four hearts. None of these hearts had other significant cardiac findings.

Next, our cardiac pathologic findings in the five PROCEED II OCS-perfused hearts that were turned down for transplant. Cardiac autopsy findings in these five hearts showed acute diffuse myocardial damage in three cases and focal myocardial damage in one case.

Further analysis of selected turned-down donor hearts provide insights into whether perfusion with the OCS Heart System provides effective organ preservation or can cause myocardial damage.

The way we approached this issue was to perform a review of those turned-down donor hearts that had normal left ventricular function in the immediate antemortem period. This analysis offers insights into the potential limitations of the OCS Heart System

to provide effective organ preservation. There were 20 individual hearts that were turned down for transplant which had an echo-documented LV ejection fraction of greater than or equal to 55% within 1 to 2 days pre-cardiectomy, 12 EXPAND, four EXPAND CAP, and four PROCEED II donor hearts. During this period, available vital sign flow sheets showed no prolonged episodes of hemodynamic instability.

Cardiac autopsy findings in 18 of these 20 individual hearts showed acute diffused ventricular myocardial damage in 12 hearts, six EXPAND, three EXPAND CAP, and three PROCEED II hearts, and acute multifocal ventricular myocardial damage in six hearts, five EXPAND and one EXPAND CAP heart.

An example of an EXPAND turned-down heart that demonstrated diffused myocardial damage following OCS heart perfusion was this donor heart from a 52-year old man with a hemorrhagic stroke approximately 3.5 days pre-cardiectomy. There was no cardiac arrest and troponin levels were not elevated. Cardiac cath showed only coronary luminal irregularities and an echo within 48 hours prior to cardiectomy showed an LV ejection fraction of 60%. Vital signs prior to cardiectomy were stable. The inclusion criteria met were a projected cross-clamp time of greater than or equal to 4 hours and coronary luminal irregularities.

The OCS heart perfusion time, coronary flow, and lactate levels are shown here. Arterial lactate peaked at around 4.5 mmol/L.

Grossly, the turned-down heart showed subendocardial hemorrhage involving the left atrium and left ventricle.

The pathology core lab noted that all gross myocardial lesions showed histologic evidence of severe and extensive changes on acute ischemic injury ranging from contraction band to coagulation necrosis with microscopic foci of tissue dissolution in the center of the damage areas. These areas accounted for approximately 25% of the myocyte area.

Damage was most severe in the myocardial defects of the left lateral ventricle near the septum where early tissue dissolution was seen. But importantly, myocardial damage was also seen in nearly all gross lesion and non-gross lesion histologic sections.

Here are representative photomicrographs. The top image shows extensive contraction band necrosis, the bottom left image shows contraction band necrosis with coagulation necrosis, and the bottom right high-power image shows contraction band necrosis, coagulation necrosis, and myocyte dropout. Note the absence of acute inflammation.

A second example of an EXPAND turned-down donor heart was from a 31-year-old man with anoxia secondary to drug intoxication approximately 7.5 days pre-cardiectomy. A cardiac arrest at presentation lasted 18 minutes. Cardiac biomarkers were not elevated and an echo within 48 hours of cardiectomy showed an LVEF of 60% with trace to mild MR and TR. There were stable vital signs prior to cardiectomy. The EXPAND inclusion criteria met were a projected cross-clamp time of greater than or equal to 4 hours and the 18-minute cardiac arrest down time.

The OCS heart perfusion time, coronary flow, and lactate levels are shown here. The arterial lactate peaked at approximately 4.5 mmol/L.

Grossly, the heart showed focal hemorrhage in the posterior and lateral LV walls with hemorrhagic mottling, mostly in the left anterior and left lateral walls.

The pathology core lab report noted that nearly all sections from the left and right ventricles and the interventricular septum showed myofiber hypereosinophilia, focal contraction band necrosis, wavy myofibers, interstitial edema, and focal coagulation necrosis with early loss of nuclei, but minimal to no neutraphilic infiltration. These findings are consistent with widespread acute ischemic injury.

Here are representative photomicrographs. The top left and right images show low

and high-power views of contraction band necrosis, coagulation necrosis, and myocyte dissolution. The bottom left image shows contraction band necrosis with marked interstitial hemorrhage, and the bottom right image shows focal contraction band necrosis with myocytolysis.

A third example of an EXPAND turned-down heart was from a 17-year old male with an intracranial hemorrhage secondary to an AVM approximately 2.5 days pre-cardiectomy. There was no cardiac arrest or cardiac biomarker elevation. An echo within 48 hours prior to cardiectomy showed an LVEF of 65% and vital signs were stable, the single EXPAND inclusion criterion met with a projected cross-clamp time of greater than or equal to 4 hours.

The OCS heart perfusion time, coronary flow, and lactate levels are shown here. The arterial lactate peaked at approximately 7.0 mmol/L.

Grossly, at autopsy, the heart showed focal subendocardial hemorrhage in the anterior and lateral LV walls.

The pathology core lab report noted an anterolateral subendocardial infarction with reperfusion and hemorrhage, and remaining myocardial section showing occasional acute microinfarcts with hypereosinophilia, contraction bands, edema, plus other areas of interstitial hemorrhage secondary to reperfusion. These findings are consistent with widespread acute ischemic injury and there was no inflammation or myocardial lesions that correlated with the antemortem intracranial hemorrhage.

Representative histologic images show diffused contraction band necrosis in the top picture, contraction band necrosis with coagulation necrosis at the bottom left, and contraction band necrosis with interstitial hemorrhage on the bottom right.

Some clinical observations support the possibility of less effective organ preservation by the OCS Heart System. In the PROCEED II randomized trial, there were more early

deaths, longer ICU stays, greater use of mechanical circulatory support, and longer hospital duration in recipients of donor hearts in the OCS group versus the standard of care group.

In EXPAND, four patients with OCS-perfused hearts had acute severe primary graft dysfunction that directly contributed to death. Three cases occurred within the first 24 hours and one within 48 hours. Pre-transplant echoes showed a normal LVEF for three of these four hearts with echo data not provided for the remaining heart. Comments in the narrative summary reports stated that mortality was possibly related to preservation.

In summary, the pathologic analysis of OCS-perfused turned-down donor hearts with (1) stable antemortem hemodynamics; (2) normal or near normal cardiac anatomy and normal ventricular function by echo; and (3) cardiac autopsy findings of acute diffuse or multifocal myocardial damage suggest that, in an important proportion of cases, the OCS Heart System did not provide effective organ preservation or its use caused severe myocardial damage to what would have been an acceptable graft for transplant.

That completes the clinicopathologic correlation analysis. I would like to reintroduce Catherine Wentz to discuss post-approval study considerations.

MS. WENTZ: This is Catherine Wentz again and I will be presenting the proposed post-approval study.

In the event of approval for the OCS Heart System, the Sponsor has proposed the following post-approval studies. First, the Sponsor has proposed a 175-patient, single-arm, prospective, multicenter, observational post-approval registry with follow-up out to 12 months and outcomes out to 5 years. The Sponsor has also proposed a single-arm observational post-approval follow-up data analysis in which outcomes obtained from the existing national Scientific Registry of Transplant Recipients database for the 75 subjects transplanted in EXPAND will be obtained and analyzed out to 5 years.

FDA has concerns with the proposed primary endpoint and the performance goal

identified for the studies. For example, the proposed primary endpoint is 12 months survival from cardiac graft-related death. However, FDA believes that the 12-month survival should be based on all-cause mortality. Additionally, the 86% performance goal for the proposed primary endpoint of cardiac graft-related death we believe is low considering that the post hoc un-adjudicated analysis of cardiac graft-related survival at 12 months in EXPAND was 95%.

I would now like to turn over the presentation to Fernando Aguel, who will provide the FDA summary.

MR. AGUEL: Good morning, my name is Fernando Aguel. I am the Assistant Division Director for the Circulatory Support Devices Team and I will be presenting the FDA summary.

The OCS Heart System and in particular, its use in an extended criteria donor heart category, is intended to advance the field of cardiac transplantation. As we covered in our presentation today, we believe there are multiple important limitations in the design, execution, and analyses of the PROCEED II, EXPAND, and EXPAND CAP studies, making an assessment of device benefit-risk challenging.

There are challenges regarding study design and results such as challenges in interpreting the randomized results from PROCEED II and how they inform EXPAND study results, and there are limitations of the single-arm study design for EXPAND and EXPAND CAP.

There are challenges in study conduct, including late adjudicated changes to investigators assigned primary endpoint classification for primary graft dysfunction and modification to the assignments of inclusion criteria met, which were revised after data lock and FDA review.

There is difficulty in defining extended criteria hearts and in the possibility of

substantial overlap between the definitions for standard and extended criteria donor hearts.

It is unclear whether the use of lactate can be confidently replied upon as a metric to determine the transplantability of a donor heart post-perfusion.

Survival analyses show the trend of decreased survival for randomized PROCEED II OCS hearts compared to standard of care and similar survival curve for EXPAND study hearts.

There is uncertainty regarding the safety of OCS heart device and whether the device used may be associated with myocardial damage.

And lastly, the public health concern regarding the unknown impact of the OCS Heart System will have on the pool of transplantable donor hearts and the impact on long-term survival for transplant recipients.

Later today, the Panel will be asked to comment on how these issues impact clinical trial data interpretation and vote on the overall safety, effectiveness, and benefit-risk profile of the OCS Heart System for the proposed indication for use.

Thank you for your attention. This concludes the FDA presentation.

DR. LANGE: Thank you. I would like to thank the FDA speakers for their presentations.

I am now willing to entertain brief clarifying questions. Again, if you'll raise your hand. I see Dr. O'Connor, Dr. -- Al Stammers, Allen, and Jason.

So Dr. O'Connor first.

DR. O'CONNOR: Thank you. An excellent presentation and analysis by the FDA team. I wanted to ask Dr. Sapirstein about his "clinically meaningful survival benefit." We all recognize that in a trial this size when there's 30 events, that it's difficult to understand whether this is a true signal or not, and one could argue whether a multiple comparison

Bonferroni correction should be made on those nominal p-values, and I think the conclusion of saying there might be a trend is more appropriate.

Given that the deaths look like they occurred late or due to infection or malignancy that caused the imbalance in the PROCEED II trial, do you think there is a lack of correlation between possible ischemia or injury or the device and this late imbalance of mortality?

DR. SAPIRSTEIN: Thank you, Dr. O'Connor. This is John Sapirstein.

First, let me just point out that we were not saying that there was a statistically significant, we said we thought that the curves showed a clinically significant difference and this was manifested from the early period and continued on, and we stand by that belief. As far as what caused the late deaths, I mean, transplantation and the support of transplant recipients in the longer term is obviously very complicated, there's a lot that happens. There's a lot of confounding that can happen the farther you move out from the index procedure. That is perhaps why all-cause mortality is the metric that FDA is looking on because I think it's very difficult to definitively tease out if any of, for example, the late infection complications that might have led to death may have been in some fashion related to the early experience and even the preservation experience. That's with small numbers and the complexities, that's very difficult to do and frankly, that's what we're asking the Panel to help us tease out.

DR. LANGE: I've got Mr. Stammers, Dr. Allen, and then Dr. Jason Connor and Dr. Yuh.

So Mr. Stammers.

MR. STAMMERS: Thank you, Dr. Lange. And I would like to thank Ms. Wentz and the entire FDA panel for that very nice summary and presentation.

My question is going to follow up what Dr. O'Connor and Dr. Sapirstein were just discussing and it's using the comparator, cardiac-related survival, and the FDA clearly is asking for all-cause mortality. I'm not familiar, and I apologize for my lack of knowledge in

this in the use of cardiac-related survival which Dr. Hassanein reported in a lot of his Kaplan-Meier curves and it was not reported in the FDA. Can you comment, anybody from the FDA, on this, on the use of cardiac-related survival, specifically as a comparator to the difference in all-cause mortality, which you are recommending?

DR. LANGE: And by the way, Al, that's a terrific question, so not only will I have the FDA talk about it, but I'm going to ask Dr. O'Connor in our after-lunch to also weigh in on that, as well. But go ahead, let me send it to the FDA first.

DR. SAPIRSTEIN: So this is John Sapirstein again and perhaps Ms. Wentz would want to comment, as well. Cardiac-related mortality was not specified as an endpoint or even as something to be evaluated in either PROCEED II or EXPAND. In fact, in both studies the time frame, specified time frame for adverse event adjudications was 30 days. So the reason FDA didn't focus on cardiac related mortality is that we feel those data, which as time goes on, as Dr. O'Connor mentioned, it can become a little bit more problematic to evaluate. Those were registry reported, not adjudicated in the sense of the trial's 30-day adverse event adjudication.

So we think that those mortality results are frankly much more confounded and difficult to interpret than a much more discrete all-cause mortality and again, I'll just stress that's partly why we see such value in the randomized study of PROCEED II, because it was randomized and that makes interpretation of all-cause mortality, though somewhat limited, as Dr. O'Connor mentioned, a little more straightforward, in our opinion.

DR. LANGE: Great. Al, did that begin to address the question? Again, we'll have Dr. Jason Connor talk about it after lunch, as well.

MR. STAMMERS: Yes, Dr. Lange. I think after lunch I'll ask another question.

DR. LANGE: Great. Thanks, Al.

I've got Dr. -- Dr. Allen, I'm sorry. Then Dr. Connor and then Dr. Yuh, Dr. Moon,

Dr. Blankenship.

DR. ALLEN: Hi there, this is Keith Allen.

I congratulate the FDA, they provided a nice counterbalance to the Sponsor's presentation earlier. I was very impressed with the clinicopathologic correlation piece that the FDA presented. While I don't want to draw conclusions, too many conclusions about three cases, what I was a bit surprised by was the extremely limited amount of animal data that was ever provided to the FDA, and some of the questions in the clinicopathologic piece that it brings up could, I think, be easily addressed with well-done animal testing. So my question to the FDA was, is the data that you presented, a couple of animals, is that truly all the animal data that's been done with this device and was that acceptable to the FDA or did the FDA ask the Sponsor to do more animal testing and they refused?

MS. WENTZ: Thank you, Dr. Allen. This is Catherine Wentz.

And yes, for the PMA itself, we received an animal study of two animals. They did that on their final design. Their explanation for not providing more animal studies than they did was that they had plenty of clinical data either from PROCEED II or from OUS. We never did receive a full comprehensive animal study.

MR. AGUEL: And this is Fernando Aguel.

If I may add, to establish the safety of the device to be able to commence the trial, we did find the experience, clinical experience already, as well as the animal studies presented, sufficient to move forward with the IDE study. However, as Catherine mentioned, we did have some questions remaining at the time of the marketing application, at the time of the PMA.

DR. FARB: And if I might add --this is Andrew Farb, FDA -- to Dr. Allen's question, is a good one because we think, based on the numerous cases we see that had evidence of at least multifocal and more commonly diffused myocardial injury, those types of questions

could begin to be addressed from insights gained from some animal studies looking at just that issue.

DR. LANGE: Thank you, the FDA.

I've got Dr. Connor, Dr. Yuh, Dr. Moon, and Dr. Blankenship.

So Dr. Connor.

DR. CONNOR: Hi, Jason Connor.

So my question is about blinding, and so I understand that the doctor excising the organ or implanting the organ is unblinded, obviously, but was the Sponsor privy to accumulating data, just because the docs on the ground know what's what, the Sponsor need not be -- you know, the data can go to a CRO and they don't see that. So given the substantial changes that occurred during the course of PROCEED, I was wondering if FDA could clarify that for me because the word "blinding" didn't appear in either executive summary.

MR. AGUEL: So I'll ask Catherine Wentz and John Sapirstein if they can comment on this.

DR. SAPIRSTEIN: Yeah, so this is John Sapirstein.

You can corroborate with the Sponsor, but our understanding is that yes, the Sponsor had ongoing and continuous understanding of the outcomes as they were developing over both trials.

DR. CONNOR: Okay. And then some of those changes that were made, like can you tell if those were made in result to accumulating data? You know, we make things for safety reasons, we make changes to increase accrual rates, things like that, but I just wonder if you saw certain things going worse in one direction and if you knew that's what led to some of those changes that you noted --

DR. SAPIRSTEIN: I think -- this is again John Sapirstein -- this can only be speculation

and that's a question I believe you should ask the Sponsor.

DR. CONNOR: Okay. Yeah, thank you.

DR. SAPIRSTEIN: Yeah.

DR. LANGE: Great.

DR. ZUCKERMAN: So, Dr. Lange, can we make sure that the Sponsor addresses Dr. Connor's question after lunch?

And Dr. Connor, is your main question centered on the slide that Ms. Wentz showed where 25 additional patients were added to EXPAND at a certain time with certain knowledge of data or can you be a little bit more specific?

DR. CONNOR: Yeah. I mean, I think it was both. I mean, that situation in EXPAND but also in PROCEED, that even though it was randomized and controlled, changes were made and that's why I was simply asking about the blinding, I figured they were unblinded in EXPAND. So kind of both of them, but particularly with PROCEED II. And I didn't know, I was asking because I didn't know if FDA had done, for instance, post hoc analyses before and after sort of those protocol revisions, but I understand that's digging deep, but thank you.

DR. LANGE: And you're right, Dr. Zuckerman, we'll ask the Sponsor to address that after lunch, as well. Thank you.

We've got Dr. Yuh, Dr. Moon, and Dr. Blankenship.

DR. YUH: Thank you. David Yuh here.

I just wanted to better understand the FDA's concern about the post hoc addition of the additional extended criteria in the EXPAND trial. Was there concern that the clinicians making these decisions weren't aware of these additional extended criteria and that that may have, in turn, impacted their decision otherwise in selecting that organ or -- I just want to better understand the concern, since it seems to be a focus.

DR. SAPIRSTEIN: Yes, this is John Sapirstein, FDA.

Yes, that's one aspect of it. As I think you might've seen, from our perspective, a lot of what could be considered an extended criterion is appropriately the judgment of the clinician at the time of donor acceptance or the decision to evaluate on site and FDA understands that completely. In terms of the trial, that's what the trial was intended to evaluate, these so-called extended criteria donor organs, and it was distinct from PROCEED II, which were more standard criteria donor organs. And so, as I said, we don't know if true data regarding a given organ actually was part of this notion of characterizing the organ as extended criteria. We're not disputing that some of these findings, data, existed in the donor heart, but that is not what the trial was designed to evaluate.

DR. YUH: Thank you.

DR. ZUCKERMAN: So, Dr. Yuh, the medical monitor for TransMedics is here. Would it be valuable, after lunch, if you query him with the same question to get a better idea of what happened during this trial?

DR. YUH: I'd be happy to. I think that would be helpful, thank you.

DR. ZUCKERMAN: If the Sponsor could note that, please, Dr. Lange.

DR. LANGE: All right, we've got Dr. Moon.

DR. MOON: Yeah, I've got a couple questions. (1) one of the criteria to rule out the use of an organ was increasing lactate while it was on the machine, but there were other reasons. Were there any hearts that were turned down without a high lactate elevation that underwent pathologic evaluation but had severe ischemia or severe myocardial damage? Because that would suggest to me that lactate elevation wouldn't tell you the whole story.

DR. FARB: Fernando -- Dr. Farb, FDA -- if you could pull up backup slide 216.

MR. AGUEL: Yes, sir.

DR. FARB: So while we're pulling up a slide for this, there were 27 total hearts that were turned down and of those 27, 15 had a lactate level less than 0.5. So why don't you go to the previous slide, please? So here are the mean and ranges for the lactate level, the 27 turned-down hearts from the three studies. And what you can see is the means were above five for EXPAND and EXPAND CAP, and below five for PROCEED II and you can see the ranges, but the bottom line, you can see of the 27. Fifteen of those 27 were peak lactate less than 5.0 mmol/L. If you go to the next slide, we look at the subset -- slide 216 -- of those 18 turned-down hearts from the three studies that had echo-documented normal EF within 1 to 2 days prior to cardiectomy with stable vital signs, and I think it's the group of hearts with the autopsy findings of acute diffused multifocal ventricular myocardial damage. While the mean was slightly above five for the peak lactate, 10 of the 18 hearts had peak lactate levels less than five, the cutoff that the Sponsor proposed.

DR. MOON: Okay. I mean, this is a little concerning to me. What we need to know is, do the standard preserved hearts also have similar damage that are implanted in the patients? Did the organs that came off the device and got implanted have similar damage or -- this needs an animal study. I'm with Dr. Allen, he hit the nail on the head. You could do this in 2 weeks. Two weeks.

DR. LANGE: All right, we'll discuss it at lunch. Dr. Moon, any other questions before we break?

DR. MOON: No, I'm good. Thanks.

DR. LANGE: Okay, I've got Dr. Blankenship.

DR. BLANKENSHIP: I had essentially the same question as Dr. Moon. Do we have any data, say, from patients who died very soon after the heart was implanted or even early biopsy data of hearts that were implanted to see if they had similar findings?

MS. WENTZ: This is Catherine.

No, to my knowledge, we do not. The only thing that we have -- Fernando, if you can pull up slide 225. I did ask for the operative reports on all hearts so that I can read through them and see whether or not any observations were made on transplanted hearts and all I could find was this one from Site Number 3 that observed a patchy, hemorrhagic appearance and the external surface of the heart was rather petechial, consistent with the appearance of several other hearts we have seen on the Organ Care System. So that's really the only evidence that we have on the hearts that have been transplanted.

DR. FARB: Andrew Farb, FDA.

Dr. Blankenship, I'd just add that this is a very unique dataset of human hearts perfused, normothermia, pressure at flow, that were preserved in such a fashion and then underwent cardiac autopsy. This is a very special dataset and that's why we think the insights of that are important.

DR. LANGE: Great. I think that answers Dr. Blankenship's question.

Dr. Hirshfeld has a follow-up question, I think, related to this.

John.

DR. HIRSHFELD: Yeah. This is John Hirshfeld.

I've been concerned all along about the quality of preservation that the Organ Care System provides and two other pieces of data that concerned me are, first of all, the coronary flow rates in these hearts are at least double what a normal coronary flow rate should be, which raises the question why are these hearts that are not working choosing to have such a very high coronary flow rate and is there some mal-distribution of coronary flow within the myocardial walls which could be possibly attributable to the -- or possibly be the reason that the -- this is occurring?

Secondly, normal happy hearts metabolize lactate, they don't release it, and so the fact that the only source of lactate in the system is the heart and the lactate levels are going

up are telling us that these hearts, even if they satisfy the criteria, are running or producing lactate rather than metabolizing lactate, and that's a source of concern.

The third thing was, and I noticed in the two animals that were described earlier, there was a weight gain of about 15 or 20% of the heart during the time that the heart was on the Organ Care System and I haven't seen any data about whether the transplanted hearts were weighed when they were harvested and weighed again before they were implanted, but if that data is available, that would be interesting to see.

DR. LANGE: Great. Thank you.

So I've got three things for the Sponsor to address before we break for lunch. One was related to Dr. Connor's question, did the Sponsor have an ongoing understanding of the outcomes and how that may have influenced change or altered subsequent outcomes and/or the study. Second is, Dr. Yuh mentioned the extended criteria concerns and did that influence -- and the physician organ acceptance. And the last, as Dr. Hirshfeld said, were hearts weighed before and after to determine if there was edema.

So with that, I'll have us have a break for lunch. We'll reconvene at, let's see, 1:45 Eastern Time, is that correct? Let me check real fast.

DR. ZUCKERMAN: You're making the conversion correctly, Dr. Lange.

DR. LANGE: All right, so at 1:45. I've got two different things, so we've got -- wow. It's 1:44 right now. So let's meet at 5 minutes to 2:00, let's take 30 minutes, we'll do that. Five minutes to 2:00. Jim Foley (ph.), I'll ask you to put the countdown on and we'll reconvene. So thank you very much.

(Whereupon, at 1:44 p.m. a lunch recess was taken.)

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

(1:55 p.m.)

DR. LANGE: All right, Jim, are we prepared? It's 1:55 and I would like to resume this Panel meeting. Thank you, everybody, for joining again.

At this point we'll now proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel, to present data, information or views relevant to the meeting agenda. Aden Asefa will now read the Open Public Hearing Disclosure Process Statement at this time.

Aden.

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

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such 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. LANGE: Great. Thank you, Ms. Asefa.

The FDA has received 11 requests to speak prior to the final date it was published in the *Federal Register*. Each speaker will be given 5 minutes to speak, and I believe the first

speaker is Nina Zeldes from the National Center for Health Research.

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

Today you are asked to discuss several issues regarding the OCS Heart System. We want to highlight the importance of the concerns that FDA scientists raised that have implications for effectiveness, safety, and the benefit-risk profile of the device. First, let's discuss several of the issues FDA raised regarding the study design and conduct.

First, as FDA pointed out, selection of high-performing sites with most patients enrolled at a single site and the overall conditions of the donor hearts may make the device seem more effective. In other words, the data might not be generalizable to the real world.

Second, these and other issues affecting the results were raised by the FDA 28 times, but many of FDA's concerns were not adequately addressed by the Sponsor. Some were apparently ignored completely.

Third, the Sponsor made several changes to the device design and the clinical protocol. Most important, the device design was changed after the controlled study, that means the Sponsor has provided no controlled study data on the device that they are submitting for approval.

In terms of the clinical protocol, the company changed the statistical plan and study definitions, for example, changes to the classification of primary graft dysfunction were major in the adjudication process months or years after the transplant took place. These protocol and statistical changes should be considered scientifically unacceptable, and we therefore agree with the FDA that this raises the possibility that individual endpoint

determinations in EXPAND were more subjective than they should have been.

Fourth, the EXPAND study lacked a control group. We strongly agree with the FDA conclusion that the EXPAND study alone is not sufficient to demonstrate a reasonable assurance of safety and effectiveness. Moreover, the control study did not show superiority of the OCS Heart System, and we agree with the FDA scientists that the non-inferiority of the OCS Heart System compared to the usual standard of care does not prove clinical value.

Let's look at data on effectiveness next. Most important, the device does not appear to be as effective as the usual standard of care. Pathology results from the hearts that were turned down for transplant suggests the perfusion of the OCS Heart System may have contributed to the myocardial damage leading to the hearts being turned down for transplant. Eighteen donor hearts in the EXPAND study were turned down, which was 19% of donor hearts perfused on the OCS Heart System.

Now let's look at safety. FDA pointed out that the Sponsor did not have any pre-specified primary endpoint hypotheses tests for the EXPAND study, which was the study with no control arm. The FDA notes that in the controlled PROCEED II study, patients transplanted with hearts perfused on the OCS Heart System had a greater need for mechanical circulatory support post-transplant, had more frequent acute rejection episodes, had a lower average cardiac index, and spent longer time in the hospital in ICU. Further, within 3 years of transplantation, 17 OCS Heart System donor patients had died compared with only six patients -- six deaths of patients receiving standard of care donor hearts.

In addition, around 80% of the donor recipients in all three studies were male. Since the studies were relatively small, a patient group that is only 20% women is not large enough to conclude whether the results for safety and effectiveness would be better or worse among women.

We wanted to be here today to strongly encourage you to consider all the shortcomings of the research raised by the FDA scientists. The materials presented have not proven that the OCS Heart System is as effective or more effective than the usual standard of care. However, FDA approval should be based on evidence that a device is proven to be safe, to be effective, and to have a positive risk-benefit profile for patients. The evidence does not support that conclusion, unfortunately.

