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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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CIRCULATORY SYSTEM DEVICES PANEL

+ + +

July 21, 2011
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

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JASON T. CONNOR, Ph.D.	Temporary Voting Member
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ROBERT DUBBS, J.D., M.B.A.	Consumer Representative
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JOE BASTA and TIM BASTA
GIL WERNOVSKY, M.D.
HENRY WALTERS, M.D.
RICHARD SMITH

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MEETING

(8:00 a.m.)

DR. YANCY: My name is Clyde Yancy from Chicago, Illinois, and I'm delighted to call this meeting of the Circulatory Systems Device Panel to order.

The Designated Federal Officer for today's meeting will be James Paul Swink, who is sitting to my left.

This is an application brought forward by the Sponsor, Berlin Heart EXCOR Pediatric VAD, H100004.

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

For today's agenda, the Panel will discuss, make recommendations, and vote on information related to the HDE for Berlin Heart EXCOR Pediatric Ventricular Assist Device.

The EXCOR Pediatric is intended to provide mechanical circulatory support as a bridge to cardiac transplantation for pediatric patients. Pediatric candidates with severe isolated left ventricular or biventricular dysfunction who are candidates for cardiac transplant and require circulatory support may be treated using EXCOR Pediatric.

Before we begin, I would like to ask our distinguished Panel

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members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. I'll begin to my right with Dr. John Hirshfeld.

DR. HIRSHFELD: My name is John Hirshfeld. I'm an adult interventional cardiologist at the University of Pennsylvania.

DR. SOMBERG: My name is John Somberg. I'm a Professor of Medicine in Pharmacology at Rush in Chicago.

DR. BORER: I'm Jeffrey Borer. I'm a cardiologist and Professor and Chairman of the Department of Medicine and Chief of the Division of Cardiovascular Medicine at State University of New York Health Sciences Center in Brooklyn.

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

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

DR. NYKANEN: David Nykanen, interventional cardiologist and Chair of the IRB at Arnold Palmer Medical Center in Orlando.

DR. HOPKINS: Richard Hopkins, pediatric cardiac surgeon at Children's Mercy Hospital in Kansas City and Director of the Cardiac Surgical Research Laboratories.

DR. CONNOR: Jason Connor, biostatistician with Berry

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Consultants. Also an Assistant Professor at the University of Central Florida College of Medicine in Orlando.

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

MR. DUBBS: Bob Dubbs. There's a thousand things I could tell you about myself, but the most important is I'm retired, and I'm a Consumer Rep.

DR. POSNER: I'm Phil Posner, and I'm the Patient Rep, and I'm a retired cardiac electrophysiologist.

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

DR. AUGUSTINE: Erika Augustine, pediatric neurologist from the University of Rochester in Rochester, New York.

DR. MOON: I'm Marc Moon. I'm a cardiac surgeon at Washington University in St. Louis.

DR. AUSTIN: I'm Erle Austin, pediatric and congenital heart surgeon at the Kosair Children's Hospital in Louisville, Kentucky, Professor at the University of Louisville.

DR. FERGUSON: Mike Ferguson. I'm an interventional cardiologist at Military Medical Center in Bethesda.

DR. WHITE: Michael White, pediatric cardiologist, Ochsner

Clinic, New Orleans.

DR. PAGE: Richard Page. I'm a clinical cardiac electrophysiologist, and I'm Chair of the Department of Medicine at the University of Wisconsin in Madison.

DR. WEINBERGER: Judah Weinberger, interventional cardiologist in New York at Columbia and NYU.

DR. LANGE: Rick Lange. I'm the Vice Chairman of Medicine at the University of Texas, San Antonio, and a former interventional cardiologist.

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

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

DR. YANCY: And I serve as Chief of Cardiology at Northwestern University, Feinberg School of Medicine, in Chicago, Illinois.

If you've not already done so, please sign the attendance sheets that are at the tables by the doors.

I'd now like to turn the meeting over to James Swink, the Designated Federal Officer for the Circulatory Systems Device Panel, who will make some additional introductory remarks. Mr. Swink.

MR. SWINK: Good morning. I will now read the Conflict of Interest Statement and the Temporary Voting Members Statements.