Thank you for your time.

DR. KLASSEN: Good afternoon, my name is Dr. David Klassen. I'm the chief medical officer of the United Network for Organ Sharing and I'm also the medical director of the Organ Procurement and Transplant Network. My views today are my own and I do not represent the United Network for Organ Sharing or the OPTN or HHS in any official capacity.

Cardiovascular disease, by any measure, I think, is one of the leading causes of death in the United States. Unfortunately, therapy for end-stage heart disease is extremely limited. Now, we're really talking about basically mechanical devices or heart transplantation. Certainly, mechanical devices are limited in accessibility for most patients and they are really not a long-term therapy that has been able to be expanded significantly.

By the same token, heart transplant, which is perhaps a more optimal therapy, really is also extremely limited. In 2020 there were about 3500 transplants done, heart transplants done across the United States. At any one time there are about 3600 patients on the list waiting for heart transplantation. Clearly, these numbers do not in any way address the needs for this sort of therapy for the citizens of the United States.

I think we all remember the first heart transplant that was done in 1967, Christiaan Barnard in South Africa. I was an adolescent at the time and I remember it very dramatically. I think one of the things that should be pointed out, however, is that the therapy or the storage technology that's used for heart transplantation today was also

developed at the same time in 1968 and that's static cold storage, which to this day is the gold standard for heart transplantation across the United States. This, however, does impose significant limitations and as, I think, is quite obvious, the major limitation or a major limitation for heart transplantation is the number of donors, there just really are not enough.

If you look back 30 years ago there were over 2,000 transplants done at that point and so heart transplantation hasn't really been able to expand to meet the needs that really are required. And again, the reason for this is limitation in donors, that is the major issue.

Clearly, in the last year one of the big impactful events has been the emergence of donation after cardiac death as a source of donation of donors for heart transplantation and this has been largely made possible through the development of perfusion technology.

At the OPTN, we really see our major goals as increasing the number of transplants across the United States and also improving equity for everybody on the list, as well. And I think these technological advances really are one of the avenues by which we hope to reach some of these goals.

Perfusion technology allows new sources of donors, it allows longer storage times, it allows us to address issues of geographic inequity. Access to transplantation is not uniform across the United States. This sort of approach to equity, I think, does have important consequences for everybody on the list and again, it is a major focus for us at the Organ Procurement and Transplant Network. Broader sharing again is something that we take extremely seriously. The way forward that we see is through some of these technologies and I think this sort of approach will have a significant impact going forward.

Thank you very much, I appreciate the opportunity to present these views to the FDA.

DR. PINNEY: Hello, I'm Dr. Sean Pinney, Director of the Advanced Heart Failure and

Cardiac Transplant Program at the University of Chicago. I would like to thank you for giving us this opportunity to spend a few minutes to speak about the potential clinical impact of the Organ Care System for patients with heart failure.

I have been practicing heart failure and transplant cardiology now for 20 years and over that time I have seen many of my patients die while waiting for a heart transplant. And my situation is certainly not unique. According to the most recent SRTR data, approximately 9 to 10 patients will die while waiting for a heart transplant for every 100 years spent waiting on the list, and the reason for this is quite clear. Simply, we have a supply-demand mismatch problem. There are simply too many people who need hearts and not enough hearts to go around. And since it's unreasonable to think that demand will go down given the fact that our population is aging and the prevalence of heart failure is increasing, the only way to achieve balance is to try to increase the supply of donor hearts.

Now, one way to do this, I think, is to use the Organ Care System. Not only have I had a chance to familiarize myself with the results of the EXPAND and the EXPAND CAP, I have, myself, taken care of patients whose hearts had been supported by the OCS. And using the Organ Care System allows for utilization of higher-risk donor hearts. These are hearts that get passed over frequently or discarded and not used. These are hearts that come from older donors, donors who are older than 55, patients who have left ventricular hypertrophy or the presence of diabetes or perhaps have had a cardiac arrest and some downtime that require further resuscitation before one has the confidence that these hearts are going to do well in our recipients.

Being able to resuscitate and to perfuse and also to observe these hearts while they're on the Organ Care System is a tremendous advancement. It gives us the confidence that these hearts are going to do well, and that that is most important to our patients who have been waiting for so long to receive a heart transplant.

I believe that the Organ Care System overcomes the limitation of cold storage, that is a significant technological advance in a field that is desperate for new advancement. It allows for greater travel distance to acquire these donor hearts and it allows us to expand the donor pool.

For all of these reasons I'm very excited about the potential use of OCS because ultimately, it will help my patients. Thank you for your attention today.

DR. COUPER: I would like to thank the Panel for the opportunity to present my thoughts in support of the TransMedics Organ Care System. My name is Greg Couper and I'm the surgical director of advanced heart failure and heart transplant at Tufts Medical Center in Boston.

My career as a heart transplant surgeon began in 1986. In that era, in routine and open complex surgery, oxygenated blood-based myocardial protection strategies were rapidly supplanting the original cold crystalloid solutions. Could this be feasible in transplantation, as well? It has been my privilege to be associated with TransMedics since those early days.

By way of disclosure, I've been a compensated member of their scientific advisory boards, pilot trial, and clinical events committees on previous trials. I was the chair of data safety monitoring board for the OCS Heart EXPAND trial being presented today. On behalf of my colleagues, I can vouch for the integrity of the data and safety of the trial. I am not currently involved in the DSMB in this trial.

Over decades of dogged, dedicated effort by TransMedics leadership, engineers, and many others with a singular focus on perfecting a normothermic, blood-perfused portable organ preservation platform has led us to the OCS multi-organ platform we see today. Over time I've seen the large prototypes morph into a compact user-friendly clinical system that is readily utilized in any donor hospital and via any mode of transportation. Many

preclinical animal studies and subsequent human clinical experiences have led to a better understanding of the management of the heart on the system.

From a transplant surgeon's perspective of heart perseveration, it is clear that our standard technique of cold solutions without oxygenation or perfusion do not allow for the resuscitation of hearts suffering from the physiologic derangement inflicted by the pathologic process of brain death. That we have a myriad of different preservation solutions and strategies used by heart programs across the world, over decades of experience, leads us to believe that no one superior concept has been found to date. There is the need for something better that could be universally applied, especially in the extended criteria donor pool.

Over many years we've heard of the great public health burden of end-stage diseases like heart failure. Despite being the gold standard therapy, heart transplantation's impact has been small in comparison. It provides a great health benefit to relatively few in that population that might benefit. The major constraint is limited donor availability as currently practiced. Growth of volume will require expansion of the donor pools for maximizing utilization. Extended criteria donors with less than perfect hearts need to constitute a major proportion of the volume if we seek to decrease wait list mortality or offer the opportunity of transplant to more candidates.

Over the last few years, the heart transplant community in the United States has brought about changes in allocation policy to address issues of geographic disparity and access to donors, and to providing donors to those with the most urgent need for transplant. By virtue of greater sharing across previously artificially derived geographic zones, programs have seen a dramatic growth in imports from outside of their region, a greater frequency of air travel and greater distances traveled. By necessity, this impacts and lengthens ischemic time. Total ischemic time factored heavily in the inclusion criteria

for this OCS Heart EXPAND trial. The OCS Heart platform has proven itself quite capable of ameliorating this prolongation of ischemic time and enabling the long-distance recovery safely with good outcomes. It has the potential to raise the performance level of all heart transplant programs across the U.S., as we strive to maximize utilization of every donor opportunity.

Thank you.

DR. SMITH: Good morning, my name is Jason William Smith. I'm a cardiac surgeon and director of the transplant program, heart transplant program at the University of Wisconsin in Madison, and was formerly a transplant surgeon at the University of Washington in Seattle, where I participated in the EXPAND trial utilizing the OCS TransMedics device, and I would like to speak this morning in support of the device based on my experience there and share a few points about that experience.

One of the great challenges we faced at the University of Washington was access to donors. In the remote areas of the Northwest, the extreme transport times that we faced truly limited the number of donors that we had access to for our large population of heart failure patients. Over the 30 years prior to this, there's really been no growth in donor availability and continued growth in patient populations meeting heart failure in the aging population and in the instance of heart failure, and that's led to a severe shortage of access to organs, exacerbated by our geographic limitations in the Northwest. Because of those, we elected to participate in the EXPAND trial utilizing the OCS device for expanded criteria donors to try and improve our access to donors.

The experience that we had there was one of improved organ function, of improved access to donors that we wouldn't have otherwise been able to use, and better performance from organs from great distances, some of them upwards of 2000 miles, that we were able to transplant in that trial. The entire program had a very positive response to

utilizing this device, both in the ultimate outcomes that the patients experienced with good organ function, with good long-term survival, and with rapid access to transplant so that patients were not waiting and languishing on the transplant list developing additional comorbidities and difficulties that they face at transplant.

So we would strongly support the use of this device more broadly to augment organ availability, to put organs into regions where they're most needed, and to improve the sharing of organs across the country. In fact, it was that experience in the EXPAND trial and the good outcomes that we had there that led us here, at the University of Wisconsin, to participate in the new trial utilizing DCD heart donors, and we're very excited about that trial, as well, and what that might mean for our patients.

DR. DANESHMAND: I want to thank the Panel for allowing me to speak today with regards to the TransMedics OCS Heart device. I feel like I can provide a unique perspective on the utility of this device in heart transplant. I am a heart and lung transplant surgeon, I trained at Duke University Medical Center in my residency and cardiothoracic fellowship training. I also did cardiothoracic research training at Duke University Medical Center. I was faculty at Duke University Medical Center up until 2019. In 2019 I transitioned to Emory University where I am the section chief for the section of thoracic transplant and mechanical circulatory support, and I continue to be an active heart and lung transplant surgeon. I participate in all of the international societies and groups with regards to heart and lung transplant surgery. I feel that I have particular expertise with regards to this topic, as I have utilized the OCS Heart and Lung devices clinically and as part of the research trials that have led to this panel discussion.

In particular, I want to focus on the OCS Heart device and its utility for providing and matching organs that otherwise would be underutilized or unavailable to patients who are in dire need. As the Panel is well aware, there is a significant shortage, both nationally and

internationally, of donor hearts. Unfortunately, despite this shortage, most of our eligible donors are not utilized and that has to do with either logistical issues, inexperience, or other donor-related or logistics-related complications that arise from the real-world experiences with transplantation. The power of the OCS device is that it can overcome a lot of these issues.

We at Duke were a very busy heart transplant program prior to getting the OCS device. Once we had the OCS device, however, we were able to be aggressive in utilizing organs that were otherwise turned down farther and farther away from our hospital. This allowed us to transplant our patients quicker and before they got very sick. Our experience with the device at Duke was very good.

After I left Duke, for a period of time while I was at Emory, we did not have access to this device and daily I would have organs that I'd be offered that I could not utilize because I did not feel comfortable with the ischemic time or maybe with a little bit of ventricular dysfunction or hypertrophy, things that with the OCS device I use not only comfortably, but effectively and prolong many patients' lives with.

Fortunately, we were able to participate in the OCS DCD trial and with the DCD trial, we have been very successful in utilizing this device again. Seeing the device again, using it again, has provided me a renewed hope for my patients and for the ability to provide the service.

In summary, the OCS device in real-world applications has a significant impact on the transplantability and the rate of transplantation for patients who are in dire need of heart allografts. And the studies are clear, the device works and I think we should have it available to use in the community.

Thank you for your time and I'm happy to address any specific questions the Committee may have either on line or off line.

MR. SULLIVAN: Hi, I'm Pat Sullivan and I'm the co-founder of the Heart Brothers Foundation out of Marlborough, Massachusetts. I'm a transplant survivor, and we have over 77 volunteers that help transplant heart failure patients across New England and Upstate New York and the Southwest. We offer peer-to-peer support and experiential help to patients going through the journey, and I can tell you that the journey is grueling and arduous. What we try to do is offer hope when, at times, it seems hopeless. And believe me, from personal experience, there are times when it seems hopeless.

One of the things that the Heart Brothers has discovered is that many patients opposed to transplant end up with PTSD because you're on a 24/7 roller coaster that you cannot get off day and night for various reasons. Those journeys are -- each one could be abrupt, some could be this thick, some could be this thick. But in the 6 years that the Heart Brothers has been in existence, we have monitored what is new and what is coming and what is exciting in the industry and one can offer that hope.

My personal journey was I was diagnosed with heart failure at 38 years old. I was a high-level executive at a major computer company and I thought I had pneumonia and several times they told me no, it's heart failure, and I didn't know what it was. The first thing you do as a heart failure patient, like I did, was you go on line and you read that 50% of all heart failure patients die within 5 years of diagnosis. And that's a tough thing to take mentally, in every aspect.

My personal experience is I was filled with ups and downs of various things because atrial fibrillation, getting shocked 26 times back into rhythm and ending up with end-stage heart failure in November of 2011, and I ended up in the hospital at Tufts Medical Center and they told me I needed a new heart and it was a year-long stay in my case. I received what is called an LVAD, left ventricular assist device, which is really not a solution or a cure because there is no real cure other than transplantation and an LVAD is really a bridge to

transplant and in my case, that bridge was filled with things such as MRSA and all the equipment that was inside my body, the drive line, the machine itself, and the defibrillator, stents, all had MRSA on it, so it was a death sentence if I didn't get a heart fast, a death sentence.

The LVAD experience is something that is hard to describe, but one of the best ways to do it is to say realizing you have to plug into a wall at night in order for you to survive. That was very daunting for me and it is the most -- my wife actually had a $10,000 generator put in our house because we lost power a lot and if we didn't have that, I could die in my sleep and so she installed that while I was in the hospital.

What we think, as Heart Brothers, and my personal experience is offering hope to patients and getting more hearts available. Like New England has always been one of the hardest to get a heart in the country. For many years it was the hardest, and it's still one of the harder places to get a transplant. Equipment such as the OCS from TransMedics, we feel, is one of the critical things that can change, in a dramatic way, the availability of hearts in America and just by knowing that the availability is increasing offers what we try to do, is offer hope.

I'm honored to be asked to speak on their behalf and I want to thank you for this opportunity.

MR. MALLORY: Hi, my name is Ron Mallory and I'm a 65-year old and I live in Charlotte, North Carolina, where it's a nice day, it's kind of chilly out, but it's okay. I have no financial disclosures.

In 2009 I was playing golf and starting having an arrhythmia attack. I spent the night in the ICU and 2 days later I was told that I would need a pacemaker defibrillator. In 2016, after 7 years of dealing with more than two dozen shocks from that defibrillator, I went to my cardiologist to find the best doctors who could perform a cardiac ablation. I was

referred to Duke. As I say, my condition had gotten worse, so the doctors immediately put me on the transplant list. I received an LVAD pump as a bridge until I could get my heart transplant. My heart was getting weaker and weaker. There was no idea how long it would take to receive a transplant. It could have taken 2 to 3 years.

During my treatment with the LVAD I had complications like internal bleeding and an infection. Previous to these complications, my doctor at Duke told me about a heart in a box and the possibility that this might give more changes to receive a donor heart. As I was talking it over with him, I decided to enroll in the OCS Heart System trial.

On February 15th, 2017, less than 1 year after having the LVAD pump installed, I got a call from my transplant coordinator to say they had a heart match for me. What was amazing was that my donor's heart was coming from Texas, roughly 1200 miles away. It's been 4 years with my heart and right now it's very good. I'm back playing golf once or twice a week, I travel, and I have a part-time job that keeps me active. I'm so blessed by God and thankful to the staff at Duke Medical Center and to the OCS Heart System.

What I want folks to remember is that this OCS System is the reason I got a new heart. It saved my life and it can save others, too, by connecting them to donor hearts no matter where they live.

Thank you for listening to me.

MR. CHIBULSKI: Hi, guys. My name is Mark Chibulski, Jr. I'm 36 years old, from Salem, New Hampshire. I have no financial disclosures.

I had received a heart transplant in December of 2019 at Mass General. Before that, I was on the waiting list for about 15 months with an LVAD. I was 34 when I found out that I had heart failure. I was very active and athletic playing baseball and fishing and going to the gym and out of nowhere I just felt sick for a couple weeks and went into the walk-in, figuring that I just had a flu or something, and they sent me to the hospital right away and I

found out my heart was only pumping at 10 to 15%. I spent almost 2 months in Mass General before they decided to go with the LVAD, which basically saved my life at the time. And from there, I ended up getting back into playing baseball even with the LVAD. I started a YouTube channel called Fish with Heart, since I'm a big fisherman, and basically that shows my story from getting the LVAD, still continuing to have the best life I could with the LVAD, but it still wasn't the best I wanted, so I really needed that heart transplant.

And after 15 months with the new program, I got the call from my surgeon and I signed up right away for this and within a week, I got the call, went in for the transplant, and have felt great afterwards. Eight weeks after my transplant I was already in the batting cages practicing and played a full season last year. Well, I'll say a half a season because of COVID. And I'm back to the gym, back to fishing, continuing to do videos to inspire people to not give up.

Actually, from two of my videos, I had two fellow patients from out of state contact me through those videos who also got on the same program and had received hearts shortly after me in the same way at Mass General. So definitely reaching out and spreading the word helped and here I am today, I got baseball practice tonight and living my best life and I just feel that this program is definitely good to help more people get that wait down from 15 months and go from there.

Thank you.

MR. KESHLER: Hello, everyone. My name is Jordan Keshler, I'm 40 years old and I'm from Central New York and was happy to be here today with no financial obligation to provide you with my testimony, the living proof of what this machine and procedure is possible of.

Before receiving my DCD heart transplant, I was living on a left ventricular assist device, also known as an LVAD, with a milrinone central line drip and a heart function of 9%.

I was told with my blood type of O, my chances of transplant were 2 to 3 years. Daily life tasks had become quite a challenge to me, including walking to the mailbox, walking up a flight of stairs or even lifting my 8-month-old baby. I started to feel more like a burden on my family rather than a provider.

One day, while on a social media support group, I came across a fellow recipient and now friend of mine that had just received a DCD trial heart. I reached out to him and he was more than willing to answer all questions I had and put me in touch with the Massachusetts General Hospital transplant team.

After discussion with my wife, it was an easy decision that this was the best choice for our family, even if I was randomized into the standard of care arm. I had seen my father pass away while on the heart transplant list and I didn't want my daughter to endure the same experience as I.

With testing concluded, Massachusetts General Hospital decided they would accept me into their program and enter me into the DCD trial with hope I would be selected. The selection process came back favorable and then 4 days later, I found myself going into surgery for a heart transplant. I never felt so scared and happy all at the same time. Following surgery, I spent 11 days in the hospital and was allowed to return home to my family.

Fast forward to today, 13 months later, I've had zero complications and at my 1-year checkup my heart function is at 66% with no rejection. I have been able to return to everything I love, such as golfing, hiking, snowmobiling, and playing with my daughter. Since transplant, I try best to help heart awareness through social media and I also had the Chronicle in Boston take my story to their TV show. By doing this, I am hoping to make people more aware of organ donation and how many lives they can save.

As you vote today, I would like you to think about my daughter that is now going on

2 years old and could've been without a father, if not for this amazing trial and OCS Heart System.

Thank you for your attention.

MR. ROCKWOOD: Good morning, my name is Glenn Rockwood. I'm 65 years old and I live in Halfmoon, New York. My family has a long history of heart disease on my father's side. My father died at 50 years of age, I had a brother die at 38 years old, and one of his sons died just 2 years ago at 32 years old, only 8 months after being married.

With my brother and my nephew, the causes were ventricular tachycardia, a condition affecting the heart's electrical system and rhythm. I had this situation, as well, and was fortunate to have been diagnosed in my forties and implanted with an internal cardiac defibrillator to monitor the rhythm of my heart. This ICD, along with medication, provided 18 years of security and insurance against this condition.

Unfortunately, in the fall of 2016, I developed a bacterial infection in my bloodstream which ultimately attached itself to the wires that connect the ICD unit to the heart. This necessitated the removal of the ICD unit along with the wires. The ICD extraction was done quickly; however, the surgeon was not able to remove all the wires during the surgery. Therefore, subsequent open heart surgery was required to remove the remaining wires. Although the operation was successful in the removal of the wire, there was considerable damage caused to the heart itself and at that time, I was given 6 months to live and immediately started the heart transplant process at Massachusetts General Hospital.

Fortunately for me, Mass General was part of the OCS Heart clinical trial during this time period and they offered me the opportunity to participate in it. Since I was facing a wait time of 45 days to a year or longer for a traditional donor heart, I was excited to have as many doors open as possible to finding a donor heart as quickly as possible. So I signed

the contract to be part of the trial and 4 days later I received my new heart. I was up and walking the day after the transplant and out of the hospital the following week and this past February, I celebrated my fourth heart birthday.

Life before transplant was fairly normal; I owned my own business, traveled extensively, and was involved in many aspects of local government. However, over the course of those 18 years, my heart disease gradually worsened, which left me with less and less energy to carry out my daily activities, let alone being able to rush through an airport to catch my next flight. I ultimately decided to sell the business because I could no longer keep up with the workload. This left me with a more sedentary lifestyle which was frustrating and devastating for me since I had always been somewhat of a workaholic and loved working outdoors. I even started to plan for a very limited future, no longer looking forward to retirement age, believing I wouldn't live that long.

Life since transplant has been more fulfilling than I could ever have imagined. According to my wife, I now have too much energy. I'm able to exercise and enjoy walking 15 to 20 miles a week and find myself living a much healthier lifestyle. Pre-COVID, we were back to enjoying social events, Friday night date nights and hosting family gatherings, which always brought us much joy.

I'm also on the advisory committee of the Heart Brothers Foundation, which is a group of transplant survivors who help people currently experiencing heart failure navigate the transplant process. I'm on the board of the Capital Region American Heart Association and two of their subcommittees. I have participated in the Heart Walk for 11 years and have raised over a hundred thousand dollars for the American Heart Association during that time. I'm now planning to retire June 30th of this year and looking forward to traveling extensively once again. And when I'm home, I'll be walking and working outdoors, which always brings me great pleasure.

I want to thank you for your time today, allowing me the opportunity to share my story. And as you vote on this important matter, please remember my story. The OCS Heart provided the opportunity for the best possible outcome for me and could do the same for thousands of other patients waiting for a new heart today.

DR. LANGE: Great, thank you. I now pronounce the Open Public Hearing to be officially closed and we'll proceed with today's agenda.

So we'll start with the Panel deliberations. Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. Additionally, we request that all persons who are asked to speak identify themselves each time so we can get it properly transcribed.

And during the next hour we'll open up the floor to questions for both the Sponsor and the FDA. Prior to that, we had posed a number of questions mostly to the Sponsor to answer during lunch and so I'll ask Dr. Hassanein to address some of these questions.

Do you need me to go over them, Dr. Hassanein?

DR. HASSANEIN: Thank you, Dr. Lange. With your permission -- Waleed Hassanein, TransMedics.

With your permission, I have them tabulated and with your permission, I'd like to start with the pathology question. We have Dr. Jake Demetris and he would like to address the Panel to specifically address all the discussion points and the presentation from FDA related to the donor heart pathology in the turn-downed hearts. Would that be okay with you, Dr. Lange?

DR. LANGE: If this addresses a specific question, yes.

DR. HASSANEIN: Yes, yes.

DR. LANGE: Okay. And the question that it's addressing?

DR. HASSANEIN: It was addressing the question about the -- I believe there was a

question in the FDA presentation specifically talking about the pathology and --

DR. LANGE: Actually, I don't recall any question --

(Cross-talk.)

DR. HASSANEIN: Okay. All right, I thought it was related to the pathology and it was a component for the pathology and a component for animal. But I'm happy to start wherever you want us to start, Dr. Lange.

DR. LANGE: So what I may do, I may pose some questions. I mean, this is not a time for you or the FDA to address each other, but actually to address the question. So let's go through those. The first was having to deal with individuals who had a longer than 4-hour ischemic time and risk factors and their outcome related to the others, and that may have been answered in the FDA.

So Dr. O'Connor, I think you had asked that question. Do you feel like the FDA had answered that with their presentation?

DR. O'CONNOR: Yeah, I think Dr. Sapirstein, on slides 159 and 160, answered that perfectly for my --

DR. LANGE: Great, so that will save some --

DR. HASSANEIN: Sorry, we were trying to put that answer -- but I'll take it down.

DR. LANGE: Oh, okay. So Dr. Hassanein, somebody had asked how many centers who were in the aggregate had refused these hearts, and I don't know if you have that information.

DR. HASSANEIN: Yes. We looked into the SRTR match run refusal data and the match run refusals are not collected by center, they're just collected by the number because that's the software that UNOS runs the match run with, so it's a combination of the patients and the centers and we don't split them out by centers and patients.

DR. LANGE: Okay, I appreciate it. Also on that slide, that slide had shown the

number of refusals for 138 hearts, but we know that only 116 were in the study and that is 22 were not suitable, so do you happen to have that data for the 116?

DR. HASSANEIN: We do. It's 66 and it was -- I believe it was a part of the EXPAND trial results from the core presentation. The average run, match run refusal for the EXPAND trial only -- oh, I apologize. That was for the transplanted hearts, was 66.

DR. LANGE: As I'm looking, I just want to make sure that I understand. I believe it's on slide 70 that you have. Do you want to put up --

DR. HASSANEIN: Yes, it's coming up, Dr. Lange.

DR. LANGE: Okay, great.

DR. HASSANEIN: Can we put the slide up, please? Slide 70, CO-70.

DR. LANGE: Yeah. See, there were actually 116 that were transplanted and there were 22 that weren't, but the 138 encompasses both of them.

DR. HASSANEIN: That's correct, that's correct. And we can get that, that was not one of the questions, we were looking only in the match run, but we have that data. We just presented it that way because that's how we assessed the match run refusal for the entire donor hearts that were entered into our trial, but we can get the exact number for the transplanted 116 patients.

DR. LANGE: That would be great, that would be great.

Dr. Connor.

DR. CONNOR: Okay, yeah. Thanks. I had a clarifying question here. So when you're talking about basically a site gets offered a heart and if the site says no, if they have 20 donors or 20 recipients, that counts as a 20, is my understanding.

DR. HASSANEIN: Yes. If the heart matches those recipients, Dr. Connor. So the way that --

DR. CONNOR: Okay, yeah. So that's good. That was my next question, was that --

how tight is the match? Is that on the list? Is that blood type, is that like precisely eligible for those 20 -- so okay, I think you answered that. Thank you.

DR. HASSANEIN: It's very tight. It's very tight and it's regulated by UNOS, it's not anything related to TransMedics or the study.

DR. CONNOR: Okay, thank you. That's helpful.

DR. LANGE: Great, thank you. Someone had asked about cross-clamp time and outcomes.

DR. HASSANEIN: Yes.

DR. LANGE: Go ahead.

DR. HASSANEIN: So can I please get cross-clamp time greater than 4 hours, equal to or greater than 4 hours and then the cross-clamp time between 2 and 3 hours? Let me start with the cross-clamp between 2 and 3 hours. There was only one patient in the EXPAND and CAP, there was only one patient that fit that criteria of cross-clamp time of 2 to 3 hours and the outcome of that patient, that patient was a long VAD recipient of 28 months on VAD, he had significant drive line infection secondary to multi-drug resistant *Pseudomonas* infection. The patient was Status 1A, was transplanted, the patient had primary graft dysfunction and the patient died on post-op Day 64 related to complication of generalized sepsis.

And then the next one was cross-clamp time, AA-6, please. Slide AA-6, please. There was another question related to cross-clamp time of greater than 4 hours and any one additional factor, and there is a total of 20 patients and their outcome is a hundred percent survival, and the slide is here. That was the question about cross-clamp time of greater than 4 hours plus one additional risk factor. Twenty patients, hundred percent survival through 12 months. So I believe, Dr. Lange, that addresses the cross-clamp questions. Please correct me if I'm wrong.

DR. LANGE: No, I think so. Any other questions concerning that issue from the Panel?

(No response.)

DR. LANGE: Great. Okay, Dr. Hassanein, thank you. There was a question about the distance traveled.

DR. HASSANEIN: Yes.

DR. LANGE: And I know you showed a map with --

DR. HASSANEIN: Yes. Can we please have AA-8, please? So this slide here, Dr. Lange, looked at EXPAND transplants, the distance traveled. Mean was 912 miles compared to the distance traveled for PROCEED between donor and recipient of 225 miles. Donor to recipient.

DR. LANGE: Terrific.

DR. SELZMAN: Do you have a range on that?

DR. HASSANEIN: Give me one second. Dr. Selzman, I'll get you the range within 2 minutes. The range is -- I apologize, it's right here. I apologize.

The range is zero to 2500 miles. There was one patient that was transplanted at the same institution due to a significant complicated VAD explant, a multi-redo procedure and a total cross-clamp time of that patient, even though it was in the same hospital, was close to 7 hours.

DR. LANGE: Great.

DR. HASSANEIN: And the outer limit is 2500 miles.

DR. LANGE: Dr. Allen, I see your hand up. Yes, sir.

DR. ALLEN: Can I ask a follow-up question, please? This is Keith Allen.

What is the distance traveled in your EXPAND patients pre and then after the allocation change 18 or 20 months ago? We know that the allocation changed and we're

not going to -- it's not a decision time to get into that discussion, but if this put a premium on travel to reallocate organs, and I'm curious if you saw a data difference or an outcome difference pre and post this allocation change.

DR. HASSANEIN: Thank you, Dr. Allen. Waleed Hassanein, TransMedics.

We have not looked at that, but we're happy to look into that through the afternoon, pre-allocation change and post-allocation change, but we have never looked at it that way.

DR. ALLEN: So how many patients, pre-allocation, are in your EXPAND versus post?

DR. HASSANEIN: I would need to get the exact date of the allocation actually going into effect and I can easily look into the database and give you the exact number. We will look into that. If that's an important question for you, we'll be happy to get that exact data for you in the afternoon.

DR. LANGE: Okay, great. Any other questions concerning distance?

Dr. Moon.

DR. MOON: No, not distance. A different topic.

DR. LANGE: Go ahead, Dr. Moon.

DR. MOON: Okay. Yeah, I know Dr. Hassanein was going to talk about the pathology. I would really like to hear that because I had concerns about the lactate levels correlating with the extent of disease. And also, how do we know the patients that got implanted hearts after being on a device didn't have that same extensive disease and just seemed to survive?

DR. HASSANEIN: Great. Thank you, Dr. Moon.

With Dr. Lange's permission, I will turn the presentation to Dr. Jake Demetris, who is the expert in transplant pathology. Dr. Demetris, can you please unmute your mike and get on the camera, please?

Dr. Demetris?

DR. DEMETRIS: Yes.

DR. HASSANEIN: Okay, great. So Dr. Demetris, I'm pulling up the slide that you asked us to pull up.

DR. DEMETRIS: Okay. First, as an introduction, Jake Demetris from the University of Pittsburgh. I'm the director of transplant pathology which includes heart transplantation, and I have extensive experience with cardiac transplantation through clinical trials and organ transplantation as a core laboratory. I reviewed all of these hearts blindly, that means without any clinical information. I didn't want to be biased before I reviewed the gross and the microscopic, and I felt that was important so that I didn't see what went on clinically and that would influence my interpretation.

The first point that I want to make is ischemia reperfusion injury is totally unavoidable regardless of the preservation method, whether you use cold storage. Taking a heart out of one body and transporting it and putting it in another body, you have to preserve it for at least a period of time.

The second point, I think, addresses a point of discussion which was raised, you know, what do hearts look like in transplantation? And there was no control group for this study, so the most appropriate control group, in my opinion, is the ischemic damage seen early after transplantation in perioperative myocyte ischemic injury.

And the published literature suggest that most hearts already harbor some type of, at least, ischemic damage or potential for ischemic damage. And the two studies are cited there. There are several others. There is one study from Italy where they did autopsies on patients that died shortly after transplantation and showed that these acute-type ischemic changes were present in a hundred percent of recipients who died within 7 days of transplantation, and that was coagulative necrosis and contraction band necrosis. One of

the problems in comparing these two arms is that the "potential" for ischemia reperfusion injury can't be detected with cold static storage until the donor heart is transplanted into the recipient, that's the whole idea behind the concept of ischemia reperfusion injury, that the pathology is recognized when you reperfuse the organ. For example, if you take a cold static storage heart and do a biopsy at 1 hour, it's going to look the same as it does at 8 hours until you put it in the recipient and then you're going to see a lot of necrosis.

From my perspective, the OCS System offers the benefit of proactive identification of dysfunction while the device is ex vivo instead of responding to what happens by chance in vivo in the transplant recipient with the cold static storage that we currently use, and that's consistent with the low rate of primary graft dysfunction in EXPAND and CAP versus literature, literature rates with cold storage.

And from my perspective, at least looking at all the material without any clinical information other than I knew that they had been turned down because they were on the OCS device, I didn't see any unusual pathology findings that OCS was actually damaging hearts. From my perspective, all the observations were consistent with ischemia reperfusion injury that would be present under any other circumstances.

Next slide. Yeah?

DR. LANGE: I'm sorry, I'm sorry. Is this in response to a question, Dr. Demetris?

DR. DEMETRIS: What's that?

DR. LANGE: Are you answering a question?

DR. DEMETRIS: No, I saw one of the panelists had the hand raised. Dr. Burke.

DR. LANGE: Yeah. Well, go ahead. I'm happy to ask Dr. Burke to speak when showing him the slide and to take our time.

Dr. Burke.

DR. BURKE: Yeah, I also have a lot of experience both in clinical as well as

experimental transplant, mostly heart, and I want to 100% agree with Dr. Demetris. I was actually not very impressed with much myocardial damage, the word "damage" was used extensively, whereas really the primary feature that I saw on the slides was contraction bands. Now, I don't know what the effect of this device is on inflammation, if there was donor blood or blood in the perfusate, but to cause contraction band necrosis you really should, at least according to some, see some inflammatory reaction, which I didn't see any here. And I can guarantee you, if you took a heart that was in cold storage, hung it on the machine, waited 5 minutes, it would look exactly the same, there would be contraction bands everywhere.

Similarly, if you transplant a patient, if you were to have the opportunity to look at the heart after a few minutes to an hour, you'd see contraction bands everywhere, similar to what we see, for example, in the baboon model I look at.

And also, I'm sure Dr. Demetris has seen heart biopsies after transplant and we often see ischemic damage in the first and second biopsies, I've seen it in up to 30% of the myocytes, and these are in patients without rejection with a normal ejection fraction. So my take-home from the pathology presentation was that the slides actually look pretty good, I didn't see anything that looked irreversible.

DR. LANGE: Great, thank you.

DR. DEMETRIS: I would like to add here that when you --

DR. LANGE: I'm sorry, Dr. Demetris. Dr. Demetris, I'm sorry. I just want to make sure we get through all the questions, so if there's a question you're answering, that's fine. If it's a point you're making, I'll ask you to just hold off on it.

DR. DEMETRIS: Okay.

DR. LANGE: All right.

DR. ZUCKERMAN: Dr. Lange, can I interject a moment? At some point, could you

allow the FDA to respond to the two pathologists, specifically, Dr. Farb?

DR. LANGE: The answer is yes. Do we want to do that now? We've got some time now, so we'll allow Dr. Farb to engage and then obviously, I held Dr. Demetris, so I'll ask -- and then I'll ask Dr. Allen to speak.

So Dr. Farb.

DR. FARB: Andrew Farb, FDA.

So I did have the benefit of reviewing the submitted pathology reports and the histomicrographs and the gross photos, but in addition to looking at the clinical data. And while there can be perhaps some debate about the clinical significance of seeing some contraction band necrosis, what is impressive here is that something has happened to these hearts, right?

We had hearts that were functionally normal in stable patients being placed on this machine and then deemed not good for transplant at the time of pericardiectomy when the surgeon was ready to do the transplant. Some of that may have been based on lactate levels, some of that may have been based on lactate plus the observations of the heart not working well, something went wrong, right, with the hearts after being perfused on this device as it was intended to be used.

Now, while one can see focal changes on biopsies and on other types of preparations looking at hearts, what's impressive in Dr. Demetris's reports of noting the diffuse nature of the ischemia reperfusion injury and damage was what impressed us at FDA, that in some proportion of cases this was occurring. The exact mechanism may not be clear. This is a complex device. We applied heart manipulations, specific infusion pressures and flows, as well as ischemia time and warm beating heart perfusion time. So we do see enough of that to note it to the Panel as a potential issue with the device either not preserving the myocardium as it's intended to do, because we think it's supposed to be physiologic

perfusion or actually part of the heart-damaging process that led the implanting surgeon to get as far as ready to implant that heart, but putting a brake on it and saying don't want to go forward with that.

DR. LANGE: Okay. Dr. Farb, thank you.

Dr. Allen, you had your hand up.

DR. ALLEN: Yeah, thank you. Keith Allen.

So I'm not a pathologist, I'm a heart surgeon that does transplants, and if I believe what Dr. Burke just told me and Dr. Demetris just told me, then the pathology seen on those rejected hearts, we would see that on any cold crystalloid heart and so why were those hearts rejected? It sounds like you would have had a hundred percent use. It doesn't make sense to me that you negate what we're seeing on pathology and those hearts ended up in the bucket. That's a real concern for me.

And similarly, to me, I go back to the question I asked the Sponsor and actually, I asked the FDA, I'm very surprised that this product has gotten as far as it has gotten on minimal, if any, animal data because what we're arguing about now could be put to rest with a good animal study. That would be easy and inexpensive to do.

DR. LANGE: Thank you.

Dr. Hassanein, are you -- actually, Dr. Bonde first. I'm sorry, go ahead.

(Off microphone response.)

DR. LANGE: Dr. Bonde, I believe you're muted. I'm sorry, you're muted, sir.

DR. BONDE: Thank you.

My question was that the histological damage that we are seeing before we attribute it to an intervention, there are multiple steps, as everybody who's involved with the transplant here knows, that it is due to inadequate cardioplegic arrest and handling of the heart while you're trying to harvest it, and then the time it takes for you to mount on the

OCS System, that is before the heart goes on the OCS System and the cross-clamp injury, which may get amplified about the system, which is natural with any perfusion system, that some injuries will get amplified. But looking at the duration of the time on the OCS System just in 2 hours, we do use perfusion system for whole body perfusion like ECMOs and all, and they don't cause that much damage. But also, as the point that has been raised, you know, whether this can be answered through animal studies or whether this can be answered through the declined human hearts is also open to question.

DR. LANGE: Great. Dr. Selzman.

Or I guess you, Hassanein.

DR. BONDE: But there is one more thing I wanted to say, that these are very high -- the physiological seems to be hyper-perfusing the coronary circulation in an empty beating heart, it's very high perfusion pressures. And one can contrast that with the hundred years of experience with --

DR. LANGE: In other words you're saying it's non-physiologic.

DR. BONDE: It's non-physiologic.

DR. LANGE: Yes, sir.

Dr. Selzman.

DR. SELZMAN: Yes, thank you.

So I don't want to beat a dead drum, but since we're on this I'd like to challenge Dr. Farb just a little bit. So because there is no control group, which has been acknowledged, how do you respond to the fact that what you're showing is actually proving the point of the Sponsor, meaning that the hearts that were not utilized actually were utilized for -- not utilized for the right reasons? In other words they saw the lactate go up, they saw these other indicators, and so the alternative explanation for your findings is actually that you're proving that their other mechanisms of evaluating this heart are

actually quite good.

DR. FARB: Well, I think a couple responses. It's a good question. This is Dr. Farb from FDA.

You know, some were turned down perhaps because of the lactate. Some lactates were not above the threshold, and the documentation of the exact reason for the turndown is not clear that the surgeon was not satisfied in some way with the appearance of the heart. But when we have a heart that is showing the pathologic findings of reperfusion-type damage, that's a cue, and we had a heart that was otherwise doing well in the body, now we have a heart that is inappropriate for transplant with diffuse myocardial damage.

DR. SELZMAN: Well, unfortunately, there's a lot of hearts that start with an EF of 60% that we accept and some of them don't work so well, right?

DR. FARB: Right.

DR. SELZMAN: So the clinical data, trying to correlate those, I think, is a little challenging. And again, there is no control group, so it's almost impossible to make that statement. And I would just add and I'm not trying to defend anybody, but the slide you showed was the peak lactate level, and I think the trend was probably just as important as the peak. And so even if it was a 4.8 or maybe it went from two-to-three to four-to-five and so that was what actually caught them. So anyway, I'm struggling a little with trying to take this great data that you're showing and trying to really convince myself that it's true/true and actually related.

DR. FARB: Well, one of the problems is the term trend was not really defined a priori and so that is a judgment, and the trending was similar between the transplants and those that were turned down. We really couldn't detect a difference between what might be -- you know, what may be termed a trend. So then we're left with hard, more objective-type criteria like a lactate, a number that we like to use and other types of criteria that are much

softer. So I understand your point, but the degree of the injury, again, this is a unique dataset, we don't have human Langengdorff models, like perhaps this one, to actually figure out what might be the more refined way to optimally perfuse them and what pressure, what temperature and what flow and for how long to have the optimal outcome. But we do see a substantial number of turn-downed cases with a good deal of diffuse myocardial injury. We don't have a control group, that's true, but this is a device that is supposed to be superior to what we're doing now and we're seeing a good amount of damage in at least the hearts that were turned down and a fair proportion of them.

DR. LANGE: Dr. O'Connor, I saw your hand --

DR. FARB: That could answer every question.

DR. LANGE: I'm sorry, Dr. Farb, I didn't mean to interrupt.

Dr. O'Connor.

DR. O'CONNOR: A quick question regarding this. Either the Sponsor or the FDA, was there any relationship between the experience of the operator or center in turndown rate?

DR. LANGE: Dr. Hassanein?

(Off microphone response.)

DR. LANGE: I'm sorry, you're on mute, sir.

DR. HASSANEIN: Dr. Lange, I have to address that. There was a question specifically about lactate trends that were turned-downed hearts that were rejected for a lactate less than five. With your permission, can I address both questions at the same time or shall I just address this question --

DR. LANGE: Go ahead.

DR. HASSANEIN: -- by Dr. O'Connor?

DR. LANGE: Go ahead.

DR. HASSANEIN: Sure. So there was a total of 10 hearts that were turned down with

a lactate less than five. The vast majority of those hearts -- and all this data was submitted for FDA -- were actually greater than 4.5. And to Dr. Selzman's early point, the lactate trend went from 1, 1 to 2 up to 4.8, 4.7, 4.4, 4.9, 4.7, 4.5, and 4.75. The reasons for those trend hearts are as follows: three hearts --

DR. LANGE: Dr. Hassanein, I think that you've answered the lactate question.

DR. HASSANEIN: Sure. Yes, to answer Dr. O'Connor's question, we noticed that of those 10, there were two hearts that were turned down, they happened to be the first case for each of the individual centers, two different centers. That's the only thing that we noticed, that those two hearts were the first experience with the OCS for these two centers and they turned them down (1) because the lactate trend was going up and approaching 4.75 and despite maximum perfusion pressure and flow. The second one was turned down because of a heart block and the operator felt uncomfortable to accept this heart.

The lactate trend was pre-specified in the protocol, so just a correction that the lactate trend was pre-specified as one of the transplantability criteria in addition to a lactate level.

And then finally, if truly the OCS is injuring donor hearts, you would have seen that in the actually transplanted hearts, not for the rejected hearts. You would have seen that in the PGD rates in the transplanted hearts. If the OCS is injuring donor hearts, we would have ended up with a PGD post-transplant in the 30, 40, or higher. The opposite is true, we saw 8%, which is one-third of that reported in the literature in the U.S. So that is where our clinical interpretation of the data, that actually the OCS weeded out bad hearts that shouldn't have been transplanted.

And the last point I'm going to make on this is to Dr. Selzman's point, many times donors with a great ejection fraction in the sixties and they resulted in non-functional severe primary failure, even with cold storage. So histological finding and contractility

really hasn't been correlated, at least in the field of heart transplant. So these are my points related to lactate.

DR. LANGE: Dr. Yuh.

DR. YUH: Thanks, David Yuh.

I just wanted to give Dr. Hassanein an opportunity to answer the direct question in terms of why not more extensive animal studies. I think there is a concern that there was perhaps even over-circulation on your system and it looks like in midcourse of the EXPAND trial you actually raise the upper limit of the coronary flow rates, and I'd just like to understand the rationale behind that when it's already supraphysiologic.

DR. HASSANEIN: Sure. Thank you, Dr. Yuh.

Dr. Lange, may I answer that question? It was actually on one of the lists of the questions that I was supposed to answer.

So I want to clarify one point, the OCS had extensive animal testing. We're confused and maybe we need to clarify the FDA's comments that we only submitted two animals. That is not true. The fundamental work around the OCS actually happened and it was independently done in a blinded fashion at Brigham and Women's Hospital by Dr. Padera there, where we actually established the perfusion, the first perfusion clinical use model based on coronary flow and lactate, where we blinded the pathologists and their experienced heart transplant pathologists --

DR. LANGE: Dr. Hassanein, was that information presented to the FDA?

DR. HASSANEIN: Absolutely. In addition, there was an additional nine animal reports, totaling 18 hearts, animal hearts got submitted to the FDA. The two that's cited by Dr. Wentz were literally the last report of the last validated version of the technology. So that's one question, that's clarification that I think ought to be clarified.

The second thing, to Dr. Yuh's question about the change in upper limit, that was

done only to make sure that we're giving the users the maximum flexibility to perfuse the donor hearts to try to minimize, as much as we could, the turndown of donor hearts and that's the only clinical reason why we increased the upper limit, to enable them to be -- to maximize perfusion, to reverse whatever picture we're seeing on the lactate to maximize utilization. And we ended up with a utilization rate of 84% with the great outcomes we described with 8% PGD and the like.

DR. LANGE: Dr. Wentz, there is some controversy about the animal studies and what you all presented and what the Sponsor is representing, could you clear that up for us?

MS. WENTZ: So I will try. So within the PMA itself, all we got was *n* equals two animals and as I stated from the beginning, there was not a comprehensive animal study done on this system. As I also said in my presentation, the Sponsor did perform several other smaller studies, either for the previous PMA or for the IDE, the EXPAND IDE, primarily to address changes in device design. So there was not a comprehensive study and we asked several times and again, like I said before, they stated that they had significant clinical data to demonstrate safety and effectiveness so they did not need to do a comprehensive animal study.

DR. LANGE: Okay. All right, thank you.

MS. WENTZ: I would also like to state that the Padera paper that we just saw, they did provide that to us. That, again, just like the Hamed one, was an abstract and that was performed back in 2006, I believe.

DR. LANGE: Great. I see Dr. Katz and Dr. Moon and Dr. Allen.

We still have some other questions I want to get to, by the way. Go ahead.

DR. KATZ: Just to follow up on that, I'm curious. If the FDA was uncomfortable that the Sponsor hadn't done adequate preliminary animal studies, why did they move ahead with the PMA?

MS. WENTZ: Right. So as you have seen, this device has a long history and it actually started in 2006 when they did some clinical studies in Europe. I believe our first study in the U.S. included a combination of some limited animal studies and the limited clinical data from Europe in order for us to allow them to move forward in the U.S. with a feasibility study. And then from there forward they relied on the clinical data and then the limited animal data to validate any design changes.

DR. LANGE: Dr. Moon.

DR. MOON: Yeah, did they do any studies to determine they should do it at normothermia or -- I mean, did you test it at 36, 34 degrees which might have had a better preservation effect on the heart?

MS. WENTZ: So as far as I know, they did. At least the studies that we got, it was done at the same parameters as the device arm, so 34 degrees.

DR. LANGE: Great. I've got Dr. Allen and Dr. Cigarroa.

DR. ALLEN: Right. I appreciate Dr. Hassanein giving me that additional animal data, but it doesn't answer my question. There's no control in that study. You put 40 hearts on the OCS and you didn't change anything, you just put it on and then looked at histology. What I've been asking for is, did you address the issue? How does that compare to standard of care, which should've been performed prior to doing your randomized trial so you could optimize your system? Where is your randomized animal data looking at OCS versus standard of care?

DR. HASSANEIN: Right. Thank you, Dr. Allen.

DR. LANGE: I'm sorry. You know, unless the FDA has had a chance to review that data, we're not going to talk about it.

So Catherine, have you seen a study of that, that is OCS versus standard -- okay, so it may have been done but we've not had a chance -- FDA has not had a chance to review it,

so we're not going to talk about it.

So Dr. Cigarroa.

DR. CIGARROA: Thank you, Dr. Lange. This is Joaquin Cigarroa and this question is directed to the pathologists from both the Sponsor and FDA.

The Sponsor misstated that they had increased the coronary blood flow -- excuse me, the coronary perfusion rates in an effort to improve perfusion of the myocardium. In observations of the donor hearts that were not transplanted, there was a notice that there was an increase in weight. Is there a concern that the supraphysiologic flow rates and the consequent edema may, in fact, adversely impact myocardial perfusion due to tensile issues that obliterate capillaries secondary to edema and may actually be causing more harm?

DR. LANGE: Great. Dr. Cigarroa, thanks for that question.

Jim, if you'll allow Dr. Demetris to answer and to respond to that, and then we'll have Dr. Farb respond.

Dr. Demetris.

DR. DEMETRIS: Yeah, I specifically looked at the microvasculature for evidence of thrombosis for a no-reflow phenomenon to see if the smaller blood vessels were not open and I was not particularly struck that that was a particular finding or was obvious in most of these grafts. I mean, there was some capillary endothelial swelling, but not a lot. And like I mentioned before, there wasn't any unique pathological findings that I wouldn't see in a heart otherwise transplanted.

For example, the interstitial hemorrhage that you see is present in a lot of hearts, even in the donor before preservation and especially after preservation. So without a control group it's very hard to rigorously compare one method with another but, my final conclusion, I didn't see anything that I thought was unusual, put it that way. There was edema in areas, but it was always associated with other signs of ischemia, like wavy

myofibers. You know, it wasn't a diffuse edematous process where all the myocytes were separated, it was always focal.

DR. LANGE: Thank you, Dr. Demetris.

Dr. Farb.

DR. FARB: Andrew Farb, FDA.

So I think Dr. Demetris and I are on the same page. I think the finer point is that interstitial edema was a common finding but associated with the acute ischemic injury, and I think that's the point here, that we have a lot of acute ischemic injury with contraction band necrosis, coagulation necrosis, interstitial edema, and interstitial hemorrhage. So that's how I would respond to Dr. Cigarroa's question.

DR. LANGE: All right, thank you.

I'm going to let Dr. Vetrovec and Dr. Kwon, and then we're going to move from this -- we've got a couple other questions I just want to make sure we get to. So I don't want to beat just a bigger horse to death, but Dr. Vetrovec.

DR. VETROVEC: Yes, one quick question --

(Audio feedback.)

DR. VETROVEC: -- increased the systolic pressure and it strikes me that that could have exacerbated all of these issues of ischemic injury by increasing wall tension. So in any of your analyses have you looked at what the impact was or is there a change in outcome or anything related to that change in the sequence? Because it seems to me that that was overloading the ventricle.

DR. LANGE: Dr. Hassanein.

DR. HASSANEIN: Thank you, Dr. Vetrovec. Waleed Hassanein, TransMedics.

Dr. Vetrovec, we did not look at that specific question, and back to my earlier point, it's because your post-transplant outcome had PGD of 8%. If the OCS --

DR. LANGE: Dr. Hassanein --

DR. HASSANEIN: Yes.

DR. LANGE: -- you know, I appreciate -- I'm going to stop for a second.

DR. HASSANEIN: Sure.

DR. LANGE: And excuse me for chastising you. You had a 90-minute presentation and the FDA had a 90-minute presentation and this is the time for the Panel to ask questions of you and the FDA, and I'm sure that you have points you'd like to make and the FDA has points they'd like to make, but what I'd like to do is to make sure that the FDA Panel has the opportunity to ask you all questions. So this is not about side comments or side points from the FDA or from the Sponsor, this is about an opportunity for the Panel to ask you all questions and to address them.

DR. HASSANEIN: Yes, sir.

DR. LANGE: So I want to make sure that that's clear --

DR. HASSANEIN: Yeah.

DR. LANGE: -- to you and to the FDA, as well. A nod of the head will be fine. Great. Okay, thank you very much. And I'm sorry about that, I know there's a lot everybody would like to talk about, but we have a limited amount of time and still more questions to get to.

In fact, Dr. Kwon, you had your hand up.

DR. KWON: Thank you. I think just looking back on the last 45 minutes or so, we're really asking one question, does this device lead to myocardial damage? And we've cited the lack of controls, we've asked if there have been animal models, we asked is it correlated to the rising lactates, which is the predominant mechanism with which these organs are evaluated on the device. We do have a simple control and I know it's not perfect, but we excise left atrial tissue on every transplant and the devices -- the ones that come off the device and the ones that are used and not used would all have -- I realize that's not the

perfect solution to the ventricular pumping chamber, but wouldn't that kind of answer our questions with a control if we saw some correlated damage in that segment that we excise on every heart that's used on a system and answer some of these questions for us?

DR. ALLEN: It wouldn't provide the control for the standard of care because the atrial appendage is removed before your control arm would be reperfused.

DR. KWON: I understand that. You know, the ventricle, taking slices of the ventricle on this device which is unloaded, I wouldn't say is a great replicate either, so it's a surrogate and it's maybe the best we have, and you'd have to standardize it to the control, which is the hearts that were utilized off of the device with those that are not and that is, I think, one mechanism of getting some answer to this question independent of slicing out a piece of the ventricle, I guess, or some other mechanism.

DR. LANGE: Thank you, Dr. Kwon.

Dr. Hassanein, somebody asked a question about how many of the PROCEED patients met EXPAND criteria and their outcomes and I don't know if you have had a chance to look at that.

DR. HASSANEIN: Sure. Can I get, please, slide AA-9? Thank you.

Yes, Dr. Lange, we looked into that. There were 17 cases in the PROCEED that matched the EXPAND criteria and this is the outcome between the two, PROCEED II OCS versus EXPAND and CAP patients with the outcomes in both groups. And the causes of death in that table.