The Food and Drug Administration is convening today's

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meeting of the Circulatory Systems Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

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

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

Related to the discussion of today's meeting, members and

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consultants of this Panel who are special Government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purpose 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 the information related to the humanitarian device exemption for the Berlin Heart EXCOR Pediatric Ventricular Assist Device sponsored by Berlin Heart, Incorporated. The Berlin Heart EXCOR Pediatric VAD Device is a pneumatically driven, extracorporeal ventricular assist device designed to provide bridge transplant mechanical support to the heart.

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 and Section 712 of the FD&C Act.

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

Mr. Burke T. Barrett is serving as the Industry Representative,

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acting on behalf of all related industry, and is employed by CardioFocus.

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

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

Dr. Philip Posner has been appointed as a temporary non-voting patient representative for the duration of this Circulatory Systems Devices Panel on July 21, 2011.

For the record, Dr. Posner serves as a consultant to the Peripheral and Central Nervous System Drugs Advisory Committee of the Center for Drug Evaluation and Research. This individual is a special Government employee who has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting.

This appointment was authorized by Jill Hartzler Warner, J.D., Acting Associate Commissioner for the Special Medical Programs on July 18, 2011.

I will now read the temporary voting status.

Pursuant to the authority granted under the Medical Devices

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Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27, 1990, and as amended August 18, 2006, I appoint the following individuals as voting members of the Circulatory Systems Devices Panel for the duration of this meeting on July 21, 2011: Dr. John Hirshfeld, Dr. Judah Weinberger, Dr. Jason Connor, Dr. Richard Lange, Dr. Michael Ferguson, Dr. Jeff Borer, Dr. Michael White, Dr. Norman Kato, Dr. David Nykanen, Dr. Richard Hopkins, Dr. Marc Moon, Dr. Erle Austin, Dr. Erika Augustine.

For the record, these individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting. This has been signed by Jeff Shuren, M.D., J.D., Director for Center of Devices and Radiological Health on July 8, 2011.

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

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

The press contact for today's meeting is Karen Riley, who is to the left of the room.

I would like to remind everyone that members of the public

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

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

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

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

DR. YANCY: Thank you, Mr. Swink.

I'd like to now ask Dr. Danica Marinac-Dabic, Director of the Division of Epidemiology, to provide a postmarket update.

Dr. Marinac-Dabic, you may now proceed with your FDA update presentation. Thank you.

DR. MARINAC-DABIC: Thank you. Good morning, ladies and gentlemen, Dr. Yancy, Dr. Zuckerman, distinguished members of the Panel.

My name is Danica Marinac-Dabic, and I serve as the Director of the Division of Epidemiology in the Office of Surveillance and Biometrics at CDRH.

This morning I would like to give you a brief update on the

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postapproval activities in our Center, and I'm speaking from the side of the division that is in charge of review and oversight of all mandated postapproval studies issued by the CDRH, and also in charge of the original epidemiologic research designed to advance the methodologies and build the national infrastructure which can be utilized to improve the regulatory science and public health responsibilities of CDRH.

As you know, FDA has legal authority to ask for the conduct of the postapproval study at the time of the approval, to continue evaluation and reporting on the safety and effectiveness and clinical reliability of the devices for their intended use.

The postapproval studies are a very important public health tool that we utilize to gather the information on longer-term performance, including effects of re-treatments and product changes. We're also looking for the routine practice, performance, and utilization of medical devices. Postapproval studies can help us address learning curve effects and effectiveness of training programs and also give us more information about the performance of medical devices in different subgroups that may not have been properly represented in the premarket clinical trials.

I also would like to acknowledge that these postapproval studies should be viewed in the broader context of other postmarket science activities done in our Center.

So as you can see, the huge body of these studies are

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represented on the last part of this slide. I can tell you that we currently have over 160 ongoing postapproval studies that we review and monitor and oversee.

In addition to that, we have close to 50 FDA-sponsored epidemiological such studies designed to advance the methods and build infrastructure for postmarket surveillance and epidemiology. And as an overarching umbrella, as many of you are familiar, there's a sentinel network again tasked to advance the methods for active surveillance.