DR. LANGE: And Dr. Selzman, I think you asked that question, does that address --

DR. SELZMAN: Yes, thank you.

DR. LANGE: Thank you for the question. I appreciate you being responsive to that. There was a question about if you had encountered either device malfunction or cannula failures.

DR. HASSANEIN: Yes. There were two device malfunctions related to cannula failure, one in the outflow tract and there was a perceived kink in the outflow cannula from the PA cannula. The investigator proceeded to disconnect the cannula from the PA line because of the perception that this might be causing backpressure on the heart. Ultimately, the lactate was rising, the RV was not pumping well despite the venting. This came in as a device issue, it wasn't logged in as a device malfunction. We looked into it and we found that that PA cannula line, the outflow tract has a pressure resistance of 2 mm, so we didn't -- we communicated that back to the investigator that it's probably not the cause, probably the RV was not adequate and that's why -- that's one.

The second one, there was also a reported case where the aorta cannula, due to a user error, was not connected properly to the device and during transport, the aorta cannula came loose and the investigator had to reconnect it. Both cases were the first cases, these are the same cases I talked about earlier. The first case is in both prospective sites and both were turned-down hearts.

DR. LANGE: Great. Excuse me, Mr. Stammers.

MR. STAMMERS: I'm sorry. I apologize, Dr. Lange, for taking long to unmute. And thank you. Al Stammers.

Dr. Hassanein, can you comment on one of Dr. Shah's last slides, and I think several other people put it up, and it was on the 70% of non-utilization of donor hearts, about 8400 hearts a year go unused. In an optimized situation with OCS being approved, what would you estimate the number of hearts of that 8400 or 8000, let's just say, could potentially be used and be transplanted?

DR. HASSANEIN: Sure. If you apply an 84% utilization achieved here in EXPAND and CAP, you can easily double the rate of heart transplant in the United States, again assuming that not every heart will be suitable for transplant. Data from Europe suggests a 50%

increase, at least from the UK, that was reported on in November of 2020. But if you just apply the EXPAND and CAP results to those unutilized DBD, you can easily double the rate of heart transplant availability in the United States.

MR. STAMMERS: That would be very generous, I would think. Getting back to what you just mentioned with 50%, do you feel that's more realizable? You know, 84% seems like it would be the gold standard or what you'd shoot for, but I don't know. I think being conservative, that seems high to me.

DR. LANGE: Great. Thanks, Al.

Dr. Selzman, I think you had a question and then Dr. Yuh.

DR. SELZMAN: Thank you. So Craig Selzman.

I'd like to ask the Sponsor to comment on some data that was presented by the FDA and also presented by you, related to the use of mechanical circulatory support in the PROCEED trial, which was about a quarter of the patients needed some type of MCS support. I think that's what I saw in your data and from your packet. And this was theoretically not as extended, the donor criteria. And then we see that there's less need for that. Okay, I think that's different than the thing that's in our packet. I thought I saw 26%.

DR. HASSANEIN: No, because the FDA double-counted the mechanical circulatory support. There were nine cases in the OCS and seven cases in control.

DR. SELZMAN: Okay.

DR. HASSANEIN: These are the results and three of the nine were the three early deaths, one related to PGD, one related to the hyperacute rejection, and one related to the acute protamine reaction.

DR. SELZMAN: Okay. Well, that's a good response to that one. Let me ask the second part of that question, which is in the EXPAND trial, we know our colleagues at Duke are special and there's some special water and derm that makes everything go perfect, but

the results coming from Duke are over 50% of the EXPAND -- I think it was over 50% had a survival that was different than the rest of the world. Could you explain that and offer -- when we open this up to different centers, how are we going to reconcile that issue?

DR. HASSANEIN: Thank you, Dr. Selzman. I think I would -- Waleed Hassanein, TransMedics.

I would refer you to the proper pooled analysis that we presented earlier. The FDA only presented half of the endpoint, they presented the survival. The poolability analysis had to include the primary effectiveness endpoint which has the component of PGD. So one center might have great survival but may be also associated with a slightly higher PGD. So that's why when we did the poolability, we did it with the appropriate poolability analysis to the primary effectiveness endpoint. So that addressed the poolability.

I think, you know, related to the broad application of this technology, I go back to my earlier point that we feel very strongly that we have a very well thought out training and support program that's been battle tested and the verification to that or validation to that is the rapidly enrolling DCD program, 25 major U.S. heart transplant centers.

DR. SELZMAN: Could I follow that up and ask Dr. Sapirstein to comment if the FDA is concerned that there's not a generalizability of this technology to the overall community?

DR. SAPIRSTEIN: Yes, John Sapirstein, FDA.

It is something we are concerned about. In any dataset that we look at, when there is, for example, domination by one site, that makes it more problematic for us for the interpretability to be generalizable. And an important fact, to get back to something I believe that Dr. O'Connor had asked, we did see some differences in, for example, the notion of turning down donor organs related to experience. Obviously, a lot of the sites, as both we and the Sponsor acknowledge, had small numbers. But when we looked at the data, we did think that there was a component of experience that did have an impact on

the interpretability of the data.

DR. LANGE: John, would you go back to slide 150? Because I think that's the one that's in question and it talked about circulatory device use in the EXPAND trial post-transplant and it looks like it's about 27%, 26.7%. Slide 1-5-0.

DR. SAPIRSTEIN: We can get that. That's correct, that's what is shown.

DR. LANGE: Okay. It's been represented that you all double-counted.

DR. SAPIRSTEIN: I would ask the Sponsor if they -- obviously, we had no intention of double-counting, so I'm not quite sure why -- on what basis we're double-counting.

DR. LANGE: Go ahead, Dr. Hassanein.

DR. HASSANEIN: Thank you, Dr. Lange. Waleed Hassanein.

My comment related to the double-counting was related to the PROCEED trial where the FDA inadvertently counted a balloon turned into an ECMO or a balloon into a VAD and double-counted, but the patients were nine and seven. And I presented that and the comment was related to the PROCEED outcome. I wasn't aware that we're talking about EXPAND.

DR. LANGE: I'm sorry. So you don't have any issue with the EXPAND data here that shows the 27% mechanical circulatory support post?

DR. HASSANEIN: I would like to verify that. Given that the severe primary graft dysfunction rate in EXPAND was 8%, that strikes me as a little bit high, so --

DR. LANGE: Well, in fact, I was going to ask you about that. I was going to ask you how we have 27%.

DR. HASSANEIN: Exactly, exactly. So I'd like to verify that. I believe there's also an element of double-counting because we know that moderate PGD includes balloons and we know that some of the centers that are cited here may have higher rates of balloons, so it will hit the safety endpoint but not the severe PGD. So please allow me to verify that,

Dr. Lange, but right -- just looking at it, it doesn't add up. Eight percent severe PGD doesn't result in a 27% mechanical circulatory support, so there's something not adding up here.

DR. SAPIRSTEIN: Dr. Lange, this is John Sapirstein, FDA. Can I just make one comment about this?

DR. LANGE: Yes.

DR. SAPIRSTEIN: Yeah, we're not talking in this slide, as everyone can see, about mechanical circulatory support in EXPAND, we're not talking about PGD. As everyone knows, PGD is defined by 24 hours. So it's not inconceivable -- I do not have these data in front of me right now -- to say that some of these incidents of mechanical circulatory support, which we're being told we double-counted, are not tied to PGD.

DR. LANGE: Right. I mean, that goes to my point. It doesn't make sense where 27% needed to be on a mechanical device while they're in the hospital yet PGD is only 8%, it just doesn't make sense.

DR. HASSANEIN: It doesn't, but if we pick it up on the --

DR. LANGE: I'm sorry, Dr. Hassanein --

(Cross-talk.)

DR. HASSANEIN: I apologize, I apologize. I'm sorry.

DR. LANGE: Thank you. Somebody had asked, and Dr. Connor asked, whether the Sponsor had ongoing understanding of the outcomes during the trial. Dr. Hassanein, you're on mute.

DR. HASSANEIN: I apologize, I apologize. I would like to ask my colleague, Dr. Miriam Provost, our head of regulatory, to address that question as it relates to EXPAND given that she's the one who's communicating with the FDA on this, and I will come back and address this specifically about PROCEED, any protocol changes in PROCEED.

DR. PROVOST: Hi, I'm Miriam Provost with TransMedics. So the question, I believe,

is related to when was the request for the expansion of the EXPAND trial made. So that was filed in 2017 and it was filed in response to some study design considerations or recommendations from FDA. FDA had actually recommended that we increase the sample size and do a poolability analysis, and so we agreed to do that, we increased the sample size by 20 subjects to 75 subjects. And that was approved by FDA in August 2017.

DR. LANGE: Great. And again, just to the broader question and not only that specific point, but obviously there's an ongoing trial and it's obvious that it's difficult to blind, but was the Sponsor aware of outcomes prior to the end of the trial?

DR. PROVOST: Well, we had to report -- one of the requirements of doing IDE studies, we have to file progress reports every year to the FDA and we have to summarize the data, it's a requirement. So we were aware of some of the results of the EXPAND trial because we had to submit it for these annual reports. But I just want to clarify that the increase in sample size did not have anything to do with the outcomes or anything related to data that we had submitted in annual reports, it was filed because it was a recommendation by FDA and we thought it was a good idea and we wanted to do it and also do the poolability analysis that they recommended.

DR. LANGE: No, in the initial EXPAND trial, one of the centers, and in fact the best performing center, composed 39% of the population and in the CAP trial it composed 59%. Is that just a statistical aberrancy or was there --

DR. PROVOST: I think Dr. Hassanein addressed that in terms of the fact that the way transplant centers work, there's some that are high volume and also the poolability analysis is a statistical test that we did and it was in our statistical analysis plan, and that's what we did and that's what it showed, is that the data could be pooled.

DR. LANGE: Right. And these are all high-performing centers, though, and one wouldn't expect that the center jumped from 39 to 59% more transplants.

DR. PROVOST: Oh. Well, also remember that the CAP is still ongoing, so that was a very experienced site and they just kept rolling as the CAP was getting going. So I mean, the CAP is not finished yet, so as far as the total percentages of any one center, we can't really say what that is but that will be, I guess.

DR. LANGE: So Dr. Connor, I know you had -- do you want to -- does this address the question that you have or just all questions directed towards the Sponsor?

DR. CONNOR: Yeah. And I think it related to PROCEED II, particularly since it was randomized without changing enrollment criteria and whether they were unblinded, particularly, to the randomized trial.

DR. PROVOST: Yes, I will ask -- Dr. Hassanein will address the PROCEED II questions.

DR. HASSANEIN: Thank you, Dr. Connor. Waleed Hassanein, TransMedics.

Related to the PROCEED protocol changes that occur in PROCEED, occurred primarily due to two reasons. Both were feedback from the investigators to increase trial enrollment, which was lagging behind because the original criteria of enrollment was really -- everybody commented to us that these are old criteria, that you don't have these types of recipients on the waiting list any longer, virgin (ph.) chests, no concomitant renal transplant, etc.

The second feedback was to streamline data collection. The original protocol that was written according or -- you know, very close to the Celsior trial included a lot of redundant data collection, and there was significant feedback from the investigators and their resource groups to streamline this process and streamline specifically the reporting. So there was nothing related to the outcome or there was nothing related to -- and it was changed for both arms. So it's really for trial logistics, not more than anything else. And at the time the trial wasn't even enrolling, given these limitations. So we can -- we didn't -- we can't really argue that this was due to outcome-related --

DR. CONNOR: No, that's good and I looked closer at lunch and realized you basically

expanded, so it wasn't like you took patients who were doing poor on yours and --

DR. HASSANEIN: Yes.

DR. CONNOR: -- exclude them, that you expand, for instance, to renal transplant patients.

DR. HASSANEIN: We actually include more high-risk recipients because the original protocol was very, very strict and the transplant center said we don't have those patients anymore or -- you know, very few of them.

DR. CONNOR: Okay, thank you.

DR. LANGE: Dr. Selzman, I believe you have a question and -- you'd like to direct.

DR. SELZMAN: Yeah. I think I see Dr. Shah and Dr. Schroder still on the call and I'm having trouble getting over this 25% support after transplant. So that's not our typical utilization of post-transplant MCS and so I'd be curious to get your insight, being in the room on the tables, if that reflects your experience, especially as you guys are both the lead -- certainly, at the Duke center, I can't remember national but -- and how you guys might explain the use of all this MCS after the EXPAND patients.

DR. LANGE: Great. So Jim, audiovisual. If you'll please allow Dr. Shah, I see he's entered the room. And if Dr. Schroder can, as well.

So Ashish, if you'll unmute.

DR. SELZMAN: Or Dr. Schroder, I see him. I see him.

(Cross-talk.)

DR. SCHRODER: This is Jacob Schroder from Duke. I appreciate your time and the question.

So what I will tell you is that our experience is that it's significantly lower and it's reflected, just like the trial, in a significantly decreased rate of primary graft dysfunction. You know, as I said in my presentation, prior to this our published rate of PGD was 31% and

now it's down below 10% and the trial shows that. I'm not sure where a 25% rate in the trial of MCS actually comes from, honestly. I think we have to understand that this expands the donor pool by successfully transplanting people and that's the most important thing about this, I guess, that if I use an extended criteria donor heart then I don't fly to Salt Lake City or Kansas City or Chicago or Nashville and take a normal heart for centers who are more risk averse. But our rate of PGD and mechanical circulatory support in the trial is very low.

DR. LANGE: Jacob, thank you.

Dr. Shah, are you able to unmute?

(No response.)

DR. LANGE: All right.

DR. SELZMAN: So maybe the Sponsor -- sorry, Dr. Lange. Maybe the Sponsor could break down MCS use by site and maybe it was the sites with less experience, if Duke Medical Center is not using the MCS, and maybe that would be a teaching point for us, but also it would be helpful to have a better sense. I mean, one out of four transplant patients getting some kind of circulatory device is unusual.

DR. LANGE: Yeah.

DR. SELZMAN: Even recognizing that --

DR. LANGE: Yeah, sorry. Fernando, go ahead.

Thank you, Craig.

MR. AGUEL: Yeah. Thank you, Dr. Lange.

DR. LANGE: Identify yourself, Fernando.

MR. AGUEL: Oh, sorry. This is Fernando Aguel, FDA.

I'd like to see if Dr. Sapirstein can clarify the timing of the endpoint for MCS use versus the timing of the primary graft dysfunction assessment because that may help clarify

things.

DR. SAPIRSTEIN: Yeah, this is John Sapirstein.

This is what I was alluding to before, the primary graft dysfunction is restricted to 24 hours by definition, that's the only time frame involved, whereas the other metric we're discussing, mechanical circulatory support, was throughout 30 days or initial hospitalization. These data would have been gotten from Sponsor datasets that we obtained and we will try to, if necessary, identify the specific area within the PMA submission where we've derived these data.

DR. LANGE: Dr. Moon.

And then I have -- I want to get to Dr. Yuh's question.

Go ahead, Dr. Moon.

DR. MOON: Yeah, just a follow-up to Sapirstein. If somebody got an intra-aortic balloon pump and then an ECMO, I presume they might have been counted twice in your report, is that right, where it was essentially just one patient getting multiple therapies. May be that literal.

DR. SAPIRSTEIN: It's difficult for me to say definitively right now. I don't believe that that is the case, thankfully, when I look at the data in front. But again, we can try to clarify this. If it's important for the Panel, we will do that.

DR. LANGE: And so actually, as I look at the data, Marc, there were 20 individuals and the devices are more than 20, there are 29 devices.

DR. MOON: Okay.

DR. LANGE: Yeah, so the 26 was by patient. A good question. Great.

I have Dr. Katz, then I want get to Dr. Yuh's question.

Go ahead, Dr. Katz.

DR. KATZ: I wonder if some of them were pre-transplant balloon pumps, if it was

after the change in the allocation scheme and maybe some centers just left them in initially for 24 hours or so post-op, and that might explain it because it said 18% of them were balloon pumps. Again, that's just a guess. I'm wondering where it came from.

DR. LANGE: A good question, a good question.

Dr. Hassanein, Dr. Yuh had asked about extended criteria concerns and did they influence in the acceptance, cardiac acceptance rates.

And then, Dr. Yuh, if you have a follow-up question to that.

DR. HASSANEIN: Would you like me to address that, Dr. Lange?

DR. LANGE: Please. Yes, sir.

DR. HASSANEIN: And with your permission, I would also turn to Dr. Schroder to correct me if I'm wrong. The data that we collected in our eCRF came directly from UNet, that is the source for all the donor information. And Dr. Schroder can comment better than I do how important the UNet information is in the donor. So every criteria we have in our eCRF came directly from the UNet, so it was an original UNet, it was an original eCRF, and whether or not that impacted the acceptability. I would ask Dr. Schroder to comment directly on it given that he's the one who's reviewing these criteria and determining whether these patients would be suitable for the EXPAND trial or not.

DR. SCHRODER: Jacob Schroder from Duke.

Sorry, Waleed, what is the question, specifically?

DR. HASSANEIN: The question, Jake, was whether investigators were aware of the donor risk factors to include them, to include these donors into the trial when you decide whether or not these donors are suitable for EXPAND protocol or not.

DR. SCHRODER: Yeah. Jacob Schroder from Duke.

Yeah, absolutely, we are. I mean, as many of the people on the Panel know, the process of choosing an appropriate donor is not A plus B equals C, there's plenty of math in

there, and so we know about the donor risk factors and it's not just the donor risk factors, but you're only willing to take on so much risk for certain recipients, too. It's a very complex process. I wasn't involved in all the turndowns, obviously, but some of the turndowns were probably related to donor factors, maybe the lactates, which may be appropriate, but then also in specific recipients and being willing to accept that much risk in a certain recipient.

But I will say that we have been very successful, as multiple people have said, and some of it is learning curve, but we also are very willing to take on risk for our patients in Durham and we're not in a major metropolitan area, and so we've always been willing and I'll say again, our results show it and that's why people here at Duke have been convinced that this works.

DR. SAPIRSTEIN: Dr. Lange, this is John Sapirstein. Can I clarify the mechanical circulatory support for you?

DR. LANGE: Yes, sir.

DR. SAPIRSTEIN: Yeah, so these numbers are correct, these were from the validated dataset that the Sponsor sent to us on use of post-transplantation mechanical circulatory support. The overall total of 26.7% is their reported number and as everyone suspects, there was potential for a given individual to have more than one type of post-transplantation support. But these numbers were from the EXPAND dataset that the Sponsor provided us.

DR. LANGE: All right. So perhaps the Sponsor can kind of explain to the Panel how the PGD rate is 8% but the mechanical device use afterwards is about 27%.

DR. HASSANEIN: Dr. Lange, I'm trying to do that as we speak because the numbers don't add up. Eight percent of severe PGD, I think that's verified between us and the FDA. And I looked even at the moderate PGD, which covers the recipient up to 30 days, and both

the FDA and TransMedics agreed that it was 15.5%. When you add 15.5 and 8, they don't add up to 27%, so I'm trying to figure out where the discrepancy is from unless there is double-counting. But we're trying to look into that ourselves and as we know, they should not be additive because the eight will probably be counted already in the 15 for this, so I'm trying to get more granular answers to this as we speak, Dr. Lange.

DR. LANGE: Thank you, Dr. Hassanein.

Dr. Kwon, you had your hand up, I see.

DR. KWON: Thank you. Maybe I'm getting hung up on this whole PGD at 24 hours and the mechanical support at 30 days kind of thing. Are we to read into this narrative that the patients do not emerge from the OR, at least for the first day, with evidence of PGD and then decline and then end up on some sort of mechanical support? That's the question I would ask both Dr. Hassanein and Dr. Sapirstein.

The other question is, is our definition of PGD too rigid? What is this 24-hour dogmatic kind of adherence to the PGD definition? Because we know that it doesn't end at 1 day. When someone's on PGD, it's a lingering effect and so maybe our definition is too stringent.

DR. LANGE: Yeah. Dr. Sapirstein.

DR. SAPIRSTEIN: Yeah, this is John Sapirstein, FDA.

We actually agree with what you just said, Dr. Kwon. It is a very strict time course and we looked at the source data and we saw, for example, that there was a patient who was on an intra-aortic balloon pump but the balloon pump was essentially placed after being on a lot of inotropic support coming out of the operating room shortly after the 24-hour time point. This patient actually was initially considered by the investigator to be primary graft dysfunction, severe, and that was re-adjudicated or adjudicated by the medical monitor in accordance with the ISHLT as not being severe primary graft dysfunction

because the balloon pump ended up being put in after 24 hours.

DR. HASSANEIN: May I provide my answer to that question, Dr. Lange?

DR. LANGE: Yes, sir.

DR. HASSANEIN: So Dr. Kwon, the strict definition of the PGD in the protocol comes directly from the ISHLT guidelines. However, to address that particular concern, we have two endpoints, the severe PGD according to the ISHLT as the composite of the primary effectiveness endpoint, which is limited to 24 hours. However, for the safety endpoint we went all the way to 30 days, so that captures all mechanical circulatory support or any moderate or severe PGD up to 30 days.

To address the specific point that Dr. Sapirstein said, there was one case that was adjudicated exactly as he described, but what he did not mention is the same medical monitor upgraded five PGDs because the center entered them as no PGD and he upgraded them to moderate PGD because a balloon was inserted after the first 24 hours. So it was done, that adjudication process was done consistently. The data clearly shows severe PGD was 8%, the safety endpoint was 15 and a half percent. I'm trying to figure out where this 27.6 or 27.5% came from because again, the FDA and TransMedics agreed that 8% is correct and 15.5 is correct. We're trying to get -- right now, my team is looking to see where that discrepancy is.

DR. LANGE: Dr. Hassanein, I appreciate it. I don't ever remember the FDA saying they agreed that the severe was --

(Cross-talk.)

DR. HASSANEIN: I apologize, I apologize. I thought that was presented as 8%, but I apologize if I mischaracterized it. I apologize.

DR. LANGE: Okay. So accepted.

We have time for, I think, one last question and we'll take a break. Dr. Yeh, it's you.

DR. YEH: Thanks, everybody. I have a question and maybe it's directed to Dr. Schroder and I'm going to ask the same question of our Panel when we talk internally, especially with the cardiac surgeons, which is, there was talk about it being unethical to randomize these sort of expanded-type patients and I'm curious, we haven't heard the evidence to support why it's unethical to have done standard of care for such patients.

And secondarily, why is it, from your standpoint, ethical to have used the TransMedics device in these patients? What is the evidence supporting both the unethical nature of randomization, as well as the ethical nature of doing this single-arm trial? Just in your thought process, kind of.

DR. SCHRODER: Jacob Schroder from Duke.

That's a great question. I'll explain it using an example. So we have a 44-year old donor who has a history of alcohol abuse, 20 minutes downtime, a little bit of coronary disease, LVH, the septum is 1.5. That is a turndown for essentially a hundred percent of centers in this country. The reason we've been successful at Duke is that in the past we've used some of these donors if they had one high-risk feature but only if they were close. So if they were in Raleigh, North Carolina, then we would probably say yeah, we'll go look at that. And so the way I've convinced people at Duke that this was a good trial and we should participate heavily, is that every time a donor would come up like this I would say well, would we go look in Raleigh and everyone would say yes.

Well, the actual ischemic time from WakeMed Hospital on the far side of Raleigh, in a standard of care cold storage heart, is over 90 minutes, so essentially the same as the TransMedics, honestly. And so again, that's why people at Duke, everybody, the whole team got behind this trial and we were very successful and have been successful. So I think if you use that example, no one -- I would not randomize that donor heart and I fully recognize that that -- you know, this is a very homogenous donor group and so you can't

generalize that to everybody, but there were a number of hearts in the trial that I would never have randomized even with our higher tolerance for risk, honestly. Does that answer your question, Dr. Yeh?

DR. YEH: It does.

DR. LANGE: It does.

Dr. Connor, you have the last comment and it's a 3-minute comment.

DR. CONNOR: I don't need three, okay. This is Jason Connor.

No, I mean, I guess my comment to their -- I keep hearing how great Duke is and that's wonderful, as someone who lives in the Southeast myself, but I mean, I'm hearing Duke is aggressive in which organs they take even with standard of care and if Duke can be so aggressive in taking organs with standard of care, why don't you take those same organs and randomize? I mean, we're all thankful for Bernard Fisher, right, who pushed and pushed and pushed to have a radical mastectomy trial when all these surgeons knew the right way and granted, that was a long time ago when we didn't understand things as well. But this idea that we really understand this, and especially when you had more deaths in PROCEED in this device, at the very least, equipoise starts out the other way.

And so I mean, I could easily design an ethical trial here and I would say inclusion criteria may be up to 4 hours where efficacy starts off in favor of standard of care. If things are equal, you expand to five because at the very least, I believe if they're equal up to five, they're probably equal beyond that and then if things are still equal, you keep going, and at some point there's a tipping point as you expand eligibility criteria.

So you basically have an adaptive trial to ensure equipoise and you train your sites that you would only have an organ eligible for randomization according to these adaptive rules and they should trust the process, because right now everyone just thinks they're doing what is right and we have no idea, and the only high-quality data shows that this is

not effective.

DR. LANGE: Very articulate. Thank you, Dr. Connor.

We're going to take a 10-minute break, we're going to convene at 4:10, so it will be an 11-minute break.

Jim, if you'll put the timer on and if people will mute themselves and take your videos, and I appreciate everybody's comments. I appreciate the responsiveness of the FDA and the Sponsor and the last comments by Dr. Connor, as well. So we'll begin our Panel questions in 10 minutes. Thank you.

(Off the record at 4:01 p.m.)

(On the record at 4:11 p.m.)

DR. LANGE: Great, welcome back to the FDA Panel. At this time let us focus our discussion on the FDA questions, but prior to doing that, I'd like to make sure that we hear from Gary Jarvis, our Industry Rep, and also from Debra Dunn, our Patient Representative, for any insights or comments that you have at this particular time.

Mr. Jarvis, let me turn it over to you first.

MR. JARVIS: I hit the wrong button. Sorry, Dr. Lange.

No, the only thing I would have to say here is I want to thank everybody for having the discussion you've been having because there's a lot of things that we talked about here today. But I think when we look at what we're here to talk about, which is the OCS Heart EXPAND trial, I think it did meet its primary endpoint at 30 days, is what they showed.

But I think there's also some other things that had been brought up today that are important, which is looking for our urgent unmet needs which is potentially expanding the number of donor hearts out there and I think that's a big piece that we should all look at, knowing that there are limitations within the studies, but there are ways I think we can look at this as we go into the future. And I think overall, when we look at the device and the

number of patients it's been used in so far, I think the benefit does outweigh the risk of the device and I would ask the Panel just to take that into consideration as we move forward with the questions and -- as well. That would just be it.

So thanks so much, Dr. Lange. Greatly appreciate the time.

DR. LANGE: Mr. Jarvis, thank you very much. Appreciate you sharing that.

Ms. Dunn.

MS. DUNN: Yes, can you hear me?

DR. LANGE: Yes, ma'am.