Some of the recent developments in the postapproval study, some of you that have been part of this Panel during these last six years, you have probably witnessed a large amount of efforts and collaborative work between our premarket and postmarket offices at CDRH to establish an integrated CDRH postapproval studies program and to begin raising the scientific rigor of postapproval studies that requires the hypothesis, clear objectives for these studies, and the part of the premarket review by all epidemiologists in CDRH.

We also developed an electronic postapproval studies tracking system to track the progress of all postapproval studies. We issued the postapproval studies guidance and created the public website, and in 2007, we started updating advisory panels on the progress of these studies because you, the Panel members, play a crucial role in recommending these postapproval studies to be started at the time of the device approval.

We also started inspecting the postapproval studies by our BIMO Division in Office of Compliance, and during the last couple of years, an increased focus had been initiated to address the infrastructure building and methods development through collaboration with other stakeholders external to the FDA.

So if you go on the postapproval studies website, you will see that we expanded dramatically the amount of information that's available to the public on these studies. Now, we have for all the ongoing studies, study populations, sample size, study endpoints, and data collection and follow-up visits. For all the studies that are completed, we now also have the number of sites and actual patients, final results, study strengths and limitations, and recommended labeling changes listed. So the public can be aware of the findings of the postapproval studies.

And this is how the public website looks like. It's searchable and it's linked to our PMA database.

So let me just very briefly walk you through the overall postapproval studies update with a focus on cardiovascular devices.

This is how many studies we have asked for at the time of the approval since 2005, and what you see in blue is how many of original PMAs and Panel-track supplements have been approved, and what is in red, how many of those that were associated with the postapproval studies imposed at the time of the approval. So the number and the proportion had been

pretty stable throughout the last several years.

But when we ask for postapproval studies, we often ask for more than one PMA to address specific questions that the PMA review team had identified during the premarket review.

Not surprisingly, the vast majority of our studies are actually prospective cohort studies if we look at the design, but there's also, as you can see, a number of them that have randomized control trials. Some of them are active surveillance type of studies or enhanced surveillance or other study designs that are utilized.

As far as the data sources used in the studies, we have increasingly encouraged the Sponsors to look at the external registries. If there is a registry out there, and it could be possibly used to address postapproval study questions, we advise sponsors to look at the quality of the data, and if there are ways to utilize existing infrastructure, we are willing to work with the Sponsors to make sure that the proper methods are used or if there are certain things that needs to be enhanced to utilize specific registry. So currently five percent of our postapproval studies utilize external registry, only just a few. INTERMACS, for example, had been a great example of how postapproval study questions imposed by the FDA can be addressed by the registry.

We also use the outside of U.S. registries in the orthopedics world. For example, the data from Australian national registry and also

some data from the Kaiser Permanente registry in the United States, as a supplement to the ongoing postapproval studies for orthopedic devices.

Twenty-five percent of our studies utilize the Sponsor's registry infrastructure, and then seventy percent have other data sources such as original and new data collection.

If you're interested in how these postapproval studies are progressing, this slide is designed to show that. So out of 207 postapproval studies that the Center asked for since 2005, 82 percent of those studies are in compliance with the postapproval study requirements, being meant that they are being done on time, that their follow-up rate doesn't go below 80 percent, and at any point per protocol, not more than 10 percent of the endpoints that have to be followed up are not missing. Eighteen percent of the studies are out of compliance, and those are the ones that we're working very closely with the Sponsors to address.

When we are getting to those that have progress inadequate, these are the main reasons why they're inadequate. Seventeen of those have such subject enrollment issues and then others have follow-up rates that are lower, and then site enrollment also sometimes is an issue, and data are missing in some of them.

This is how many final postapproval studies had been posted on the web during the last two years, and this study also shows the labeling change requests based on the postapproval studies during the last several

years, since 2005.

So that actually means that these postapproval study results are really used to inform the clinicians and the patients about new knowledge gained in the postapproval setting.

So how are the postapproval studies in the cardiovascular arena compared to the ones that I just explained?

So these are the studies that had been asked in the Circulatory Devices arena since 2005, and this is how many studies individually we have requested at the time of the approval.

As you can compare, these cardiovascular studies are progressing much better than the general body of the postapproval studies. We have only 11 percent of the ones that are out of compliance, and nearly 90 percent are progressing well.

And, again, here are some of the issues. When you compare it with the general body of the postapproval studies, you'll see that with cardiovascular, the vast majority, there is a problem with the -- if we listed them as progress inadequate, the vast majority had a problem with the subject enrollments. Once the studies are up and running, then we don't have studies that have data endpoints missing and very small number of studies have follow-up rates that are below 80 percent.

And, again, these are the labeling changes requests, based on postapproval final results during the last six years.

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And I would like just to finish with giving you a brief overview of where the Center is going in terms of building the national infrastructure and trying to actually utilize the existing data much better in the regulatory decision-making and the public health responsibilities from CDRH.

So on these slides I have just briefly stated, I'm not going to go into details, the registry efforts sponsored by the FDA or where the FDA plays really a critical role, and you'll see some of them you'll recognize. They are from cardiovascular arena, where we are trying to use existing registries for postapproval studies to facilitate new registry development or to use existing registries for discretionary studies or for methodological development.

I will leave that as a reference to you. I certainly don't have time to explain all these projects, but they're all exciting and new innovative ways of how CDRH can be working better with other stakeholders.

And then as far as the methodologies, we have recently published the framework for evidence appraisal for medical devices, in the medical care in our corroborative work with Agency for Healthcare Research and Quality and academic sensors, and we are trying to explore the ways how the more innovative methods of data integration can be utilized in the device world by simultaneous application of meta-analyses, network meta-analyses, cross design synthesis, and really applying Bayesian methodologies more in the postmarket setting.

Again, a couple of reference articles that in this particular case focus on orthopedic devices, but we're also moving to our cardiovascular application as well, and certainly FDA cannot do that. We cannot do all these activities alone.

Our focus is increasingly on developing strategic partnerships with academia and other stakeholders. So you, the Panel members, are very important bridge between us and the academic world.

I wanted to let you all know that in 2010, we have launched the large Medical Device Epidemiology Network, or we call it MDEpiNet for short, Initiative, which is meant to actually formalize the relationship between the FDA and academic centers through a cooperative network of centers that have relevant clinical, statistical, and epidemiologic expertise, and this is our logo.

We already have confidential disclosure agreements with 16 universities, and we are working on putting together the final infrastructure for public/private partnership with universities and other stakeholders, and what we are trying to accomplish by this is really to systematically appraise all available evidence, build evidence-based regulatory science, and work much better with our stakeholders.

And this is my last slide. Just to give you a heads up about some interesting epidemiology, CDRH epidemiology and postmarket efforts that are blocked already for the next fiscal year. We have five public

meetings set up to talk about 522 studies and the EpiNet postapproval studies, registries for regulatory science conference, and also an interesting European-FDA corroboration in the area of surgical devices called IDEAL that started in Oxford and we are now trying to bridge that concept with the TPLC concept at CDRH.

So I thank you for your attention, and I would like to wish you a successful day. Thank you.

DR. YANCY: Thank you, Dr. Marinac-Dabic. We are on time, and we will move forward now with the Sponsor presentation.

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

The Sponsor will introduce the speakers. You have 60 minutes. I understand that Dr. Charles Fraser and Dr. Charles Canter will be presenting. The Sponsor, please.

MR. KROSLOWITZ: Good morning. My name is Bob Kroslowitz. I'm the Vice President of Clinical Affairs for Berlin Heart, Incorporated, the Sponsor of the HDE application that is the subject of today's FDA Advisory Panel meeting.

Before we begin, I'd like to thank the Advisory Panel members and the FDA reviewers for the time and effort expended in preparing for this meeting. I would also like to thank our presenters, advisors, investigators,

and my colleagues from Berlin Heart and their tremendous efforts and continued support in bringing this important technology before you today.

I would like to start by giving you a brief overview of Berlin Heart, introducing our presenters and advisors and then turning the podium over to them.