MS. DUNN: Yeah. So I agree. The training that I've received with the FDA, I'm not a medical professional, I am a patient and I look at the patient perspective, this risk over benefit, and I believe -- and that probably is my road, is a transplant at some point. If my physician sat down with me and explained the data at hand and that was my choice to expedite me getting a quality life or existing and maybe a subpar life, I definitely would choose the benefit over the risk for this. I was very impressed by my fellow patients that spoke their stories, I think it was very touching. I appreciate all of the clinical data, but I do feel that this will give a lot of us hope, which I think we need, so thank you.

DR. LANGE: Great. Thank you, Ms. Dunn.

Again, thank you, Mr. Jarvis, for your opinions as well.

We'll move now into the discussion on the FDA questions. Panel members, copies of those questions are in your folder. I'd ask each Panel member to identify him or herself each time he or she speaks to facilitate the transcription. The FDA will put the first question up. While they're doing that, I will just remind everybody we have 20 voting members and so what I'll try to do is summarize what the prevailing opinion is and if there's any dissenting things, I'll present those to Dr. Zuckerman and see if he has any other clarifying questions. Unfortunately, we probably won't get to have all 20 people comment on each question, but certainly if there's

an opinion that's been presented that you may not agree with and you want to present a dissenting one or have an alternative opinion or perspective, please let me know. So with that, let me turn it over to the FDA.

MS. WENTZ: Great. Thank you, Dr. Lange. So this is Catherine Wentz and I will be presenting or reading the questions into the record. I do want to let you know that there are two slides that I could not get both the graphic and the text, so while the graphic is up I will be reading the text. It's the text that's in your written document. And just for additional clarification for the second one, I'm basically just reading the key to you just to clarify the figure.

All right, so to start, EXPAND Study Design and Conduct:

The following important trial design and study conduct issues may affect the interpretability and validity of the study dataset and analyses:

Study Design

a. Design: EXPAND was carried out as a single-arm investigation and there were limited data for subjects not included in a Per Protocol population (equivalent to Transplant Recipient population).
b. Safety: There was no pre-specified primary safety endpoint hypothesis test.
c. Effectiveness: The primary effectiveness endpoint was defined as allograft survival at Postoperative Day 30 following transplantation in the absence of severe Primary Graft Dysfunction involving the left or right ventricle in the first 24 hours post-transplantation. This endpoint was tested against a performance goal of 65%, and moderate PGD was not included.
d. Donor heart inclusion criteria: EXPAND's donor heart eligibility criteria do not identify organs that are uniformly deemed unacceptable for transplantation if preserved using cold static preservation techniques, raising the possibility that there

was overlap between hearts accepted for OCS Heart perfusion in the EXPAND (including EXPAND CAP) and PROCEED II studies.

Study Conduct

e. Revisions to Donor Heart Inclusion Criteria: The Sponsor's dataset reflects EXPAND donor heart inclusion criteria that were revised after data lock and after the PMA had undergone FDA review. The donor heart inclusion criteria modifications affected 20 donor hearts. Additional criteria were assigned in all instances where donor heart inclusion criteria were revised, of which 17 modifications changed the assignment of single-criterion hearts to multiple-criteria hearts. There were no donor hearts for which criteria were removed.

f. PGD Classification Changes: Despite objective definitions of PGD intended to standardize classifications using data collected within 24 hours after completion of transplant surgery, multiple site-identified PGD classifications in EXPAND were changed during the adjudication process, which took place months or years after the transplant. These changes raise the possibility that individual endpoint determinations in EXPAND were subjective to some degree.

Question Number 1: Please discuss the impact of these study design and study conduct issues on assessing the safety and effectiveness and benefit-risk profile of the OCS Heart System.

DR. LANGE: So Dr. Connor, I'm going to come to you first because you kind of -- we left the last conversation, we were discussing some of these things, so let me let you lead off and then I'll let other people bat after you.

DR. CONNOR: Yeah, thank you. This is Jason Connor.

Yeah, I mean, I'm going to punt to my clinical colleagues here because I think the issue in my struggle is that after PROCEED there were a number of important open questions that

needed to be answered and the study design of EXPAND provided no insight to basically those open questions because we needed to compare to a control. You know, I fully appreciate how hard it is to randomize to some of these controls, as the Duke folks mentioned, but I think as design, this is very difficult to interpret that way.

Relative to some of the later points about the data changing afterwards, I completely agree with that. I mean, it seems like one adjudicator is not typical, at least having two with a third tiebreaker, but I also think that not being adjudicated is fair, right? I mean, time is of the essence when we're talking about organ transplant and so treating outcomes as if they are kind of in that intent-to-treat setting makes sense to me rather than having a committee, having time to sit down, get together, and using that as a sensitivity analysis I agree makes sense, but I would still want some -- you know, at least two or three people to outside adjudicate that. But I think that some of the big questions I'm comfortable deferring to my clinical colleagues here because without good control data it's really hard for me to think about this statistically.

DR. LANGE: Yeah. Dr. Hirshfeld, your thoughts?

DR. HIRSHFELD: Yeah, I'm really concerned by the lack of a valid comparison to the findings in EXPAND. The initially proposed non-inferiority boundary at 65% seems to me to be really not based on any rigorous data and so I think that we don't have clear-cut evidence that this is making a difference compared to if we actually gritted our teeth and did the randomized trial in the expanded use cohort, we don't really know how much of a difference this is making.

And I'm also bothered by what we discussed also is that how successfully this device actually does preserve or I think it's still really open to question given the lactate production and all of the histology that we saw in the turned-down organs. So my concern is that although it would be nice to be hopeful that this would expand the population of donor organs, we're not really sure it's making a difference.

DR. LANGE: Dr. O'Connor.

DR. O'CONNOR: Yeah, I mean, I agree with the comments that have been made today. This is one of the most challenged development programs that I've ever seen, beginning with the preclinical, the randomized trial, and then an open-label study. Having said that, there is a significant unmet need of hearts that aren't being utilized and potential recipients that are not receiving the potential benefit of a heart transplant.

When I look at the PROCEED II study, you know, we're in this gray zone of trying to understand whether 30 deaths at 3 years, 19 in one arm and 10 in the other, is clinically meaningful, as the FDA said. I think that we're way underpowered to even comment on survival in a study of that small a number of endpoints. That study met the non-inferiority on its proposed endpoints. And then a group of investigators deemed it unethical to have a randomized trial. Now, I think we can debate that as a panel, but that's what went forward and that they met their endpoint in their open-label arm. So I think this is a really great sort of set of datasets and I'm not convinced that moving forward with another randomized trial is the way to go.

DR. LANGE: Dr. Connor.

DR. CONNOR: Yeah. And I'd say to Dr. O'Connor, I mean, just a reminder that the company gets to choose 65%. FDA at least encouraged them to identify nonrandomized controls which, I appreciate that that's really hard, but there's probably some way to do that. So meeting the endpoint doesn't mean a lot when you get to define your own endpoint and when FDA isn't legally or within regulatory bounds allowed to say no, you can't run the trial because there wasn't the safety concern. So I mean, the 65 can be a bit of a straw man, but I appreciate your other comments here, too.

DR. LANGE: Any other comments not expressed?

Dr. Cigarroa and then Dr. Katz.

DR. CIGARROA: This is Joaquin Cirgarroa and my one comment regarding study conduct

is really more study methodology and on an open-label trial like this, to have a single individual adjudicate concerns me relative to the confidence I have in that adjudication process. I don't recall a scenario in which I have been asked in a panel to make judgments on a single adjudicator for safety. And that concerns me.

DR. LANGE: Thank you.

Dr. Katz.

DR. KATZ: I find it really frustrating that at this point in the process we're discussing study design. And I'm pointing fingers at both the Sponsor and the FDA, it seems like those should have been things that were being worked out throughout the process and our job isn't to go back to ground zero and say geez, it should've been done this way or that way. These are questions that should've been answered as you go along, I mean, all of us have been in studies and there's multiple times there's back and forth between the two. I just don't -- maybe I'm missing something here, why we're going back basically to ground zero and talking about how the conduct of the study --

DR. LANGE: I'll get to that in just a second, Dr. Katz.

Dr. Bonde.

DR. BONDE: Yeah, I think to take it from Dr. Katz, I think we had to consider what population we are going to help. Is it are we going to help this patient or no, and I think overwhelmingly, these patients, they really do not have an option, they really don't, and in a perfect world, you would want to have a perfect trial and a perfect outcome and comparison, but this is a very, very difficult population. You get a call in the middle of the night, you're making decisions in a very short period of time, organizing a complex transplant.

This certainly, the OCS System may have some drawbacks, I don't deny that, but I think overwhelmingly, at least, if it is approved, say for example, simply for people who have a projected ischemic time more than 4 hours there is currently no option, there's just no option.

If your heart is going to go 4 hours, there's no standard option. And so you want, at least for those -- those organs can be utilized and so I think I would request the Panel to keep that in mind that there is a group of donors who are beyond their 4 or 5 hours distance, for example, who can be utilized, even if only 80% of them can be utilized or maybe even 50%, that's still a little bit increase, what is desperately in patients.

DR. LANGE: So two comments with regard to Dr. Katz. Again, the FDA and the sponsors generally discuss trial design and trial outcomes and safety endpoints. The sponsor's not under any obligation to take the FDA's advice and the FDA is not allowed to shut down a trial just because they don't agree. So what happens is -- and this is a good example, where the FDA and the Sponsor, throughout the duration of the studies have had differences of opinions and the Sponsor decided to go its particular way and it sits before the Panel now saying are the data sufficient to assess the safety and effectiveness, so that's where we're at.

Dr. Bonde, and I don't disagree, we certainly want to do something, but I would take Dr. Connor's stance, there's equipoise, as well. If you believe the results from the PROCEED data that people do worse on this, then who's to say that at 4 or 5 or 4 to 6 hours on routine preservation, that it's still not better than this particular device and that what we would be doing is offering people suboptimal care and so we just haven't studied it, we don't know.

Dr. Brindis and then Dr. Selzman.

DR. BRINDIS: I agree with all the comments made today. This is a perfect lesson in the importance of having randomized clinical trials. Having an open-label, single-arm trial has left us with incredible questions downstream over both safety and efficacy. And I do appreciate the unmet need and I do appreciate that this device can meet a lot of the unmet need, but one thing that I'm also concerned about is the issue of indications creep if this device becomes available when we still have all these questions related to the study design, as between safety and efficacy.

DR. LANGE: Thank you, Dr. Brindis.

And then Dr. Selzman.

DR. SELZMAN: So Craig Selzman.

I'm going to say something that's probably going to make someone like Dr. Connor and a true clinical trial group have a seizure, but if we were to add and to address the FDA concern about the study design and conduct right now, and if we even change the definition and if we say the PGD and we included the moderate group ,as well, and we added all of those events, we would probably still be above the 65th percent performance guideline.

And so I would just say that the question that FDA is asking right now, I'm not sure it would change too much the way that I think about this, if we added a number of events that were adjudicated and agree, it should not just be a single human being, but let's say there were five people and they adjudicated 18 more events or something like that, my back-of-the-envelope math would suggest that they probably would still beat their performance and so I wonder about spending too much time on this one specific question.

DR. LANGE: Okay.

DR. ZUCKERMAN: Dr. Lange, can you see me? I think my video has gone off.

DR. LANGE: I cannot see you, but I was about to summarize. Go ahead, Dr. Zuckerman.

DR. ZUCKERMAN: Okay. If the AV people could try to work on my video.

But no, the intent of this question is not to talk about randomized versus non-randomized but was summarized well by Dr. Lange. If we're going to use an observational study, how do we make it as objective as possible? So I would ask Dr. Selzman, given practical realities, this is an unblinded observational study, what recommendations would you have for choosing the right donor, transplant, and adjudicating events in a more objective manner such that there are fewer questions at the end of the day? Because as Dr. Lange pointed out, there have been real differences of opinion between Sponsor and FDA as to how to do this. Can you

give us some suggestions?

DR. SELZMAN: That's a loaded question. I guess you're allowed to do that, Dr. Zuckerman, ask loaded questions.

DR. ZUCKERMAN: Yes.

DR. SELZMAN: I don't have an easy solution for this. I do think that it should have a true clinical events committee, I think that's just standard. I personally have some issues with the indication so that a future trial, I think, would be a little bit more specific and not have five, six, seven indications. I think one thing that you might be able to take out of this is to look at travel distance rather than expected time.

I think expected time is a guess, you don't really know if it's going to be 3 hours or 6 hours, but you absolutely know that the donor hospital and your hospital are X miles apart and that's the way that UNOS allocation works, so that might be something to consider in terms of the design of a future trial and as a potential indication, you would say that it's indicated for donors that are more than a thousand miles away or something like that.

And then in terms of the -- I'm going to restate, it was the very first thing on my legal pad of things, stuff that Dr. Allen and others have mentioned, is that there's so many questions about the biology of what's happening right now that are not informed by well-designed preclinical studies that would certainly help inform the prospective trials and trying to answer this -- a lot of these questions in humans is almost impossible.

DR. LANGE: Dr. Selzman, that's a great summary. I'm going to summarize.

Dr. Moon, do you have something that was not mentioned?

DR. MOON: Yeah, I just wanted to -- we discussed whether it should be a randomized or a non-randomized study. I would say that we here at Wash U are very aggressive, but we would not take a heart that was more than 4 hours cross-clamp ischemia time. And so there's no way to randomize those patients.

DR. LANGE: Okay. So Bram, if I'm going to summarize, I think people are frustrated by the fact that there's a lack of valid comparison, they're not sure -- it looks like it's underpowered for some of the significant clinical things we're looking at. There's not a concern that there's not a way to find a comparator group that's ethical, our group feels like there is a way to do that. And then as Dr. Selzman mentioned, is to provide more specific indications, which will make it more meaningful. So Bram, does that -- for the FDA, you've heard the discussion, does that summarize and does that answer the question sufficiently?

DR. ZUCKERMAN: This was a great discussion and I do appreciate Dr. Selzman's reply to a loaded question, it was excellent. Thank you.

DR. LANGE: Bram, did you appreciate anybody else's reply or just Craig's?

DR. ZUCKERMAN: Everyone's reply was great and Dr. Selzman really helped us here.

DR. LANGE: Great. If not, I was going to send everybody else home and just let Craig answer the rest of the questions.

DR. ZUCKERMAN: Okay.

DR. SELZMAN: I'm just saying that I'm not moving to D.C.

DR. LANGE: All right. Dr. Wentz, Question Number 2.

(Off microphone response.)

DR. LANGE: You're on mute, Dr. Wentz. Still on mute.

MS. WENTZ: Unmute, there we go. Okay, now can you hear me?

DR. LANGE: Yes, ma'am.

MS. WENTZ: Okay. I'm not quite sure how I got on mute to begin with.

Okay, so the preamble to Question Number 2, EXPAND Inclusion Criteria: The EXPAND study intended to utilize hearts that otherwise would not have been accepted for transplant. However, EXPAND's donor heart eligibility criteria do not identify organs that are uniformly deemed unacceptable for transplantation if preserved using cold static preservation

techniques. For example, 40 of 75 or 53% of transplanted EXPAND donor hearts met a single inclusion criterion, and of these 40 hearts, 18 or 45% of them met the single inclusion criterion of expected cross-clamp time for ECCT of ≥ 4 hours. In the pooled EXPAND plus EXPAND CAP dataset, 64 of 116 transplanted donor hearts met a single criterion of which 33 or 52% met the single inclusion criterion of expected cross-clamp time of ≥ 4 hours. Additionally, at least one donor heart met EXPAND study criteria but due to a logistical error this heart was transported via cold static storage and successfully transplanted.

So Question Number 2: Please discuss whether there was overlap between the standard hearts studied in the PROCEED II randomized trial and hearts studied in EXPAND and EXPAND CAP. If you believe there was overlap between "extended" and standard donor hearts, please discuss the effect that commercial availability of the OCS Heart device may have on the availability of acceptable donor hearts for transplantation, and overall long-term survival.

DR. LANGE: Dr. Allen, do you want to take a stab at that first?

DR. ALLEN: Keith Allen. Yes, I'd love to.

So when I think about this product, I'm terribly conflicted because a heart is a precious thing to waste and there are a lot of hearts that go in the bucket. My concern, though, is exactly what this question brings up regarding indication creep when this device becomes available and my concern is -- and this is why the PROCEED II trial, I think, is actually critically important because this device, if approved, is not going to simply be used for expanded criteria patients.

You will increasingly begin to use this to facilitate and expedite transplant timing, you will begin to use it on runs that are well under 500 miles because there may be issues with your perceived thought that the timing will be long. And I don't see how the FDA can put proper controls post-approval on this device to negate those concerns and I certainly haven't seen post-approval plans from the company that would provide proper controls to provide that type

of oversight and to me that is a real problem. As much as I want to believe in it, I'm concerned about Dr. Hassanein's statement early on about "I'm a cardiac surgeon, I believe in science, but I really believe in this product," and I truly do believe he does and I believe all of the users of this product are fervent believers in this product and I'm concerned that they may believe that this is better than standard of care and a "scoop and run" philosophy. You know, it used to be thought that trauma patients needed to be resuscitated in the field, and they don't. You put them in the ambulance and bring them to the tertiary care center and then they get fixed, and I think that's an analogy to keep in mind with this product. So if the FDA and the company can provide proper controls so that it's only going to used in very specific patients, like DCD, then I would be all in but I don't know how you're going to do that.

DR. LANGE: Dr. O'Connor and then Dr. Bonde.

DR. O'CONNOR: Chris O'Connor.

I think Dr. Allen made some very important points and that is "as is," I think there would be -- and Dr. Brindis mentioned this also, that there would be, I think, indication creep that would go into that PROCEED II criteria, but is there a bar that one could find that's high enough that would protect the public from and protect people from this device going into the standard donor criteria, and there may be. I think that Dr. Saperstein showed an interesting piece of data on slide 159 and 160 that said that the expected cross-clamp time greater than 4 hours plus risk factors actually had better outcomes than those without the risk factors. So perhaps you could park a high bar with this patient population that would be far enough away from the creep, and I think that Craig had mentioned the mileage one, which is an interesting concept that I hadn't thought of before.

DR. LANGE: Um-hum. Thank you, Chris.

Dr. Bonde.

DR. BONDE: Yeah, I think, taking from what Dr. Allen said, the word "extended" in

transplant essentially depends basically on how much can you extend yourself. If the donor is in the next-door operating room, I'm sure the surgeons will extend their criteria and it depends on how far the patient goes and so the -- you know, just giving approval based on extended criteria will not be a correct way of doing it because there is a lot of overlap between what one considers standard and one considers extended. It just depends on other factors other than the donor itself.

And I think there's a serious concern about the bias, the way the trial is conducted, as well as the statement that we heard and one of them struck me pretty clearly was flying blind with the cold storage. That's a very good way of saying that, you know, what will happen to the standard practice of cold storage which we consider as a gold standard, by the way. Heart transplant is a gold standard and the gold standard depends on cold storage, that's what it means. But we heard about the flying blind with cold storage and actually that may be just trying to get a point across, but in reality, that's what will happen, that somehow it will just be not the right way to do things.

DR. LANGE: Great. So Dr. Moon and then Dr. Kwon, and then I'll summarize.

DR. MOON: Yeah, I'm pretty convinced that the long-term survival is not going to be as good, but what I don't know is whether it's not going to be as good because we're using marginal donors or because the heart was on the machine, and that's where I think the animal studies come into play, is to be able to tell you if the machine is hurting the heart or not. We aren't going to be able to do 4 to 6-hour cross-clamp patients without this machine, so it will increase our donor pool, but I think it probably will decrease our donor pool with a worse product and our long-term survival won't be as good.

DR. LANGE: Thank you, Dr. Moon.

Dr. Kwon last, and then I'll summarize.

DR. KWON: Yes. You know, I think if you are -- the question is asking is there overlap

between our extended and standard donors. I think one bit of evidence that was presented, I think, during the FDA presentation was that there was a lower survival in the single inclusion criteria group, 74%, versus the multiples group, which is 88%. And that multiple group would've been somebody who had a 2-hour ischemic time plus a history of diabetes or alcohol, and I find that a very liberal application of an extended criteria. So I think one of the problems with that initial study design is that those inclusion criteria were a little too liberal.

And now how do we get around it? I mean, we're besieged, on the one side, by patients who consider the donor organ availability issue and on the other side our discomfort with a lot of the design of this trial.

I think one parameter that hasn't been discussed but that might be utilized is if nobody wants the heart, if it's coming in to you as Sequence 400 -- I'm throwing that as an arbitrary number, but there's some number where you could say okay, nobody wants this heart and it's kind of like the ultimate donor list that we had 15 years ago, you know, consideration for that, and I think that might be one way to work in a rational sort of combination of respecting the donor availability issue versus our kind of concerns about some of the pump -- I mean, the device, patients on the donor organ.

DR. LANGE: Okay, great.

Dr. Vetrovec, I'll let you have the last word and then I'll summarize and move on to the next question.

DR. VETROVEC: All right. This is a question for Bram. Many years ago on a panel, I remember you chastising the panel for worrying about how the device would be misused outside what was approved and you said that was not the issue, the issue is, is whether it's safe and efficacious for the indication that was provided. So are we way off the target on this last discussion?

DR. LANGE: Well, Dr. Zuckerman, you get the last word, then.

MR. AGUEL: Dr. Lange, this is Fernando Aguel, FDA.

I think Bram had to sign off for a few minutes, but I'm happy to comment on that, at least maybe not with Bram's gravitas, on behalf of FDA. I think that we do focus on just the indicated population and trying to assess reasonable assurance of safety and effectiveness within that indication, and I think later on today we'll have a question about that indication for use, as well.

DR. LANGE: Great. Normally, I would summarize for Bram. Since he's not here, Catherine and Fernando, I'm going to summarize for you all, are you comfortable with that?

MS. WENTZ: Yeah.

MR. AGUEL: Okay.

DR. LANGE: What I've heard is there is concern about indication creep, there's concern that the current indications may be too liberal and kind of soft and difficult. There is some general concern about who really -- if there is a group that would benefit, who would that group be, and I don't think that anybody knows who that group is. There's some concern that there won't be proper controls, the limit to the extended group, and that again, there's creep, and people have suggested other ways of looking at this. As Dr. Bonde said, maybe it's the last heart standing where nobody wants it or maybe we do it based upon mileage, but -- so I mean, I appreciate the discussion on this, I think we can appreciate the fact that people do feel like there's overlap and there's concern that if it's adopted with the current information we have is that there will be indication creep.

MS. WENTZ: I just wanted to clarify for Dr. Vetrovec that his question was specifically asking about overlap, not about off-label use but specifically about overlap and how there is overlap into the standard heart criteria.

DR. LANGE: Okay. Go to Question Number 3, please.

MS. WENTZ: Yeah. All right, question preamble: Transplantability. OCS Heart

arterial lactate level was the principal criterion given for not continuing to transplantation after preservation of the donor organ on the OCS Heart System for 5 PROCEED II donor hearts, 18 EXPAND donor hearts, and 4 EXPAND CAP donor hearts. FDA is unclear as to the utility of this metric as the principle criterion for determining transplantability, noting that 2 EXPAND CAP hearts were transplanted with arterial lactate levels of 6.3 and 7.8 mmol/L at the end of OCS perfusion (one of which had an initial arterial lactate > 5 mmol/L), as well as the many (approximately 50%) turned-down hearts that had final arterial lactate levels < 5 mmol/L.

So Question Number 3: Please discuss the accuracy and reliability of lactate levels as the principle determinant for not transplanting accepted donor hearts. In your discussion, please consider the impact on patients who undergo sternotomy in preparation for transplant in whom the transplant was not performed due to lactate levels greater than the target range.

DR. LANGE: Dr. Moon and then Dr. Allen.

DR. MOON: Well, a patient should never undergo a sternotomy until it's been determined that the lactate levels are acceptable, so that should just absolutely happen zero times. I have questions about the accuracy and reliability of lactate levels as a principal determinant and I think that's why animal studies need to be done, they need to measure troponins, lactate, all sorts of stuff, and then correlate that to the degree of heart injury.

DR. LANGE: Thank you.

Dr. Allen and then Dr. Bonde.

DR. ALLEN: Yeah, I would agree with Marc's comments in that number one, I believe the Sponsor even said in there, I don't -- nobody is doing a sternotomy and cutting out the donor heart until the heart in the OCS box has been deemed transplantable. So I think that's a

misunderstanding over the last part of that question. I'm not as hung up on lactate levels, I think you got to hang your hat on something. You know, determining transplantability of a heart is always subjective and I think lactate does give you something to hang your hat on, but if you look hard at some of the other things like complete heart block or the RV wasn't working very well, there were other visual cues that went into lactate, it really wasn't just lactate but that's what is being -- the hat is being hung on.

DR. LANGE: Great. Dr. Bonde.

DR. BONDE: Yeah, I think, as we consider extended criteria, if we were to use this in clinical practice, the lactate level of less than 5 -- because we will consider those hearts as extended criteria, from 6 to 7 or 7 or more, for example. So I think that's kind of just an indicator of what quality that organ has, but other factors will decide, you know, because this is such a rare resource, that centers will utilize even a donor heart at 6 or 7.

DR. LANGE: Great. So I'm going to --

MS. WENTZ: Dr. Lange, this is Catherine Wentz. Would I be able to clarify for Dr. Allen the second part of the question about the sternotomy?

DR. LANGE: Yes, go ahead, Catherine.

MS. WENTZ: Thank you. So this is not a misunderstanding, there were several subjects in the PROCEED II and the EXPAND study that did undergo sternotomy before the heart got there. One for sure in the PROCEED II was a turned-down heart, we could not discern whether or not sternotomies were done on the turndowns in EXPAND, we did not receive the op notes, but there were several subjects who were transplanted who did undergo sternotomy beforehand. I'm not saying that that's wrong, I mean, that's typical practice, I think today, but that's just a fact, so that's why the sternotomy was in this question.

DR. ALLEN: Yeah. Thank you, Catherine, that's interesting that somebody that had a

heart block would actually do the sternotomy before they had a chance to make the final decision with that. You are correct, I mean, we do, as soon as the team lands, visually inspect the donor when we're doing just cold preservation, you know, the team back home will begin a sternotomy and we don't cut the heart out until the heart is back in the room but yeah, that happened. The whole advantage, though, of the box is to take these organs and in theory resuscitate them and make them usable. So maybe it's my misunderstanding, but if that was the plan, I think that's a big mistake with this box to do sternotomy prior to actually getting everything okay.

DR. MOON: I agree because if the machine is working, it should be able to sit there another hour while you open the chest up.

DR. LANGE: Yeah. So I'm going to summarize this -- one is there's no enthusiasm for doing a sternotomy unless we know we're going to use the heart, whether that's cold or whether that's a beating heart in a box, number one. Number two is there's a general feeling that lactate shouldn't be the sole determinant, it can certainly be a piece of the puzzle and there's not enough information, was it a lactate of 3 or a lactate of 4, is it a lactate of 5 and what's the trend and how long -- so there's a lot of unknowns about it, but nobody feels comfortable with hanging their hat on a lactate level.

DR. ZUCKERMAN: So that's a good summary from my perspective, Dr. Lange.

Catherine.

MS. WENTZ: Can I move on?

DR. ZUCKERMAN: Yes.