Our parent company, Berlin Heart GmbH, is focused on the development, production, and worldwide distribution of mechanical circulatory support devices. We are the only company worldwide with devices designed to provide circulatory support for patients of every age and size, from newborns to adults. The EXCOR Pediatric, which we will review in detail today, is the only Berlin Heart device that is available in the United States.

The first pediatric application of the EXCOR system which received CE mark approval in 1996 was more than 20 years ago in 1990. Worldwide acceptance of the device grew over the first decade, and use of the EXCOR Pediatric emerged as an alternative for children requiring mechanical circulatory support in the U.S. in 2000 when it was introduced under the compassionate use regulations.

With growing experience in the U.S. and continued request for the device by the medical community, Berlin Heart and the FDA recognized the need for a clinical trial, and in 2005, the approval process began. IDE approval for the study was granted in 2007, and the initial results were

submitted to the FDA in an HDE application in 2010.

The EXCOR Pediatric has now been reviewed by the FDA in the HDE application that is the subject of this Advisory Panel meeting. This HDE application, unlike PMA applications that address safety and efficacy, addresses safety and probable benefit in children at risk from death of heart failure despite medical management.

Two of our investigators, Dr. Charles Fraser, Surgeon-in-Chief and Chief of Pediatric Cardiac Surgery at Texas Children's Hospital, and Dr. Charles Canter, Medical Director of the Heart Failure and Transplant Program at St. Louis Children's Hospital, will present the majority of the clinical information that is included in our HDE application.

Neither Dr. Fraser nor Dr. Canter receives any compensation from Berlin Heart. Their institutions were reimbursed for the cost directly associated with the conduct of the EXCOR Pediatric study, and their travel expenses to this meeting will be reimbursed.

My colleagues, Mary Beth Kepler, Vice President of Regulatory and Quality Affairs, Christine Tjossem, Director of Statistical Operations, and I will be participating on behalf of the company and are all employed on a full-time capacity by Berlin Heart.

Additionally, we have a number of advisors that are expert pediatric subspecialists in the specific fields of pediatric medicine, including cardiac surgery, cardiology, heart failure, critical care, hematology and

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thrombosis, neurology and infectious disease present to support Berlin Heart as necessary at this meeting. None of these advisors received compensation from Berlin Heart for attending this meeting. Their institutions were reimbursed for costs directly associated with the conduct of the EXCOR Pediatric study, and their travel expenses to this meeting will be reimbursed.

Dr. Christopher Almond from Boston Children's Hospital is supported by a grant that is associated with this study. Drs. Ichord, Massicotte, Rosenthal, and Wearden are all members of the clinical events committee for this study. Dr. Naftel assisted Berlin Heart with the statistical plan and analysis for the EXCOR IDE study and is a paid consultant.

I would now like to ask Dr. Fraser to come forward and continue with our presentation.

DR. FRASER: Good morning. I'm Dr. Charles Fraser. I am the Surgeon-in-Chief at Texas Children's Hospital and also Director of Pediatric Cardiac Surgery. I'm also a Professor of Surgery in the Michael E. DeBakey Department of Surgery, Baylor College of Medicine.

I also would like to thank the Panel, the representatives of the FDA, my fellow investigators in the Berlin Heart Corporation for bringing this day to fruition. I know we all consider this an extreme step forward for children dying of heart failure.

As you probably also know, this is the first ever prospective

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pediatric ventricular assist device trial.

The EXCOR Pediatric Ventricular Assist Device is intended to provide mechanical circulatory support as a bridge to cardiac transplantation in children with heart failure. Pediatric candidates with severe isolated left ventricular or biventricular dysfunction who are candidates for cardiac transplant and require circulatory support may be treated using the EXCOR Pediatric device.

Children with refractory heart failure have a high risk of death. Once their illness progresses to the need of cardiac transplantation, they face a high wait list mortality rate of at least 20 percent and a median waiting time for a suitable cardiac donor of 119 days. Many children cannot wait that long.

Unfortunately, the opportunity for cardiac transplantation is severely limited by donor organ availability. As these OPTN data confirm, between 1988 and 2007, the number of heart transplants performed annually in children in the United States remained static with many children in need succumbing to heart failure before receiving a donor heart.

Interestingly, we believe there is an encouraging trend in numbers of transplants being performed since the EXCOR Pediatric device started being applied in North America in 2000.