MS. WENTZ: Okay. It's not working, there we go. Okay, PROCEED II and EXPAND Study Analysis. Long-term survival: In PROCEED II, the observed all-cause mortality rate following transplantation was higher after donor heart preservation using the OCS Heart device than after cold static preservation (SOC); the magnitude of the survival benefit for

patients transplanted with standard of care hearts was clinically meaningful and persisted over the long term. The Kaplan-Meier survival analysis for EXPAND demonstrates survival rates of 83.8% at 1 year, 82.2% at 2 years, and 77.7% at 3 years, and the Kaplan-Meier survival analyses for EXPAND plus CAP demonstrates survival rates of 87.2% at 1 year, 85.5% at 2 years, and 80.8% at 3 years. The table below includes contemporary survival rates for 1 and 3 years from the 2019 Scientific Registry of Transplant Recipients Annual Report, just published a few weeks ago.

Figure 22 from your Executive Summary combines the K-M curves for PROCEED II, EXPAND, EXPAND plus CAP, and the Piecewise modeling, and is shown here.

So this Kaplan-Meier graph is a busy graph and I will briefly step through the key in this figure. The yellow curve on top represents the transplanted PROCEED II donor hearts preserved with cold static storage or standard of care. The purple curve on the bottom represents the transplanted PROCEED II donor hearts preserved on the OCS Heart System. In between those two curves you have the OCS EXPAND curve in green and the pooled EXPAND plus CAP curve in dark brown, and the straight or diagonal lines represent the Piecewise modeling for EXPAND, the bluish line, and for the pooled EXPAND plus CAP, the red line. At the bottom, you see the number of patients at risk and as was discussed previously, there was substantial censoring, especially for the CAP subjects, where there are data for only six subjects out to 1 year.

So question 4a: Please discuss the clinical implications of these results with respect to whether there is a longer-term benefit of preserving donor hearts using the OCS Heart System.

DR. LANGE: So Jason, I'm going to throw this to you first. Again, I want to make two points that Catharine mentioned. One is we have 116 patients, we only have 33 data points after 2 years; so in other words, we're basing this on 33 of 116 and I want you to address

that. And as Catherine said, only six of the CAP patients have been followed through 1 year. So Jason, with that information and your broad statistical knowledge, I'm going to let you take a first stab at this.

DR. CONNOR: I was afraid of that. Jason Connor here.

So yeah, I think this is really hard, right? I mean, I do a lot of these piecewise exponentials myself, I've designed a lot that are reviewed by the circulatory group and Dr. Zuckerman. I mean, we can see from the plot when those lines go parallel and get steeper at the end, right, I mean, do we really believe that the hazard, even if the slope is kind of the hazard, is it really getting steeper right there at 2 years? Probably not, there's no reason to think so, but it's highly data driven by just a few people, right? So there's 33 people left at that time. We can see there's only, I think, one event, right, someone drops, we see that drop right below Year 3. So basically, that one event is really driving everything and if you move the cut point from where you kind of see the slope changing, if you move that at all, you're changing the denominator a lot.

So that's a long answer to say that I think this is really sensitive to the very little amount of data. I would actually prefer to see even PROCEED or even just from the TransMedics database what long-term outcomes are, use those like 2-year data and append them to the end of EXPAND. I mean, I'm not exactly sure that long-term outcomes are different versus some of these short-term outcomes that we saw in PROCEED were very, very different. Even the lung trial for TransMedics that went to panel in 2017, 30-day survival was quite a bit worse in the device group than in the standard group, so something's happening short on, so my concern is much less actually the long term than what we see here is this difference from zero to 6 months.

DR. LANGE: So based upon the numbers we have, you feel, in the 116 patients, the vast majority of them -- actually, 65 have been followed out to Year 1 and 33 to Year 2.

Would you feel comfortable with the Year 1 data and what they show?

DR. CONNOR: Yeah. And I think even through Year 2 and we can say they're in the middle, but I think that there's just simply not enough data to make these long-term projections.

DR. LANGE: Okay. Dr. Yeh.

DR. YEH: You know, I think this question is really challenging because when I see there's a longer -- whether there's a longer-term benefit at preserving hearts using the OCS Heart System, my first question is, compared to what? And compared to standard of care in PROCEED is not the right comparator group because I think we think well, there's overlap, they are certainly different populations. And the second is compared to a person who doesn't get a transplant and then sits on the waiting list and then maybe later on gets a transplant through standard of care and is at risk for mortality during that time, well then I think we would say that's probably maybe a benefit compared to that because maybe that patient otherwise doesn't get transplanted.

So I find that so much of this challenge to this whole, I think, Panel is due to the fact that we have no idea what would happen in the control group here and part of that is driven by the fact that as the people, as Dr. Moon has stated, Dr. Schroder stated, there's no ethical control group to the clinical community and I think that if there's no ethical control group and it really truly is that these patients are such that there is no actual feasible alternative to study or to assess, then actually it changes my thinking about it, whether or not that is a true statement, that there's truly -- whether standard of care can actually just be flexed. You know, I don't know.

What we did hear is that what OCS does is make clinicians comfortable transplanting patients who otherwise actually they are uncomfortable transplanting, but if they were just more comfortable, this is what I think Dr. Connor was getting at earlier, if they were just

more comfortable they would find that their outcomes were, in fact, just as good as they achieved here, if not potentially better or worse. We really have no idea and so that is, I think, the challenge with this question and more globally, I think many of the questions we're trying to answer.

DR. LANGE: Great. I mean, I think I can summarize it based upon two things. One is there's little long-term follow up and more importantly, as Dr. Yeh said, there's no comparison group, so how do we know if there's long-term benefit without some sort of a comparison?

Dr. Moon.

DR. MOON: Yeah, I just want to make a specific point because this could be an issue, is that there's absolutely no evidence that says you should take a standard of care appropriate heart and put it on this machine to try to spruce it up, there's no evidence to that, so it should only be used for the marginal donor.

DR. CONNOR: When there's evidence we shouldn't.

DR. MOON: Agreed.

DR. LANGE: Yeah. So Dr. Zuckerman, does that sufficiently address the question?

DR. ZUCKERMAN: No, I'd like to hear more from the transplant surgeons and maybe I could pick on Dr. Selzman to being with again.

Dr. Selzman, when you look at the EXPAND curves and compare them to the original PROCEED II OCS curve, do you see some evidence of learning or improvement with time? Does that help you put these survival estimates in perspective?

DR. SELZMAN: Not really. I think one of the things that's resonating in my brain right now is that usually long term, if we're going to relate something -- and I don't want to get caught in the heart graft-related SAEs, necessarily, but if a patient has acute rejection or a lot of problems early on in the first 30 days, it often will portend a worse outcome down

the road, and we're asking the Sponsor and the FDA and this Panel to make assumptions that are just unable to be made right now. We can't assume 2-year survival, 3-year survival. The 1-year, I think, is important because that's how we're all graded right now with UNOS so that it has a clinical impact on our day-to-day practice. But if you change PGD definitions and you see that the primary endpoint is lower and then that, in itself, portends a worse outcome, I think that's meaningful, but I -- with the number of patients that are in this right now, a clinically relevant -- I'm not really kind of getting into this, trying to extrapolate this long-term data right now, I'm sorry to say.

DR. LANGE: Dr. O'Connor. And then Dr. Bonde.

DR. O'CONNOR: Dr. O'Connor here, just a comment.

Again, I think, as everyone's mentioned, it's very difficult to be informed by 29 deaths, 19 in the OCS and 10 in the control, of which of those excess nine deaths, six were either late infection or malignancy. And so as we've tried to connect dots with perhaps is there ischemic injury with this device, I'm troubled by trying to connect the excess deaths to infection or malignancy.

DR. LANGE: Thank you, Chris.

Dr. Bonde and then Dr. Kwon.

DR. BONDE: I think the concern, when you want to predict something when you're starting off with more than 10% difference in the 1-year survival compared to the SRTR or the standard of care, that's very concerning. So that usually portends that the more years you'll be on this, on the -- in a post-transplant survival is never going to be as good as what you would expect. One can understand the initial drop or the initial mortality, but the issue is that a quarter of the patients, more than 25% of patients are requiring mechanical circulatory support. There's an implication of that because mechanical circulatory support can cause non-cardiac death, either massive stroke or something or other or bleeding or something, so that

means you are never going to -- you're only going to catch up, you're never going to be able to improve. So most of the times when you're needing the mechanical circulatory support, you are in dire circumstances post-heart transplant, you're just about trying to keep the patient alive rather than looking for long-term survival, that's what I feel.

DR. LANGE: Yes. Dr. Kwon.

DR. KWON: So looking at the survival decrement of the OCS in the PROCEED II trial, it's pretty striking and I agree with Dr. O'Connor, I don't know, do we attribute it to these patients that are more likely to be in car accidents or have cirrhosis or some of the other things that the Sponsor mentioned as explaining their non-cardiac sources of death in their trial.

Now, if you look at the EXPAND and EXPAND CAP, I agree, you cannot compare them -- I think it was Dr. Yeh's comment -- to the standard of care from PROCEED because those donors are different. But I do think we have a good control group because all transplant surgeons have done transplants with ischemic times over 4 hours and I think it doesn't take you to go farther than the UNOS database to know what these survivals will stack up vis-a-vis 4-plus hour ischemic time in the UNOS database.

DR. LANGE: To your point, Dr. Kwon, there were 1700 people of the 10,000 that were -- had an ischemic time over 4 hours.

So Dr. Zuckerman, does -- anybody else you'd like to direct this to in particular?

DR. ZUCKERMAN: No, sir.

DR. LANGE: Okay. All right.

MS. WENTZ: Should I move on?

DR. LANGE: Please.

MS. WENTZ: Okay, wait times: According to the Scientific Registry of Transplant Recipients, nearly 40% of patients newly listed in 2018 underwent heart transplantation within 3 months, and approximately 57% had undergone transplantation within one year of

listing. In 2019, 3% of subjects died while waiting for a donor organ, while 12% were removed from the list for reasons other than death or transplantation; 6-month mortality for patients removed from the list was approximately 20%. Although EXPAND was not prospectively designed to use the SRTR as a comparator, the EXPAND OCS Heart group had shorter wait times than patients in the SRTR.

So Question 4(b): Please discuss the strengths and limitations of this comparison, and whether the results of EXPAND indicate a probable benefit of shorter wait times. In addition, please discuss the wait time analysis in the context of post-transplantation long-term survival.

DR. LANGE: And to our surgeons. Dr. Allen.

DR. ALLEN: Yes, Keith Allen.

So this is a difficult question. Once again, it all comes back to the fact that we don't have a really good control. So to give an example, we make selections of high-risk hearts all the time, you know, the patient that's on an LVAD that's having a complication, we are more willing to take a risk with that heart just simply because you know that patient is not going to survive very long, whereas somebody that's at home and waiting on a heart, you're not going to offer them that high-risk heart.

And so the data that's up there would suggest that while patients do poorly when they wait, they actually don't do as bad. In 2019 only 3% died while waiting for a donor organ. The contrary would be that you take an organ that is perhaps not the best, extend it with this device, and at 1 year, if I go back to the EXPAND group, the 1-year mortality was 15%. So it all comes down to the fact that you just don't have a good control and it's too bad that through either SRTR or UNOS that you weren't able to come to some agreement on how to look at data and find a concurrent control group.

DR. LANGE: Okay. Dr. Connor.

DR. CONNOR: Yeah, I mean -- so this is Jason Connor.

I think part of it is this might be the wrong question, too, right? I mean this can definitely shorten wait times. The question is then not would you get an organ sooner with that, I accept that answer is yes; the question is, is it better to wait for a different organ or would it have been better to get standard of care equally as fast?

And again, I go back to, I think the FDA invited non-randomized controls and I can imagine -- I forget the gentleman's name during Open Public Hearing from Boston who said he discussed it with his wife, he was the one with the little girl, and then he agreed to participate in this and take such an organ from here. You could probably have gotten people who didn't want to do that, put them as a control, but when they matched, identify them, right?

And so now you're following them prospectively, they may have gotten an organ 6 months later and be doing just as fine with a standard of care heart versus this and I think that's the appropriate control, so it's not necessarily just can we get more organs into people faster, that's easy. That's even easy to do with standard organs and bad outcomes potentially, right, but it's are you getting the right one in with good long-term outcomes and I think that there was a way to study that and it didn't get done here.

DR. LANGE: Great. Dr. Selzman.

DR. SELZMAN: Just to counter that perspective -- Craig Selzman -- that Jason just brought up, though, is that -- and this could be figured out with UNOS or perhaps is that by shortening the waiting list, and we saw this with the allocation, right, instead of putting an LVAD in a patient you put a balloon pump in them and you get them an organ faster, and that's one of the reasons why you see the 40% there. But one of the things that's missing in this analysis is that if we have patients that have access to more organs, it's probably going to decrease the durable LVAD insertions, and durable LVADs have their complications. You

know, probably one to two out of 10 of those patients are going to have something really bad happen to them and then they're going to be taken off the list and you can kind of find that with TCR and TRR on the UNOS datasets, but it takes a little bit of work to get through. So I would say, for the folks that are not on the Panel that are not in this day to day, that that's an important piece, is that an LVAD is not always a great thing for patients and that if you can get a heart, sometimes that works out better and this could shorten the time for that, so that perspective, I think, is important to keep.

DR. LANGE: Dr. Selzman, thank you.

So, so far what I have is that there's general consensus it will shorten the waiting time, there's some enthusiasm for doing that if it keeps people off mechanical circulatory support, but obviously not much enthusiasm if we give them a suboptimal heart to do so. So those are the things that are -- Bram, that people are weighing. Any other opinions besides those?

Dr. Bonde.

DR. BONDE: Yeah, I think I'm just going to throw this out there. I think that this trial was conducted during the unique period when the allocation policy changed and allowed a lot of organs to be eligible which normally would not have been, like going to find it through -- that's another thing. And another thing that no trial can capture is our transplantations, my transplantation would have immense faith in me if I tell him this is a new toy, they're now going to do something with this, they will sign up, there's no doubt about it. And another thing is also only large centers participated in the trial, so they already had large systems to go out and bring the organ. So those are things that would not get captured in an analysis like this, keep that in mind. So yes, you can shorten the wait times but you will also shorten them at a cost of 16 to 18% mortality at 1 year.

DR. LANGE: Okay. So Dr. Zuckerman, does -- I've tried to summarize. Is that

sufficient? Do you have -- feel like you have the Panel's opinion?

DR. ZUCKERMAN: Yes, but I have one small additional question for the heart transplant surgeons. Were any of them impressed with what seemed to me to be a markedly shorter wait time for the blood group O population?

DR. SELZMAN: Craig here.

I can just do a quick -- it's not surprising, but it makes sense.

DR. BONDE: And it's pretty expected because those are the patients who are higher on the list and waiting longer.

DR. ZUCKERMAN: Thank you.

DR. LANGE: Dr. Wentz.

MS. WENTZ: Yeah. All right, FDA believes that collectively the analyses from PROCEED II, EXPAND, and EXPAND CAP may suggest suboptimal survival when the device is used to preserve structurally and/or functionally "standard" donor organs whose only criterion for device use is preservation time anticipated to be prolonged (≥ 4 hours).

Question 4(c): Please discuss whether you believe the device, if approved, has demonstrated sufficient safety and effectiveness for donor hearts considered non-standard on the basis of anticipated prolonged preservation time only.

DR. LANGE: Dr. Allen.

DR. ALLEN: Keith Allen.

So the short answer for this, Catherine, for me is no, I don't believe that data has suggested this, particularly when the whole idea is it's anticipated to be prolonged. I think there needs to be firmer guidelines or firmer inclusion than just the transplant surgeon decides that I think we're going to have a 5-hour ischemic time. I also think that it's going to be hard to come up with other surrogates besides this, so somebody has suggested -- I like the -- I love the idea of, you know, if a heart's been refused 60 or 80 or 90 or 100 times,

that's a pretty good indication that it's a marginal heart. I think that's actually maybe the answer. Mileage isn't the answer because with the UNOS allocation change 18 months ago, by definition, from Kansas City, 90% of our organs were harvested locally, now 90% of our organs we have to fly someplace to get them. So I think looking at the UNOS allocation, miles have kind of become the standard and I think we still haven't decided if that allocation change is a good thing or not, particularly for some centers that are in geographically favorable places like the Midwest.

DR. LANGE: Is there anybody that, based on this question, believes the device, if approved, has demonstrated sufficient safety and effectiveness for donor hearts considered non-standard? So is there anybody on the Panel that wants to speak to yes, they do believe it has?

Craig.

DR. SELZMAN: I don't have a picture of the slide in front of me, but --

DR. LANGE: This is Dr. Craig Selzman.

DR. SELZMAN: Craig Selzman, I'm sorry. Thank you. Craig Selzman.

I don't have a picture of it right in front of me, but the data that I think the FDA and the Sponsor showed, and I think the Sponsor showed it pretty well, is that over 900 miles, 6-plus hours of ischemic time -- I should say, we use the word ischemic time but it's probably better to say out-of-body time is -- the results speak for themselves. Although 55% of it came from one institution, I haven't seen anything to suggest that it is not working. Correct me if I'm wrong on the data, I'd be happy to see another slide, but the EXPAND and the EXPAND CAP, the primary endpoint, even if you change the definition, it's probably still going to be over 90%, which is pretty good.

DR. LANGE: I've got Dr. Blankenship and Dr. Katz.

Thank you, Dr. Selzman.

DR. BLANKENSHIP: One of our surgeons -- Jim Blankenship.

One of our surgeons categorically stated that over 4 hours is a non-go and so if the alternative is wasting the heart, then I think that you can make a case that it would be adequately safe.

DR. LANGE: Okay. Dr. Katz, Dr. Kwon.

DR. KATZ: If you just go by the primary graft dysfunction, if it's really down to 8%, then yes, I mean, then there is a significant benefit. The problem is, is the mechanical circulatory support question which we didn't really answer and how that jives with the primary graft dysfunction question. So if we had an answer to that and indeed, we're looking at 8% versus 30%, that's a big deal.

DR. LANGE: I've got Dr. Kwon and Dr. Bonde.

DR. KWON: What Dr. Blankenship had just mentioned, I just want to comment on. You know, I don't consider being on the device equal to perfusion, it's you're in a state of suspended animation, I guess, with a proprietary solution, I don't know what's in there, being pumped by a device that I'm taking great leaps of faith in. So having a 2-hour ischemic time in the standard of care is not a 2-hour ischemic time with all things considered on the device, the device is different, so that's one thing. I don't think there's a hard red line in terms of ischemic time, as well, but I would say I don't think this device has moved the needle sufficiently to suggest that there is safety or efficacy on the time that we can consider for a foundation of the --

DR. LANGE: Okay. Dr. Bonde.

DR. BONDE: I respectfully disagree. I think the Sponsor, as well as the FDA, did show the safety of transporting an organ more than 600, a thousand miles across a large geographic area in a jet on this machine and a vast majority of the organs utilized, you know, they worked and so I think that's not in dispute. It just depends on what our

definition of anticipated prolonged preservation time will be, that needs to be very firmly defined as to what that cutoff is for the applicability, that's what I think.

DR. LANGE: Okay. So Bram, I'm going to summarize. There are a diversity of opinions here, some believe that it has not been shown to be safe and effective, some are willing to accept the fact that the heart might otherwise not be used and because it has been implanted that, in fact, there is some safety signal there. I suspect what's going to happen is we're going to come down to the vote at the end and you'll get everybody's opinion, but I think we can appreciate that there is a diversity of opinion even based upon the data we've looked at.

DR. ZUCKERMAN: Yes, that's a very good summary. Thank you.

MS. WENTZ: This is Catherine. Can I get one piece of clarification? So twice now we've heard that the refusal indication might be a good surrogate or something that in fact could be used as an indication for all hearts that can be used on the device. Do you all believe that the data presented today could support that or is this something that would require a new study in order to identify hearts that are refused greater than 400 times or whatever as a new indication?

DR. LANGE: Dr. Allen has his hand up and I want to answer that, as well. Go ahead.

DR. ALLEN: So Catherine, I do believe that there is data to support that and I think it comes down to the conflict that I have with this product is that if a heart is going to go in the bucket and you're going to lose a heart, I do believe that this device has utility. My concern has always been, though, is defining which heart is actually going to go in the bucket and not be used because there's not a good control, so having a surrogate like it's been refused 60 times or 90 times or a hundred times, you know, I think that would be okay.

DR. LANGE: Catherine, I'm going to chime in, as well. I mean, the assumption is that

if a person doesn't get the heart today, this refused heart, they're going to die and as Dr. Connor mentioned, it may be better if that person doesn't get a suboptimal heart and waits 30 days and gets an optimal heart and has a better outcome. We know that the 1-year mortality isn't 83%, it's 95%. Not mortality, survival. Eighty-three. It's 95%. So I don't think it's as simple again, in my opinion, as saying gosh, we don't want to throw the heart away so let's implant it, let's put it in the machine and implant it in somebody. There are other options besides that.

MS. WENTZ: Okay. Thank you very much. Okay, pathophysiology and pathology. In PROCEED II, compared to patients transplanted with standard of care donor hearts, the group of patients transplanted with the OCS Heart System-perfused donor hearts had a numerically greater need for mechanical circulatory support post-transplant, more frequent acute rejection episodes, lower average cardiac index, longer average ICU stay, and longer average initial hospital duration. In EXPAND and EXPAND CAP, pathology results from hearts perfused on the OCS System but turned down for transplant suggested that the OCS Heart System may have contributed to myocardial damage in some donor hearts.

So Question 5: Please discuss the implications of these pathophysiologic and pathologic observations on the effectiveness of heart preservation and/or potential myocardial damage associated with donor heart perfusion using the OCS Heart System. In addition, please discuss the potential impact of hearts turned down for transplantation following OCS Heart perfusion on the pooled available donor hearts.

DR. LANGE: Dr. Borer. Unmute. Go ahead, sir.

DR. BORER: Okay. Obviously, these findings that were just enumerated make one concerned about the impact of the OCS Heart System. On the other hand, the problem here is the same as the problem that has affected every one of the other questions, that is the numbers are too small to be able to define performance descriptors, to define positive

predictive value and negative predictive value, we're just guessing. So yeah, I think that the implications of these observations on the effectiveness of heart preservation and myocardial damage associated with donor heart perfusion using the OCS System are potentially very important.

However, the name of the game is who survived and who didn't. And we don't really know because we don't have the numbers. So I think that it's not so much that new studies have to be designed to ask questions that haven't been asked, that may help, but the major issue is, if additional studies are going to be done, they have to have the numbers of subjects so that very useful and precise outcomes can be defined and we can't do that with the numbers we have, so we're just guessing. And that's okay, we're just guessing. But that's the problem.

DR. LANGE: Dr. Selzman.

DR. SELZMAN: Craig Selzman.

So we're going to just put the preclinical stuff aside because that just should happen. But I will restate the thing that I said to Dr. Farb because I actually think that this piece weighs on the safety side of the OCS System, meaning that if we had had a true control group and you had cold storage, 16% of those hearts probably wouldn't have worked that you would have implanted and 84% worked or close or something like that. So I actually look at this as a safety -- on the side of safety for the OCS.

DR. LANGE: I'm sorry, Craig. I just want to make sure I understand. To summarize, you believe that the OCS is safe.

DR. SELZMAN: I'm saying it's safe, it provides an element of safety for the population that's being studied.

DR. LANGE: Got it.

DR. SELZMAN: Since we don't have a control group that got cold storage that had

the 7-hour out-of-body time, what this study showed was that 16% of those patients were saved from getting potentially a bad heart because of the OCS System.

DR. LANGE: Okay. Dr. Hassanein, I'm not going to call on you because I'm sorry, you're not allowed to participate in this part of it, so my apologies. I just don't want your hand to get tired.

Dr. Cigarroa and then Dr. Kwon.

DR. CIGARROA: So in PROCEED II, the group of patients transplanted with the OCS Heart System-perfused donor hearts actually had an overall longer out-of-body time and what I would say is a combination of a more prolonged duration of ischemia both cold, coupled with the warm during the perfused OCS component. So the way I think about this is the area under the curve of ongoing ischemia for a much longer period than the standard of care, so area under the curve of the component, and that translated into the need for greater mechanical circulatory support and lower average cardiac indices and longer ICU stays.

So this concept of being on OCS and not having ongoing ischemia or injury is one that I would like to challenge because I think that it is evidenced by ongoing lactate production rather than consumption and so that also in PROCEED II led to, I believe, 7% of organs not being used for various reasons compared to standard of care. So I am concerned about the ongoing myocardial ischemia and damage using the OCS compared to standard of care in PROCEED II. Now, in contrast, in the EXPAND and EXPAND CAP, it is clear that most transplant programs will not use a donor heart with greater than 4 hours ongoing ischemic injury and this then makes available more hearts than otherwise would not be based on the consensus of most transplant programs.

DR. LANGE: So again, Bram, a divergence or a diversity, not a divergence, a diversity of opinion, some who felt like the OCS System, in fact, prevented suboptimal hearts from being implanted in individuals, others concerned that the OCS System may be responsible

because of the prolonged cross-clamp time associated with getting people cold, warm, and cold again, so --

DR. ZUCKERMAN: Thank you, Dr. Lange.

MS. WENTZ: Question 6: TransMedics Organ Care System Heart System is a portable extracorporeal heart perfusion and monitoring system indicated for the resuscitation, preservation, and assessment of donor hearts in a near-physiologic, normothermic, and beating state intended for a potential transplant recipient. OCS Heart is indicated for donor hearts with one or more of the following characteristics:

- Expected cross-clamp time or ischemic time > 4 hours due to donor or recipient characteristics; or
- Expected total cross-clamp time of ≥ 2 hours PLUS one of the following risk factors:
  - Donor Age ≥ 55 years;
  - Donors with history of cardiac arrest and downtime ≥ 20 minutes;
  - Donor history of alcoholism;
  - Donor history of diabetes;
  - Donor Left Ventricular Ejection Fraction ≤ 50% but ≥ 40%;
  - Donor history of Left Ventricular Hypertrophy (septal or posterior wall thickness of > 12 ≤ 16 mm); or
  - Donor angiogram with luminal irregularities but no significant coronary artery disease.

Question Number 6: Please discuss whether the EXPAND study donor heart inclusion criteria (or an inclusion criteria subset) identifies a reasonable set of objective "extended" or "expanded" heart criteria that define hearts not routinely used for transplantation after cold static storage. If so, please provide additional discussion as

follows:

a. Based on the available data, please discuss whether the objective set of inclusion criteria that can be defined as "extended" donor hearts intended for preservation on the OCS Heart System will result in an increase in donor heart utilization and acceptable survival for recipients.

DR. LANGE: Dr. Moon and then Dr. O'Connor and then Dr. Bonde.

DR. MOON: Yeah, certainly the 4-hour time makes sense and you can clearly say that. I'm just not sure what good it does to a 2-hour patient that has diabetes or an ejection fraction of 40-50%. What's going to change on the device, unless you put a qualifier that says also while they're on the device the lactate is below five or something because there's going to be absolutely nothing different about your evaluation after you put it on the machine for an EF of 40 to 50 because you're not going to re-measure the EF and you're really not even going to be able to assess contractility. I don't know that, I just -- I mean, that increased the number of patients in the study, for sure, but I don't know what -- other than if you put a qualifier on how you determine whether it's good or not after it's been on the machine.