Children with progressive heart failure currently have few options for mechanical circulatory support to provide a bridge to cardiac

transplantation. Extracorporeal membrane oxygenation or centrifugal ventricular assist device support are used off label and are of limited durability, requires cervical or open chest cannulation, and preclude rehabilitative measures including extubation, ambulation, and in most cases, enteral nutrition. Successful support with these devices beyond three weeks is rare.

FDA-approved adult VADs have limited utility in children and are not suitable for smaller patients.

The only FDA-approved pediatric-specific VAD has not been clinically adopted due to marginal outcomes. This device is also not suitable for smaller children.

This is a comparative list of device availability in adults and children. The historical paucity of suitable pediatric devices for children has been a source of tremendous clinical frustration for those of us who treat children with heart failure.

I apologize in advance for the graphic nature of this next slide, but this is the unfortunate reality we face when having to support a child with open chest ECMO or centrifugal VAD support. It is often a gruesome situation with clear limitations in support duration and no option for rehabilitation.

The EXCOR Pediatric VAD is a pneumatically driven, paracorporeal blood pump available in graded sizes from 10 to 60 milliliters.

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The pump contains three membranes which separate the blood and inner chambers. The blood surfaces are heparin-coated to discourage thrombogenesis. The clear nature of the polyurethane housing of the blood pathway facilitates visual inspection.

The device did not undergo any modifications during the course of this study.

The device is implanted for either univentricular support, typically left ventricular apex to ascending aorta or with the addition of right atrium to main pulmonary artery cannulation for biventricular support.

The wide selection of pumps and cannulas allows tailoring support to individual patient need. This is particularly advantageous given the wide range of body size in children with heart failure where truly one size does not fit all. The smallest pump with a 10 milliliter chamber is the only durable device suitable for chronic support of very small babies. The ease of visual inspection facilitates observation for pump deposits.

Supported patients are typically extubated and ambulatory, assuming they're old enough. Supported children are able to participate in rehabilitation making them potentially much better transplant candidates.

Blood pumps are selected based on the size of the patient. For biventricular support, a larger pump is always used in the left ventricular assist device position.

When necessary, pump exchange is quickly and easily

achieved. These exchanges are not considered device failure. The pumps are easy to prime and de-air. Pump changes are typically bedside procedures that don't require an escalation in therapy or other surgical intervention.

Cannulas are available in a wide selection of sizes, configurations, and diameter appropriate for the size of the patient, size of the pump, and the anatomical connection. The cannulas are coated with velour where they exit the skin to promote ingrowth of tissue and prevent ascending infection.

The Ikus driving unit is an electropneumatic system suitable for use with all of the various sizes of the EXCOR blood pumps. The system can be used for either univentricular or biventricular support and has backup, redundant systems incorporated.

The EXCOR Pediatric VAD was approved in Europe to apply the CE mark in 1996 and approved in Canada in 2009. In North America, there have been 301 implants since 2000. From 2000 until the commencement of the IDE trial in 2007, there were 97 implants in North America under compassionate use regulations.

The IDE study was conditionally approved in May of 2007 with full approval in October of 2008, for 48 patients in the primary cohorts. The data for the 48 patients undergoing EXCOR implantation and the primary cohorts are submitted for HDE approval.

Patients not meeting study entrance criteria were enrolled into a compassionate use arm. After the primary cohorts were completed, any patients meeting entrance criteria were enrolled under a continued access protocol.

The HDE application is focused on the primary cohorts, those patients that were enrolled under the study entrance criteria.

Data for implants under the continued access protocol and under a compassionate use regulation, at both IDE and non-IDE sites, were also included as supporting documentation.

Please note that HDE approval regulations call for probable benefit. However, the FDA asked statistical measures for the primary and secondary effectiveness endpoints in the IDE study.

The primary objective of the study was to demonstrate that the survival rate in subjects treated with the EXCOR Pediatric VAD was different from the survival rate in the historical control of subjects treated with ECMO as a bridge to cardiac transplantation.

Survival time is defined by the interval of timeframe from initiation of mechanical support to an endpoint, cardiac transplantation, death, or recovery where recovery is the longer of hospital discharge or 30 days after explant.

The primary safety objective of the study was to summarize the serious adverse event rate as a ratio, the total number of serious

adverse events experienced over the total time of device support.

A clinical events committee was established and consisted of a multidisciplinary team representing the following pediatric subspecialties: neurology, hematology, cardiology, and cardiac surgery. The members were responsible for adjudicating each patient's serious adverse event, all deaths, and any unacceptable neurologic outcomes.

A data safety monitoring board was convened and was composed of five members who were not directly involved in the conduct of the study. The data safety monitoring board evaluated the conduct of the study twice per year to ensure safety of the subjects enrolled.

The entrance criteria are included in the protocol in the clinical report which has been provided. These inclusion criteria are briefly summarized here. The criteria include children with refractory heart failure with two ventricle circulations. The children were listed for cardiac transplantation.

Listed here are some of the key exclusion criteria, which include children whose underlying disease would compromise the evaluation of the contribution of the EXCOR device to their management. There are many of those types of children enrolled in the compassionate use cohorts who were otherwise believed candidates for cardiac transplantation.

The study design included evaluations within 48 hours of implant, at implant, at 1, 2, 4, and 6 weeks, and then every 3 months until

transplant or recovery. A head CT scan was performed within 48 hours of implant along with baseline neurologic assessment. Neurologic assessment occurred one week, three months, and every three months while the child was on device.

Pediatric stroke outcomes measure, PSOM evaluations, were performed 30 and 60 days following a neurologic dysfunction adverse event.

At one year, post-explant, each patient had a comprehensive neurocognitive assessment. The protocol included guidelines for pump size selection, quality of life assessments, anticoagulation management, and weaning.

The data presented today are focused on the primary study cohorts labeled Cohort 1 and Cohort 2. Cohort 1 is comprised of the smaller children with body surface area up to .7 meters squared, which is typically children less than 4 years of age. Cohort 2 is comprised of larger children with body surface area greater than .7 meters squared but less than 1.5 meters squared.

As mentioned during the entrance criteria summary, sites were allowed to implant the device under compassionate use regulations during the course of the study. Data from these implants are summarized and labeled as Cohort 3 and are truly reflective of the clinical demand for the device.

The smaller patients are represented as Cohort 3A and the

larger patients as Cohort 3B. This is true for IDE and non-IDE site enrollment. Data from Cohort 3 is for safety information only. Approval is being requested based on data from the primary cohorts.

There were also 20 patients who were eligible for enrollment into the smaller patient cohort, Cohort 1, but since the enrollment maximum had been met, they were enrolled into a continued access protocol cohort. At the time of the submission, there were only smaller sized patients enrolled into the continued access protocol, but larger sized children may also be enrolled.

I would now like to turn the podium over to my colleague, Dr. Canter.

DR. CANTER: My name is Charles Canter. I'm the Medical Director of the Heart Failure and Transplant Program at St. Louis Children's Hospital, and a Professor of Pediatrics at Washington University School of Medicine.

During the initial phases of protocol development, in lieu of a randomized prospective trial, in collaboration with FDA and study investigators, the use of pediatric patients placed on ECMO from the ELSO database was determined to be the appropriate comparator as it was the only available multicenter dataset of patients placed on ECMO for cardiac support.

Therefore, the ELSO registry, which contains a registry of

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subjects treated with ECMO, was chosen to be the source of subjects used for the control group.

We do note that there are limitations to this dataset. The ELSO registry relies on voluntary reporting and unmonitored data collection. The serious adverse events were not clearly defined nor were the reported adverse events monitored or adjudicated.

Outcomes data in the ELSO database is incomplete, limited to mortality with limited discharge information. Data regarding heart transplantation was not collected.

The ELSO database was filtered to best match the EXCOR IDE study population, which involved limiting ELSO patients to age 0 to 16 years, with a weight greater than 3 kilogram, ECMO used for cardiac support only, ECMO patients from the current era, 2000 to 2007, in the absence of use of ECMO use for complex congenital heart diseases or trauma.