DR. LANGE: Okay. Dr. O'Connor.

Thank you, Dr. Moon.

DR. O'CONNOR: Yeah, my concern is mitigating the potential creep into the standard criteria heart, so I think having looking at 4 hours and one of those criteria might be a sweet spot to protect against getting into the normal heart criteria and maybe it's that 4 hours defined as geographic distance.

DR. LANGE: Thank you, Chris.

Dr. Bonde.

DR. BONDE: Yeah, I think I would disagree with the last comment that distance on

its own should be a criteria. It is the quality of the donor whether extended or not because those transplants just are not taking place. And the second issue is that distance plus -- some kind of risk factors in the extended criteria in the donor, that should also be included, but I think the distance should be the primary kind of criteria that should definitely be taken into account. The more well-defined extended donor criteria can be the second group that this device can be certainly used for because that's what the data so far has shown. I'm not going to go into the controversy part, but I'm just looking at what I see. I see definitely there are more numbers that are patients who did get the transplants who would not have got it because of the distance of the donors, for example, or the condition of the donors. So I think we must take that into account.

DR. LANGE: Dr. Katz.

(Off microphone response.)

DR. LANGE: Hold on, Dr. Katz, you're still muted. There you go.

DR. KATZ: Sorry. The issue for me is which recipient is going to get this. You know, a patient who's relatively stable at home, I don't think I would increase their potential risks by doing this. Now, somebody who's having major issues, who's had device issues, who's truly got one foot on the banana peel, then you're willing to extend the criteria and I think that's where this would really come into play in that you can take a heart that you normally wouldn't have taken otherwise and give that person an opportunity.

DR. LANGE: Dr. Selzman.

DR. SELZMAN: Craig Selzman.

So I want to follow up with Dr. O'Connor's statement and also bring in what Murray and Keith brought in because there is some concern that if we just go straight by travel distance, that you could poach organs from different OPOs, different centers that might otherwise really need that organ. So bringing in the thing that Murray brought up with the

declines, not to try to make an overly complicated algorithm, but it would kind of stink if someone comes in and you have a high-status patient and it's taken away from you when you have your own because somebody was 200 or 2000 miles away. So there needs to be some way to kind of balance those needs across the country so -- but it sounds like we might be creating a complicated formula, though.

DR. LANGE: All right. Dr. Hirshfeld, and then I'll try to summarize.

DR. HIRSHFELD: I just think it's important to emphasize that this discussion we just had is all predicated on the fact that people are still harboring a belief that this actually makes a difference, and so that the idea being that if you have an extended-risk heart, donor heart, for a patient who's very desperate, then not only will you accept that heart but you will accept it and use the Organ Care System because you think that will somehow give you an advantage and I think we just finished a discussion in which we said we weren't convinced that it actually did make a difference in terms of organ viability.

DR. LANGE: Okay. So if I'm going to summarize, I think there is some sense that it will result in an increase in donor heart utilization. There's some concern that there will be creep and so people would want to make sure that it would only be used for organs that would not otherwise be used, for example, maybe those preserved for more than 4 hours and with one or more risk factors. And again, there's also genuine concern about whether it gives an acceptable survival for the patients. Again, we're going to come to that at the end, but I saw some genuine concern about that.

DR. ZUCKERMAN: Okay. And Dr. Lange, that's a very good summary, but Dr. Katz also had a very good point about trying to pick a higher-risk recipient for this particular procedure. Are the other cardiac surgeons in agreement with his point to try to better define the recipient population?

DR. LANGE: Dr. Allen.

DR. ALLEN: In general, I do agree with that, but you could also have the mindset that I'm more careful with this, you know, having a high-risk recipient and putting in a high-risk heart often turns out to have a bad outcome, so oftentimes your high-risk recipient needs the best heart it can get. And I'm not sure the data on what we've studied so far addresses that question. I don't know if that answers it for you, Bram, or not.

DR. LANGE: Dr. Moon had his hand raised, as well.

Thank you, Keith.

DR. MOON: Yeah, Marc Moon.

I think that's another reason it's important to do these animal studies, maybe the hearts are as good as every other heart, but the data we saw today suggests there's potentially some problems and we've had -- Murray mentioned earlier in the day that we used to have the alternative donor list patients and we really don't do that anymore, and I don't think we should sort of make one list of patients that can get one and one another. You know, the patients don't really get to learn anything about their donor, but it's up to us to make sure that we're doing our best for all of our patients.

DR. LANGE: Dr. Selzman.

DR. SELZMAN: Bram, I think the other piece is that the allocation system has been redesigned to address your question, so there's high-risk features but theoretically, if someone is high risk, they're kind of moving up the ladder, if you will, so that they're going to have more exposure to donor offers.

DR. ALLEN: Yeah, except --

(Cross-talk.)

DR. ALLEN: Can I just comment on that? The problem with that mindset is yeah, the allocation is changed and they move up on the list and they're more likely to have somebody travel a long distance to get that heart and so you're betting that this is a good

device for that when under the old allocation -- and we're not arguing about this, but you brought it up, under the old allocation system, that heart would've gone someplace more locally and probably would have been harvested with standard of care.

DR. SELZMAN: Fair enough, fair enough.

DR. LANGE: Dr. Zuckerman, does that address the question you had?

DR. ZUCKERMAN: Yes, these have been very helpful additional comments. Thank you.

DR. LANGE: Thank you.

Catherine.

MS. WENTZ: Okay, 6b: Please discuss whether the available study data provide a reasonable assurance of safety and effectiveness for donor hearts defined by each of the individual donor heart criteria. If not, please explain your concerns.

DR. LANGE: Keith and then Murray.

DR. ALLEN: Catherine, since nobody's speaking, I will. I'm a little bit confused by your question, are you talking about you want us to go through each of the individual exclusions or inclusions and say whether those individually are reasonable, is that what you're asking?

MS. WENTZ: Basically. Are they appropriate for what we're talking about for this device?

DR. ALLEN: Yeah. And I'm not sure --

MS. WENTZ: For the extended heart.

DR. ALLEN: Yeah. And I'm not sure you can really ask it in that way because individually a lot of them aren't, but the totality of what is -- as somebody who takes all night to decide on a heart, you kind of put it in your brain and you're looking at the acuity of the person getting the heart, you know, what you know about his comorbidities, and then

you have to also then think about what's the donor heart look like and all of the issues that we've discussed already to then make a decision. I'm not sure it's as simple as does that one check the box or does that not check the box.

MS. WENTZ: Right. Basically, what we're trying to get at is, is there some set of inclusion criteria that would be acceptable as a defined extended donor heart pool.

DR. ALLEN: So I think if you could be assured of the fact that your donor times were going to be greater than 4 hours, and even that's questionable because we take hearts that are -- you know, we'll go to Chicago or up and down, they're 5 hours away, or our donor times would be 5 hours in the right patient. So then it comes down to who is your recipient going to be and do you think that they warrant taking that additional risk. I think it does come down to -- and it is amazing when you get the call in the middle of the night, I mean, one of the first questions I ask is where am I on your call list and when they say well, you're 280, you know, I'd start thinking about well, yeah, this would be great, let's use the heart in a box. But if they tell me I'm number one, it's a whole different mindset.

MS. WENTZ: Right.

DR. LANGE: Dr. Kwon.

MS. WENTZ: But for clarification, when you state the donor heart time is greater than 4 hours, don't forget the -- it takes time to instrument the heart, so are you talking about perfusion time, are you talking about prospect time, are you talking about out-of-body time when you're talking about donor heart times greater than 4 hours?

DR. ALLEN: I'm talking about for the time that my team, on the retrieval, puts the clamp on the aorta and starts giving cold crystalloid and cuts that heart out until I take the clamp off and reperfuse the coronaries.

MS. WENTZ: Okay, so --

DR. ALLEN: To me, that's the ischemic time, period.

DR. LANGE: Dr. Kwon.

DR. KWON: Yeah, I'm not starting anything new necessarily because it's been said, but in answer to (b) I would say a lot of those secondary criteria with the 2 hours plus this or that, I'll mirror Dr. Moon's point, I think they're somewhat arbitrary and I don't know how this system will help a 2-hour ischemic time plus alcohol history or luminal narrowing on -- irregularities on a coronary angiogram. How does this device help that? And none of the data, I think, that we've been presented with even come remotely close to answering whether those inclusion criteria will be benefitted by this or not. So we talked about indication creep many times already, but I mean, I think that's one entryway where a study can recruit more patients and potentially lead the way for indication creep once it becomes a commercial device. My answer to (b) is no.

DR. LANGE: And Dr. Kwon, I would agree. This is a group that would be easy to study using standard of care or in the OCS System to determine those less than 2 hours with diabetes or alcoholism or luminal irregularities, so this would be a very easy group to study.

Al Stammers.

MR. STAMMERS: Yeah, Al Stammers.

Just one quick point. Should there be an upper boundary on the donor age? Just seems greater than 55 is open for interpretation.

DR. LANGE: Point well taken. We're not going to -- I mean, we're going to note that for the FDA to consider for the Sponsor. We won't resolve that as a Panel, though. Especially those of us who are over 55 years of age, we're not going to resolve this.

All right, Catherine.

Bram, do you feel like you have sufficient input into that question?

DR. ZUCKERMAN: Yes, I do. Thank you.

DR. LANGE: Great. Go ahead.

MS. WENTZ: All right, benefit-risk. The EXPAND single-arm study was designed to leverage the results of the PROCEED II randomized controlled trial for standard criteria donor hearts, to allow for expanded indications for use in non-standard criteria donor hearts. However, reasonable assurance of safety and effectiveness was not determined for the OCS Heart System for the preservation and transplantation of standard criteria donor hearts. In FDA's opinion, the OCS Heart System studied under the EXPAND clinical study for extended criteria donor hearts was not designed as a standalone clinical study, and it is for this reason that FDA is considering the results from both the PROCEED II and the EXPAND studies in its assessment of the OCS Heart System benefit-risk assessment.

The OCS Heart EXPAND study met its 30-day primary endpoint of transplant recipient and allograft survival in the absence of severe primary graft dysfunction in the first 24 hours post-transplantation (tested against a performance goal of 65%). However, lower survival with the OCS-preserved standard hearts (sustained over the long term), high turndown rate for hearts preserved on the OCS Heart System (13% overall), potential injury to some donor hearts being preserved on the OCS System, and the subjectivity of the "extended" donor heart inclusion criteria creating potential overlap with standard hearts, raise concerns related to how the OCS System may affect the pool of viable donor hearts available to recipients, as well as overall longer-term survival for heart transplant patients.

So Question 7: Given the totality of the evidence regarding the effectiveness and safety profile of the OCS Heart System (i.e., the results of the pivotal randomized PROCEED II study, the single-arm EXPAND study, and the supplementary EXPAND CAP data), please discuss whether the benefits of the OCS Heart System outweigh the risks.

DR. LANGE: So Bram, I'm going to ask you a question. Obviously, we're going to vote on this and given the time, we can have that discussion now, if you would prefer to vote and then discuss it afterwards. So Bram, what would be your preference?

DR. ZUCKERMAN: Well, the FDA would like a short discussion at a minimum for the public record. I recognize that there will be a divergence of opinions probably, but it's important to get that on the record now --

DR. LANGE: All right.

DR. ZUCKERMAN: -- before the vote.

DR. LANGE: Thank you, Dr. Zuckerman.

So Dr. Moon would like to start.

DR. MOON: Yeah, I think, since organs that are over 4 hours are essentially off limits for the most part. I mean, there's some give and take, but generally most people wouldn't take them. So I think this device is better than leaving the organ in the bucket and not using it. The ones that have the 2-hour plus the soft criteria, we don't know that it's better than just doing the standard of care in that case. And so given a couple options, one, a standard of care versus OCS study in those patients, which is a much smaller group, so difficult to accomplish, or some animal work that suggests that it's as safe or creates as much or as little damage as every other approach would be fine, too.

DR. LANGE: Great. Dr. O'Connor.

DR. O'CONNOR: Chris O'Connor.

I think the FDA is correct and that they should use the pivotal randomized PROCEED II study to be informative on particularly safety and perhaps some of the efficacy. But I agree with Dr. Moon, I think that one can find a sweet spot where -- and I think it's greater than 4 hours plus risk factors, that's about 20% of the population where one could find safety and efficacy.

DR. LANGE: Dr. Cigarroa.

(Off microphone response.)

DR. LANGE: You're on mute, Dr. Cigarroa.

DR. CIGARROA: Thank you, sir.

So I find it incredibly challenging to not include the pivotal randomized PROCEED II study and find it challenging to know, in individuals who would otherwise be transplanted with an ischemic time burden of less than 4 hours, whether there is safety and efficacy.

Conversely, in those that are going to have ischemic times of greater than 4 hours, there is also difficulty in interpreting the EXPAND and the EXPAND CAP given the number of patients performed by one or two sites and having confidence that one can translate that into smaller volume sites and programs across the country.

DR. LANGE: Dr. Allen.

DR. ALLEN: So I can't ignore the PROCEED II study, the company did it. I actually wish they hadn't done it. And we just did this expanded study and you were looking at hearts that were going to go in the bucket, that's a lot easier sell. My concern, though, is that I really don't think this device is better than standard of care in short ischemic time. I think it actually may be a lot worse. But I do think in a population who is -- that we're not going to use that hard, I think it has some benefit and that's where the conflict comes and that's where the benefit-risk of this product, to me, is predicated on how well the FDA can put in place appropriate controls for its appropriate use in an appropriately defined population.

DR. LANGE: So Bram, as you predicted, divergent views. Some people said better to use a heart than throw it away. If I'm the patient, I'd say better to wait for a good heart than get a bad heart. There was real genuine concern about using it for people that had an ischemic time that's less than 2 hours, and more enthusiasm for using it for individuals in whom the ischemic time would be more than 4 hours plus additional risk factors. Some concern about whether all sites would see the same benefits as the Duke site, and then somebody that expressed they believe it's actually worse than the standard of care. So

we'll vote this out, but I think for the record, you have a good record that everybody has actually paid a lot of attention to the detail and are weighing it pretty heavily and being very thoughtful.

DR. LANGE: Thank you, Dr. Lange.

DR. LANGE: Dr. Connor, we're going to read Question 8, get ready for it.

MS. WENTZ: All right, I'm going to read this into the record, the top part and the small part. This is the post-approval study slide. Note: This requested discussion item related to the proposed Post-Approval Study should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA. The presence of a post-approval study plan or commitment does not alter the requirements for premarket approval and a recommendation from the Panel on whether the benefits of the device outweigh the risks. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study can be considered.

And with that said, under the post-approval study that has been proposed.

Post-approval studies are often required at the time of approval of a PMA to address remaining questions or provide information on the continued safety and effectiveness of the approved device. These studies are not intended to provide initial support for reasonable assurance of safety and effectiveness, as this determination must be established prior to device approval. If a post-approval study is requested, the Sponsor has proposed two post-approval studies to continue to evaluate the performance of the OCS Heart System:

- A 175-patient, single-arm, prospective, multicenter, observational post-approval registry with follow-up out to 12 months, and outcomes out to 5 years; and
- A single-arm, observational post-approval follow-up data analysis in which

outcomes obtained from the existing national Scientific Registry of Transplant Recipients (SRTR)/OPTN database for the 75 subjects transplanted in EXPAND will be obtained and analyzed out to 5 years.

Please comment on whether additional study objectives, design features, or surveillance are recommended for the Post-Approval Studies. Specifically, please discuss the appropriateness of the proposed primary endpoint (e.g., 12-month survival from cardiac graft-related death), and the 86% performance goal (considering a post hoc, un-adjudicated analysis of cardiac graft-related survival at 12 months in EXPAND was 95%), as well as other follow-up assessments necessary to evaluate the long-term safety and effectiveness of the device.

DR. LANGE: All right, Dr. Connor.

DR. CONNOR: All right, I appreciate the warning on this one.

So one of the common concerns we've heard from a lot of people that is not addressed here is this idea of creep and I think that's study-able, so I would say any site that participates in this should at least track all patients who end up using the OCS and identify whether they're basically on label or not. That way, in the yearly report of a post-approval study, it would be very clear to FDA how many people were using this essentially off label and measure this creep. I fully appreciate that FDA cannot police the practice of medicine, but at least that data would be available.

The other part then, as Dr. Lange just recently said too, some patients may want to say no, I'll wait for the right heart; that doesn't answer this question and I proposed earlier that I think you can still run an observational trial like you're running or proposing, but try to measure that so you prospectively identify people on a wait list who would want an OCS heart and those who would want to wait, and when an OCS heart becomes available, you essentially try to match one of those wait patients right away and you have then

prospective controls and you can see are patients who are getting an OCS heart, how do they do compared to that other person who wanted to wait. Some may die on the wait list, unfortunately; some may wait and get a heart that's better for them, and I think that's the real clinical question. And you can still run your post-approval study as a one-arm trial and answer some of these more meaningful questions. So I would really keep that in mind because I think, as written here, this is equally uninformative as EXPAND.

DR. LANGE: Dr. O'Connor.

Then Ralph, I'm going to come to you to talk about whether UNOS -- we can use registry data to help out with comparison.

Dr. O'Connor, you first.

DR. O'CONNOR: Dr. O'Connor.

I totally agree with Dr. Connor and that is that we should absolutely have a post-approval study, and I think the bar here is way too low, I think we should think about every recipient of this device. If they think it's going to be a thousand new recipients, then I think we should be talking a registry on the order of a thousand and some comparator to the wait list patients would be optimal.

DR. LANGE: Thank you, Chris.

Ralph.

DR. BRINDIS: Yes. Thanks, Rick. Certainly, the challenges of actually doing true randomized clinical trial work going forward is going to be off, very difficult, and I don't sense a lot of enthusiasm in particular for that. So I'm wondering again how we can utilize the database of UNOS potentially with propensity matching or other techniques to be able to compare results related to a post-approval study and what's going on in the community. One of the challenges I don't know is what are some of the data elements in UNOS, it may be that additional elements will need to be done. A comment was made earlier that UNOS

didn't feel that it could do such work, I wasn't sure why that was, the bandwidth or the difficulty in actually doing good propensity matching. I wonder if Bobby Yeh also has some thoughts in this direction.

DR. LANGE: Go ahead, Dr. Yeh.

DR. YEH: I mean, I agree with Ralph and -- Dr. Brindis and Dr. Katz. This is Bobby Yeh. Both of their comments that something more comprehensive should be done that can allow for the assessment --

(Audio malfunction.)

DR. YEH: -- seems to be the right approach for that. I don't have experience with UNOS, but I agree that the explanation that they couldn't run a propensity match because of the distribution of the covariates were not overlapping, didn't seem -- it didn't seem adequate at the time, but I think that there would be opportunities there given how much data are collected on all transplant patients in the United States to be able to do something that was more comprehensive than what's proposed here. And it could be done at relatively lower cost than something that would be done without using those registries.

DR. LANGE: Great. Dr. Connor, I see your hand up again.

DR. CONNOR: Yeah. And I was just going to clarify about the propensity match, I totally agree with what Dr. Yeh said, that the key is not to propensity match for people getting a standard of care heart at the same time because we're not giving standard of care hearts to these people. It's propensity matched to someone who wants to wait and that's the key and that's not hard to do and so it's not an excuse not to be able to do that.

DR. LANGE: So I'm going to summarize the points I have to date after Dr. Hirshfeld talks and then we'll see if there's any additional comments.

Dr. Hirshfeld.

DR. HIRSHFELD: This may be redundant, but it's not explicitly stated, that I think the

unit of analysis on this should be the donor heart, not the recipient, because we need to track hearts that are harvested and placed on the machine but then are not used.

DR. LANGE: Okay. Great.

So Dr. Zuckerman, the points that have been brought up, one is there needs to be a comparator and again, that could be individuals that are on a waiting list, it could be the UNOS database that provides information; there needs to be a larger patient population; we need to examine whether there, in fact, is creep or whether people are using it for the right indication or not; and as Dr. Yeh said, it needs to be more comprehensive. And then finally, as Dr. Hirshfeld mentioned, the unit of analysis is the donor heart, not necessarily the recipient.

So are there -- Dr. Kwon, I see your hand, as well. Go ahead, sir.

DR. KWON: I would just respond to Dr. Connor. I'm mindful of what you said, but I wouldn't necessarily underestimate the ability to do a direct comparison to a 4-hour ischemic time group protected with standard of care, I don't think that's an inconsequential group.

DR. CONNOR: No, that's great. If they can do it, I would totally encourage that. Agreed.

DR. LANGE: Murray, as you mentioned, 15% of the current hearts transplanted have an ischemic time of over 4 hours already, that's 1500 of the 10,000 done, so your point is well taken, Dr. Kwon.

Any other points that we haven't mentioned with regard to a post-approval study?

(No response.)

DR. LANGE: Dr. Zuckerman, would you like some additional questions regarding that or do you have enough direction?

DR. ZUCKERMAN: No. I think, in summary, the Panel has suggested that a very

rigorous post-approval study needs to be conducted with quite a thoughtful design. Just in concluding, I was wondering if Dr. Allen had any other comments, given that he's previously made some good suggestions also about a PAS study.

DR. LANGE: Dr. Allen?

DR. ALLEN: Bram, to be honest, I don't know that beyond what we've already talked about is -- I'm going to elucidate much more. I really do think, though, that in order for this post-approval study to be meaningful and we're going to target this extended group, I think you may actually come up -- and I love Dr. Kwon's idea, I really like this idea about donor rejection and where you are on the list and some conversation with UNOS about not only what that number is, when you get to be the 90th or a hundredth turndown, there has to be some sweet spot where the chance of that heart being used is negligible and incorporating that into that post-approval study, I think, would give you a firm endpoint on hearts that maybe weren't going to be used.

DR. LANGE: Dr. Bonde.

DR. BONDE: Yeah, I think when choosing the extended donor criteria, we really do, in the postmarket, post-approval study, we need to define which factors actually affect the donor heart performance in 30 days or the first year, for example, compared to risk factors which has got a long-term impact on vascularity and graft versus host reactions. That's very important to identify what those intended criteria would be and ischemic time is one of them, but there are other ones which needs to be identified and confirmed during this post-approval study.

DR. LANGE: And Bram, I'm going to add one last point. Obviously, I've been participating on the Panel for gosh, it's probably 12 years now, either as a participant or now as the chair for a couple of years, and the devices that I see that are most helpful and the studies that I see that are most helpful is when the sponsor and the FDA work together,

that it is when the sponsor decides to go in a different direction and the sponsor decides to thumb their nose at the FDA or thumb their nose at the Panel, it doesn't usually work out very well.

So if we're going to talk about a post-approval study, I want to make sure that the Sponsor here is very clearly -- the expectations of the Panel, that they would follow the lead and direction and assistance of the FDA. The Panel's been very clear about what are the limitations of the data we have and the uncertainties there are, what needs to be done. So I just want to make that for the record.

DR. ZUCKERMAN: Thank you, Dr. Lange, for those comments and I wish -- I want to thank the Panel members for an extremely good discussion about a rigorous post-approval study.

DR. LANGE: At this point, it's time to summarize. We'll ask the FDA first if they'd like to speak and you have up to 10 minutes if you'd like to do so.

MR. AGUEL: This is Fernando Aguel, FDA.

I think in interest of time I'll try to keep this very short and rather than summarize, I think, Dr. Lange, you've done a great job of summarizing after each question and we'll be able to take a look at transcripts. But I do want to take the opportunity to thank all the speakers today, the Sponsor; Open Public Hearing speakers; you, Dr. Lange; and the rest of the Panel members, for what's been a robust and insightful discussion. In the interest of time, I'll end my comments there and pass it back it to you.

DR. LANGE: Great. And with that, I want to make sure that the Sponsor also has time. And again, I want to reiterate, I think the FDA and the Sponsor have both been responsive to the questions and to the leadership, so I want to thank you very much for that.

So Dr. Hassanein, you have up to 10 minutes if you'd like to take so to summarize.

DR. HASSANEIN: Thank you, Dr. Lange. I'd like to yield my time to Dr. Carmelo Milano to summarize on behalf of the EXPAND trial investigator, with your permission.

DR. LANGE: Yes, sir.

DR. HASSANEIN: Dr. Milano, can you please unmute and join the camera?

DR. MILANO: Thank you. I'm Carmelo Milano, I'm the chief of the section of adult heart surgery and a Professor of Surgery at Duke University, and I've been an investigator in this trial and the EXPAND trial. I've been involved in heart transplant for 30 years. I've heard a lot of discussion this afternoon about cold static storage being a gold standard, but in my opinion this is a primitive and limiting strategy.

You've seen a lot of data today with some disagreements between the FDA and TransMedics in their interpretation. In my opinion, TransMedics has provided clear answers that address each of the FDA's concerns.

One final slide that we'd like to show is just a display of the 1-year survival for the EXPAND and CAP cohort. Basically, at 1 year 87% of patients are alive and that survival is quite similar to SRTR data for general heart transplantation, so that's more than 80 hearts which would not have been utilized and have achieved survival outcomes that are quite similar to the SRTR overall population.

While much of the discussion today has been about details, I don't want the Panel to lose sight of what the OCS would mean for the field of heart transplantation and more importantly, for thousands of critically ill patients with end-stage heart failure who need a heart. We heard from patients who were desperately waiting on the transplant list and didn't know if they would survive another 6 months. Some of them reported being able to receive a transplant within weeks when they enrolled in the EXPAND trial. They're the reasons I'm here today and why I'm proud to support the approval of OCS, because it will allow us to transplant hearts that would otherwise not be used and ultimately save more

patients' lives. The current problem we face in heart transplant is not with the survival outcomes. We know that patients live, on average, for 14 years following heart transplant, so the outcome, the survival outcome and the functionality are excellent. The problem is how few patients get this chance. There are more than a hundred thousand patients in the U.S. with end-stage heart failure who could potentially benefit from transplant, yet we only perform about 3600 transplants a year. So our treatment with heart transplant really doesn't get at the larger population of patients with end-stage heart failure and trying to find ways to utilize more hearts is critical to make the therapy effective and meaningful.

Today, we can only routinely transplant the healthiest hearts from the youngest donors, we cannot take a chance of transplanting marginal donor hearts because we just can't be confident in how they will perform. We also can't risk long-distance retrievals.

There's been quite a bit of discussion about a randomized trial, but while that is a theoretical solution to understand this space better, I would argue that a randomized trial would enroll poorly because we simply cannot take the hearts that we put in EXPAND and randomize them to cold static storage. I and other surgeons would not be willing to travel 4 hours to get a heart with cold static storage understanding the risks associated with cold static storage.

We should not lose sight of the fact that every donor heart is a selfless gift from a person whose life was prematurely cut short. But because of the limitations of cold storage, we discard thousands of hearts every year that could be lifesaving. OCS would put an end to this waste of precious resources. We can assess, monitor, preserve, and literally resuscitate hearts on this system and when a heart can't be revived on the OCS, we can be confident in our decision not to transplant it. This is the very definition of evidence-based medicine, making informed decisions about the care of each patient using the best available information.

OCS has the potential to significantly expand the number of heart transplants that we can perform in this country. Since its approval in Europe, the number of transplants performed has increased by more than 40% in the UK in the last 5 years. It's worth reminding the Panel also that the OCS System evaluated in PROCEED II was a first generation technology. EXPAND evaluated a more advanced system and if approved, will open the door for even more improvements. I'm excited not only about what OCS can accomplish today by expanding the donor pool with extended criteria donors, but I'm optimistic about the future opportunities as TransMedics continues to advance its technology.

This device is already being used to preserve and resuscitate DCD hearts for transplant I thought that was unimaginable even a few years ago. And there are multiple examples in the cardiovascular space where a technology progresses after its initial application and the improvement in outcomes will also result from our clinicians' familiarity and application of the technology. The FDA has raised many issues for your consideration today. The Agency points to individual cases where exceptions were made such as when the final lactate level was above five on the OCS.

In fact, one of those cases was mine, I made a decision to transplant the heart based on the fact that the recipient had a critical need to be transplanted and the other OCS parameters were stable. We have to remember that heart transplantation is an extremely complex therapy, surgeons make life and death decisions when minutes matter and they need to rely on their clinical judgment and at times that judgment interfered with some of the parameters of the trial. So before you vote, I want to leave you with my most important consideration. The Organ Care System will save hundreds, if not thousands, of lives each year by accessing donor organs that are currently not utilized.

Thank you for the opportunity to provide my perspective and what I view as a

transformational technology which will advance this field. Thank you.

DR. LANGE: Dr. Milano, thank you for those comments.

And just for the record, the slide that was shown had not been previously reviewed by the FDA and Dr. Hassanein has made that point, as well, just for the record. That's all. I mean, it's not important, they're not valid, but just for the record.

So thank you, Dr. Milano.

At this time I'd like to reach out to our Consumer Rep. Oh, to our Industry Rep, Gary Jarvis, and our Patient Rep, Debra Dunn, to see if they have any additional comments.

Mr. Jarvis, you first.

MR. JARVIS: I do not have any additional comments at this time, Dr. Lange. Thank you.

DR. LANGE: Thank you.

Ms. Dunn.

MS. DUNN: Yes. It's very confusing, but I think Dr. Milano --

DR. LANGE: Sorry, Ms. Dunn, can you move a little bit closer to your microphone?

MS. DUNN: Can you hear?

DR. LANGE: We can hear now.

MS. DUNN: Okay, sorry. I think that I concur with Dr. Milano, his thought process. I do understand the risk factors, but I think this is an advancement in cardiology and saving lives, so it's been very insightful for me, so thank you.

DR. LANGE: Thanks. Again, I want to thank both of you for participating and everybody for hanging on. There was a lot of discussion, very important decision.

So at this point, I'd like to move on to vote. We are now ready to vote on the Panel's recommendation to the FDA for the TransMedics Organ Care System (OCS) Heart System. The Panel is expected to respond to three questions relating to safety, efficacy, and benefit

versus risk. Aden Asefa will now read the proposed indication for use statement and two definitions that will assist n the voting process.

Aden.

MS. ASEFA: 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 applications (PMAs) 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 and effectiveness are as follows: Safety as defined in 21 C.F.R. Section 860.7(d)(1) - There is 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 risks.

Effectiveness as defined in 21 C.F.R. Section 860.7(e)(1) - There is 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.

I will now read the proposed indications for use statement. The TransMedics Organ Care System Heart System is a portable extracorporeal heart perfusion and monitoring system indicated for the resuscitation, preservation, and assessment of donor hearts in a near-physiologic, normothermic, and beating state intended for a potential transplant recipient. OCS Heart is indicated for donor hearts with one or more of the following

characteristics:

- Expected cross-clamp or ischemic time ≥ 4 hours due to donor or recipient characteristics;
- Expected total cross-clamp time of ≥ 2 hours PLUS one of the following risk factors:
  - Donor Age ≥ 55 years; or
  - Donors with history of cardiac arrest and downtime ≥ 20 minutes; or
  - Donor history of alcoholism; or
  - Donor history of diabetes; or
  - Donor Left Ventricular Ejection Fraction (LVEF) ≤ 50% but ≥ 40%; or
  - Donor history of Left Ventricular Hypertrophy; or
  - Donor angiogram with luminal irregularities but no significant coronary artery disease.

Panel members, we will now begin the voting process. I will read each of the three voting questions. I will read the questions and we will tally the votes and read them into the record.

DR. LANGE: Now, Aden --

MS. ASEFA: Voting Question Number 1.

DR. LANGE: Aden, before you do that --

MS. ASEFA: Based on data in the briefing --

DR. LANGE: I'm sorry, Aden, just before you do that, I just want to make sure everybody has access to the voting link. If you don't, at this particular time if you'll indicate by raising your hand. Okay, Dr. Allen needs access to it. So Jim, if you'll provide -- and Dr. Moon needs access to the voting link.

DR. MOON: No, I've got it. I've got it.

DR. ALLEN: I have access. I thought you were asking us to raise your hand if you had it.

DR. LANGE: That's fine. I just want to make sure everybody has it.

Okay, Aden, I'm sorry to interrupt, but I wanted to make sure everybody could vote, so please continue. My apologies.

MS. ASEFA: -- materials and presentations at today's meeting, do you believe that there is reasonable assurance that the OCS Heart System is safe for use in patients who meet the criteria specified in the proposed indication?

Please vote now yes, no, or abstain.

(Panel vote.)

MS. ASEFA: Voting Question 2: Is there reasonable assurance that the OCS Heart System is effective for use in patients who meet the criteria specified in the proposed indication?

Please vote now yes, no, or abstain.

(Panel vote.)

DR. LANGE: Dr. Blankenship, do you need access to the voting link?

DR. BLANKENSHIP: Yeah, I just have the question about lunch still up. Do you have to go back into the link again for it?

MS. ASEFA: Voting Question --

MR. VEIZIS: You could just hit F5, it will refresh the page.

DR. LANGE: Do you have it, Dr. Blankenship?

DR. BLANKENSHIP: No, I don't. Let me just go back into the original link again and pull it up from the original e-mail. I'm sorry for the delay here.

DR. LANGE: No, no. We'll wait.

MR. VEIZIS: No problems.

DR. LANGE: Every vote is important, thank you.

(Pause.)

DR. BLANKENSHIP: Okay, got it. Thank you.

DR. LANGE: All right, so -- okay. So have you had a chance to vote on Number 1, Dr. Blankenship?

DR. BLANKENSHIP: Yeah.

MR. VEIZIS: Yeah, you can vote on all three and just put your first name, last name and submit your votes.

DR. LANGE: Terrific.

MR. VEIZIS: Go ahead and play the rest of the video.

MS. ASEFA: -- Number 3: Do the benefits of the OCS Heart System outweigh the risks for use in patients who meet the criteria specified in the proposed indication?

Please vote now yes, no, or abstain.

(Panel vote.)

MS. ASEFA: Please give us a moment as we tally and verify the official votes.

(Vote tally.)

DR. LANGE: All right. The votes have been tallied, they've not been revealed yet. The audiovisual team was actually preparing a graphic during this time, but I'll take this time just to say after the votes, I'm going to ask the Panel members, at that time, to discuss their votes. If you answered no to any question, I'm going to ask you to state whether any changes to labeling, restrictions on use or other controls would have made a difference in your answer. When you give your answer and I'll call the roll, if you would please state your name and how you voted for each question for the record. In this brief time, again, I would like to thank the FDA for their presentation, the Sponsor for their presentation and their responsiveness to the questions, to all the public, Open Public Hearing speakers that

participated, for their contributions to today's meeting, and also to our Industry Rep and our Patient Rep, as well, for Debra Dunn and for Gary Jarvis, as well.

So with that, if you'll please read the votes into the record.

MS. ASEFA: The votes have been captured and I will now read the votes into the record.

On Question Number 1, the Panel voted nine yes, seven no, and two abstain that the data shows reasonable assurance that the OCS Heart System is safe for use in patients who meet the criteria specified in the proposed indication.

On Question Number 2, the Panel voted 10 yes, seven no, and two abstain that there is a reasonable assurance that the OCS Heart System is effective for use in patients who meet the criteria specified in the proposed indication.

DR. LANGE: Aden, I'm going to stop right there for a second because I think Question 2, if I'm not mistaken, there are 10 yeses, six no's, and two abstentions, just for the record.

Go ahead, please proceed. Question 3.

MS. ASEFA: Okay. On Question 3, the Panel voted 12 yes, five no's, and one abstain that the benefits of the OCS Heart System outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

DR. LANGE: Great.

MS. ASEFA: The three voting questions are now complete.

DR. LANGE: Aden, thank you very much. I'm sorry to interrupt, my apologies. Thank you.

Let's go around the room. Dr. Vetrovec.

DR. VETROVEC: Yes, I voted yes for all three. It seems to me that while the data is certainly not robust, it seems to me that it is safe and effective, particularly given the choice

of not using a heart and hopefully, the final decisions will be that the chosen donors will be appropriate in terms of distance where it makes a difference and the patient really needs it appropriately timed.

DR. LANGE: Thank you, George.

Dr. Blankenship.

DR. BLANKENSHIP: I voted yes to all three and I would have felt more comfortable if we had had a comparator. So if it had been compared to standard of care, I would have voted no for all three. If it's compared to getting an LVAD, I would say yes and if it's compared to getting -- not getting a heart at all over a given period of time, I would say that the benefits outweigh the risks and would say yes to all three. And again, I would say that I hope that if it is approved, that it would be with the caveats that it would mean that it's not competing with standard of care hearts.

DR. LANGE: Great. Thank you, Jim.

Dr. Connor, Jason Connor.

DR. CONNOR: Yes, Jason Connor.

I voted no to all three. It was a really hard vote, I think this is my 28th panel and it may have been my hardest vote. I think there's definitely a place for this and I think that place is definitely in those 4-hour and longer hearts. I voted no because I just wasn't sure that the part B of the label, those under four with certain characteristics, that there was actually benefit there or even right above four.

I admit, I expected the Sponsor to be optimistic. I was actually very concerned in how optimistic the transplant surgeons were and that optimism really leads me -- like the fact that they were more optimistic than critical of the data, leads me to be worried about that creep. So I definitely thinks there a place for it, but I voted no to this specific question about the specific label.

DR. LANGE: Thank you, Jason.

Dr. Brindis.

DR. BRINDIS: Yes. So I voted no on safety, no on efficacy, but I voted yes that the benefits exceed the risk. And clearly, we heard today about a great need to expand the donor heart pool for patients with end-stage heart failure and that would clearly decrease transplant wait times and should save many lives of those presently dying while waiting for a potential transplant.

Something also worth emphasizing is that the ability to safely and effectively prolong the estimated time from heart donor harvest to recipient implantation is going to help alleviate disparities in care due to present geographic transport barriers and also, as mentioned earlier during the presentation, with patients for O blood type.

I thought that the FDA and Sponsor did a terrific job and in particular, the FDA beautifully articulated the challenges in assessing all the data of safety and efficacy related to the OCS Heart System, and in terms of designs, conduct, role of lactate levels, transplant viability assessment, concerns of safety of the system itself, as well as long-term patient survival, which all beg for a necessary further study.

I again want to emphasize the concerns with potential adverse effects of indication to creep with the widespread access of the device. And more robust animal data and clinical evaluation is needed to shed important insights for aiding the assessment of the OCS Heart System and the management of these end-stage heart patients who have great needs. And I am convinced that an ethical randomized clinical trial or at least prospective observational data analysis with better comparisons via UNOS can be devised.

DR. LANGE: Thank you, Ralph.

Dr. Allen.

DR. ALLEN: So I voted no on safety. I'm not going to give the company a pass. I

think their animal data was sorely lacking and I think a lot of issues over the last 10 years could've been addressed with some key animal studies, particularly regarding safety.

However, for efficacy and risk-benefit, I voted yes for both of those. Had this been versus standard of care and only the PROCEED II, I would have voted no. But I do think there are a lot of hearts that go in the bucket and I think that this is a challenging population. I just hope that the post-approval study is designed in a collaborative way and the FDA can provide controls for preventing creep of indication.

DR. LANGE: Thank you, Keith.

Dr. Kwon.

DR. KWON: Dr. Connor, I'm a surgeon and I voted no on all three counts, just so you know. And I'm going to answer this in the purest sense. If you look at the data on safety, I was troubled by the quarter of the patients who ended up on MCS in the first 30 days after transplant, I find that highly aberrant.

The efficacy group, I think if you don't have the proper controls, I don't know how you can argue efficacy. Even a lack of a historical control from a database, I don't know how you can argue against that.

And as far as risk-benefit, if it was just limited to one group, the 4-hour-plus, I would say yes, but if you're going to tell me that there's a risk-benefit for the 2-hour with the alcoholic, I don't know how that was proved in anything. So in the purest sense, I voted no.

But I do think, like many have mentioned, that there is a space for this platform. I don't know yet whether it's snake oil or whether it's doing something, is there a value add, because we don't have the proper controls in this group. Somebody said before, earlier today, that this device saved 16% of patients from getting a bad heart and I don't know that to be the right term because how do you know that this platform just does not sustain organs over the time period? We don't. So in the purest sense, that's why I have my

concerns, but I do think there is a role for this. If there's one utility in this at all, it is that it shepherded in some group to take these high-risk patients and they have some gratifying results. And that's it. As far as proving that it led to those great results, I haven't seen the data to support that, but I'm looking forward to seeing it in the future.

DR. ZUCKERMAN: So Dr. Kwon, if I can ask you a quick follow-up. You said that if it was just labeled for 4 hours plus you would vote yes on benefit-risk. Would you vote yes on safety and effectiveness also if the label was just for 4 hours plus?

DR. KWON: I think I would say no because there's been no data that shows in that 4-hour-plus group, in my opinion, these are all lumped up together that I've seen. But I do think there's a role for these emerging technologies, I just don't think you can make the assertions that we're making, that somehow we're heralding in this great thing that's going to make all the difference and we can go out to 8 hours, go to Hawaii and go to Alaska and get these organs and I don't know that to be the case.

The only thing I know is that it is a conduit to those high-risk and people are doing it because they have this proposed option, but is it a true value add or if it's just you would have gotten the same -- he or she would've gotten the same result with standard of care, nobody can tell me they've shown me any data to show that. There's not even a historical control that was shown to us that this would stack up favorably to the standard of care group who had a 5-hour ischemic time, for example, and I think -- but I do think there's room for that to be discerned in the future. And again, the one utility of this device that I could see from sitting here today was that it allowed certain patients to get organs that would not have otherwise been entertained and whether the device did anything or not, the data, to me, didn't prove it.

DR. ZUCKERMAN: Thank you for your comments.

DR. LANGE: Great. Thank you very much.

Dr. Bonde.

DR. BONDE: I chose to vote yes for all the three questions in spite of the 25% use of MCS support after the transplant in this data that -- and serious limitations of the preclinical data that typified the discretion that we had. And all -- planned were well-intentioned studies and trials, I voted yes because I still feel that the platform does give an opportunity and options to those who would not benefit from transplant and particularly those organs which cannot be utilized today, can be utilized using this platform.

DR. LANGE: Great.

DR. BONDE: I chose to vote yes this time rather than waiting for another 10 years for another study to be done because heart transplant world is rigorously controlled both internally and externally, and I think that the utility of this device and the improved MCS system which will decide whether they really are able to address the issue of donor limitation or donor scarcity or whether we have reached that point where you're going to be exploring this market, which is very unlikely.

DR. LANGE: Thank you, Dr. Bonde.

Dr. Gallagher.

DR. GALLAGHER: Yes, I voted to say no to Question 1 on safety because I think that the data that we were provided does not actually prove that this is truly safe as the use of a device because of some of the questions that were raised for complications and things afterward.

I did vote yes on whether or not it was effective because I considered the population as a whole, as well as subpopulations, so I can see that for some patients, they would consider that it has some efficacy that is acceptable to them.

I also said yes to the benefits outweighing the burdens and did that because of the larger number of patients in need who would be served and would most likely be accepting.

Having said that, I want to be very conscious of the fact that more technology is not necessarily better than not having that technology. So I would certainly want to make sure that any labeling for use of the device would be such that the strictness or tightness of the reasons for its use would be given. Thank you.

DR. LANGE: Thank you, Colleen.

Mr. Stammers.

MR. STAMMERS: Yes, I voted no on all three. And it was extremely difficult in understanding what occurred during the Open Public Hearing and listening to all the surgeons give their comments, it was very challenging to come to the decision. My many reasons stemmed from really a lack of data from the safety and efficacy to compel me to think that we've reached an area of use that would benefit patients without imposing some additional risk.

As far as the benefit-risk, that's a real hard one and I think I mirror Dr. Kwon's comments, I think that if the indications for use were basically -- or just at the level A indication for greater than 4 hours, I probably would have voted yes in that situation, but I just don't believe, from the data that was presented, that the category B indication for use is really adequate to show the benefit of the device.

DR. LANGE: Thank you, Al.

Dr. Yeh.

DR. YEH: You know, I thought obviously incredibly difficult trial space and a usually compelling clinical need and the challenge I had was that had no ability to discern whether or not the device causes injury, prevents it or has no role compared to cold storage, at least, but the data are really consistent with all three possibilities, but cold storage is not really the right comparator due to lack of equipoise that the clinicians have really spoken about. So I do know that it appears to make docs more comfortable using hearts that might

otherwise not be used and in the indications as written, it includes a mix, I think, of hearts that might go to standard of care patients, who might transplant with standard of care, as well as hearts that might otherwise not be used and for that reason I couldn't give it a definitive no or a definitive yes and I sort of hedged and I abstained from all three.

And the reason I abstained from all three is because I actually think, with a very short amount of modification, as outlined by some of the previous comments, more stringent criteria, I would have been a more definitive yes and I didn't think a no across the board, which probably would've been technically more accurate but didn't convey my true thoughts about how close they were to providing something which I do think would be overall of clinical benefit.

DR. LANGE: Robert, thank you. Appreciate that.

Dr. Selzman.

DR. SELZMAN: Thank you. Craig Selzman.

So I did abstain/yes/yes. I abstained on safety because I just couldn't figure it out, 8%, 26%. I still have some biologic concerns about taking a warm organ, cooling it, warming it, cooling it again, there's some biology in there that would be really great to understand, but we can't understand that right now and so like others, I encourage some additional preclinical work. I'm sure somebody could put in a good STTR or something like that with that.

So yes and yes on efficacy. I think the data that I saw with the EXPAND group meeting their performance goals, even if you adjudicated it just a little bit different, I thought it was reasonable.

And then I'll just say that I said yes on benefits but put the caveat in there that giving the FDA the benefit of the doubt that they're not going to allow the exact indications that were submitted there. And I agree with many of the others that the level A or the four-plus

would be important on the indication piece. Thank you.

DR. ZUCKERMAN: So Dr. Selzman, very important comments. In your ideal scenario, do you think an animal study should be a requirement as part of post-approval commitments along the lines that was discussed today?

(Off microphone response.)

DR. LANGE: You're on mute, Craig.

DR. SELZMAN: Sorry, sir. If I put my academic hat on, I would say yes, you should have it. From a regulatory standpoint, I'm not sure you need it if you define what your indications are very specifically. We're all curious. I mean, I could've jotted down 18 different studies that could've been done on pigs right now to help us better inform everything that's going on. All of us could create a bunch of different studies right now. But I'm not sure that it's going to change your decision on the regulatory aspects of what the indication would be.

DR. LANGE: Dr. Zuckerman, Dr. Vetrovec would like to raise -- like to chime in, is that okay?

DR. ZUCKERMAN: Absolutely.

DR. LANGE: George.

DR. VETROVEC: I would support having an animal trial, absolutely. I think there are some real questions that bothered all of us about mechanism and I think if you understand those, particularly about the issues of injury, that would be very, very helpful in terms of what you do going forward or whether you reevaluate where you are. So I would definitely support that.

DR. ZUCKERMAN: Thank you, very helpful.

DR. LANGE: Great. Thank you very much.

I've got Dr. Katz.

DR. KATZ: I voted yes on all three. Hypothermic protection of transplanted hearts began with Lower and Shumway in the late '50s, presented at the surgical forum in 1960 and that's basically what we're still doing today. The number of transplants that's being done has been basically pretty flat for quite some time now and I think this is a big step forward towards being able to expand that number.

Now, that all said, it obviously was a very far less-than-perfect study. I do think there needs to be some constraints put on the utilization, as has been spoken about by others and I would certainly be in favor of an animal study to clarify some of the questions, as well.

DR. LANGE: Thank you, Marc.

Dr. Cigarroa.

DR. CIGARROA: So I'd like to thank FDA and the Sponsors for outstanding presentations and their responses to clarifying questions that all the Panel members had, so thank you.

This issue of the unmet need for patients with refractory end-stage heart failure is challenging and quite emotional. We clearly need to do better. Despite that tremendous emotion and unmet need for patients and their families, I voted no across all three.

As it relates to safety, the ongoing production of lactate and the longer overall out-of-body and ischemic time concerns me.

As it relates to efficacy, efficacy compared to what? It certainly makes transplant programs more willing to operate on people who otherwise would have donor hearts greater than 4 hours and that is true, but I don't know what to compare it to and I do know that relative to 1-year outcomes, there's about a 10% discount on survival.

As it relates to risk-benefit, I thought long and hard about voting yes despite all of the unknowns because of this emotion but ultimately, I voted no because of the secondary

2-hours-plus alcoholism or diabetes or minor coronary disease in which the ischemic burden and ongoing lactate production concerned me. If it was restricted to patients that would be not treated because of an ischemic burden time of greater than 4 hours and therefore continue on the wait list, for those patients with a very narrow indication for use, I would state that I would vote yes for risk-benefit with a very careful two-component requirement and one would be animal studies and two would be a very carefully designed large registry with the PMA, as we had discussed.

DR. LANGE: Thank you, Joaquin.

Dr. Nuszkowski.

DR. NUSZKOWSKI: Hi, thank you. I'm happy to be here, this is my first vote, so I thank Dr. Connor for saying this was probably his most difficult of all of his panel participation.

I'm a perfusionist that worked out at Seattle Children's for a bit in 2007 to 2009, so I was well aware of the resources available for the pediatric population. We used to go down to Texas to harvest organs and they would end up on ECMO just because they had longer than 4 hours. So that was back in 2007 to '09 knowing that we had mechanical circulatory needs.

I think the transplant program is the most protected. Pretty much patients, every surgeon, everybody decides three times over whether they would take that organ or not. So I really think it's a good thing for the community and I voted yes for all three. And I am with Dr. Bonde, that the community will move forward or they won't with whether this will work in the long term.

But from a pediatric standpoint, any time we go to meetings, anybody comes back from meetings, somebody talked about this success, that success, it changes so quickly, so I think that the Sponsor is going to have a bigger job in just trying to keep selling their

program to -- or their machine to make sure that it stays up to date, as Dr. Milano had said, version 1, version 2. You know, I'm excited for version 3 of what it will look like. So I think good things are going to come from it.

DR. LANGE: Thank you, Mark, appreciate it.

Dr. O'Connor.

DR. O'CONNOR: Hi, Chris O'Connor.

I voted yes/abstain/yes and my belief is that there is a large unmet need, that doing a randomized trial in the expanded population would be unethical, and I think my abstain is really to signal that I believe there should be a restricted indication of greater than 4 hours and including risk factors.

DR. LANGE: Great. Chris, thank you very much.

Dr. Borer.

(Off microphone response.)

DR. LANGE: You're on mute, Jeff.

Jim, can you take Dr. Borer off mute? Thank you. Jeff --

MR. VIEZIS: Unfortunately, I can't do that, he has to do that. Yeah, he did it.

DR. BORER: Okay. I voted yes for all three questions. Really, there are problems with the data that were presented to us and I think Dr. Kwon articulated them very well and I agree with everything he said. But at the end of the day, if a heart is not provided to many of these people, they're going to die and they're going to die fairly quickly. So I think that the only solution to that is to make more hearts available and this technology seems to me to provide a reasonable approach to improving the supply of donor hearts. Given that, I think that it ought to be approved.

DR. LANGE: Jeff, thank you.

Dr. Moon.

DR. MOON: Yeah, I thought it was a very interesting day. You know, we try not to use organs that we know are going to be more than 4 hours of ischemic time. It occasionally does happen because of the ways and whatnot. But if we had a mechanism in which we felt more comfortable doing this, we would probably welcome it even if it wasn't as good as a standard of care organ that's done within a good time frame.

So the results were pretty good, they weren't perfect but pretty good. There was no evidence it was better than standard of care, but it's not intended to replace standard of care, it's intended to offer a treatment for organs that would otherwise not have been used.

And we talked about creep, but I'm not so worried about that. I mean, if we have a 2-hour -- I don't see the benefit of putting somebody on a device who's got diabetes, CAD, EF, just to put them on it. If the heart is otherwise within a time, you either pick the organ or you don't pick the organ. So I think the standard of care works well and most people are going to use that, if it's within the time frame that's acceptable, if they're going to accept the organ, so I'm not too worried about creep. But I do think whether it's an indication of four-plus only, I could support that, as well, but we'll leave that up to the FDA to decide.

DR. LANGE: So Dr. Moon, your vote was what?

DR. MOON: Oh. I went yes/yes/yes, banking on surgeons using it appropriately and using it for what I think it's intended and the benefit will be.

DR. LANGE: Great. Thank you, Dr. Moon. Appreciate it, Marc.

I saved Dr. Hirshfeld for last because he was the chair before and he knows how difficult it can be, so John.

DR. HIRSHFELD: Thank you, Rick. And a great job today, by the way.

So let me say, first of all, I voted yes for safety, no for efficacy, and no for approval and I'd just like to say I found this to be the most difficult vote in my experience on this

Panel. I was very concerned that the PROCEED data suggests a possible harm and in the absence of an interpretable comparator for the EXPAND trial, it's really not possible to decide whether or not there is efficacy. So once I felt that I could not vote yes on efficacy, I thought that precluded voting for approval.

I also feel that there are no data to support the proposed category B indication statement and if this device is approved, that portion of the indication should be removed and people should stick with the 4-hour cross-clamp time as the threshold.

I think I'd really like to believe that this device has some efficacy, but I think it's going to be necessary to demonstrate that conclusively because once it's approved and it's in general clinical use and once again, we won't have the opportunity to find out whether it's effective or not because everything will be anecdotal, so that's how I came down.

DR. LANGE: I did not vote, I'm a non-voting member, but I would've voted no/no/no. I don't have anything to add other than it was very thoughtful and considerate and sage comments that have been made. I've already expressed my appreciation to the FDA and to the Sponsor and to the Panel.

Bram, I'll turn it over to you, Dr. Zuckerman, for any last comments.

DR. ZUCKERMAN: Thank you. Certainly, on behalf of the FDA, I want to thank the Panel for an extremely thoughtful session today. I especially want to thank Dr. Lange for his leadership and guiding us through a very challenging submission.

DR. LANGE: Great. With that, we'll close this particular Panel. Again, thanks, everybody, for hanging in there. Appreciate it. Thank you very much.

(Whereupon, at 7:07 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

April 6, 2021

Via Microsoft Teams Videoconference

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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