A propensity score analysis was performed to match EXCOR subjects to controls from the ELSO database to create the control group. The propensity score for each subject is the conditional probability of receiving an EXCOR rather than ECMO, given age, weight, diagnosis, ventilator status, inotrope use, and prior cardiac arrest. Each EXCOR subject was matched to two ELSO controls.

You can see here in this table the results of the match variables for the smaller size, Cohort 1. You can see from the p-values noted

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for age, weight, and diagnostic group, the age, weight, and diagnostic group variables were not significantly different from the EXCOR group to the matched ELSO group.

If you look at variables associated with support, proportionate of patients on inotropic support, mechanical ventilatory support, and prior cardiac arrest were also not different between the two groups.

The results are the same for the larger sized Cohort 2 subjects in terms of age, weight, and diagnostic groups.

In addition, as you can see here, it is also true that the control group for Cohort 2 was not significantly different in regards to proportion of patients on inotropes, mechanical ventilatory support, or who had a previous cardiac arrest.

In conclusion, the propensity matched ELSO control group as constructed is comparable on several measured critical clinical variables. It is possible that there are unmeasured clinical variables in variation and clinical site experience and care protocols within the ELSO control group. However, the experience and the propensity matched ELSO group represents a reasonable reference group to compare to the EXCOR study group.

I'll now let Dr. Fraser proceed with the results of the study.

DR. FRASER: Thank you. Again, I'm Charles Fraser from Houston.

The FDA approved 15 United States and 2 Canadian sites for

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participation in the study. These sites comprise a broad representation of leading centers involved in the care of children with heart failure and pediatric cardiac transplantation. This slide lists patient enrollment numbers by site. Twelve sites enrolled into the primary cohorts. The last patient in Cohort 1 was implanted in August 2009, and the last patient in Cohort 2 was implanted in August of 2010.

The primary objective of the study was to demonstrate that the survival rate in patients treated with the EXCOR Pediatric Ventricular Assist Device was different from the survival rate in the group of historical controls treated with ECMO as a bridge to cardiac transplantation. Survival estimates were assessed utilizing the Kaplan-Meier method, and significance was determined using the log-rank test.

For construction of the survival curves, the following definitions were used for deaths and censoring.

A death was defined as death while being supported on the EXCOR Ventricular Assist Device or on ECMO.

A weaned failure was defined as a patient who, after being weaned from the EXCOR device or ECMO, died within 30 days or before hospital discharge, whichever was longer.

For weaned EXCOR patients, failure was also defined as anyone suffering a devastating neurologic event within 30 days or before discharge, whichever was longer.

Please note that follow-up data on neurologic outcomes were not available for the ECMO patients after they came off ECMO.

Alive means that the patient is no longer at risk of death, in other words, was transplanted or was weaned.

This graph demonstrates Kaplan-Meier estimates of freedom from death or unacceptable neurologic outcome in Cohort 1 or the smaller patients implanted with the EXCOR device compared with ECMO propensity matched two for one. Clearly, there is a difference between the study group and the control group. No patient in the smaller control group survived on ECMO support beyond 30 days.

This competing outcomes analysis shows a more complete picture of the terminal endpoints. At each of the time points along the abscissa, the percentages add up to 100. This plot is for Cohort 1's ECMO control group. At 30 days, 29 percent of control patients were dead and none were still alive on ECMO.

In sharp contrast, this graph demonstrates the competing outcomes for Cohort 1 patients implanted with the EXCOR Ventricular Assist Device. At 174 days, 87.5 percent of the patients had been successfully transplanted and 12.5 percent of patients had died or failed weaning. Again, in contrast to the ECMO group, at 30 days, 96 percent of the EXCOR patient were either transplanted or alive on the device.

In a similar fashion, this series of graphs reveals the results for

Cohort 2 or the larger patients. These are the Kaplan-Meier survival curves for Cohort 2 and matched control group. Note again the striking differences in duration of successful support.

This graph demonstrates the competing outcomes analysis for Cohort 2 matched control group supported with ECMO. Note again that no patient in the control group for Cohort 2 survived on ECMO beyond 48 days. At that time point, 39.6 percent of patients had died.

In sharp contrast to the propensity matched control group, patients in Cohort 2 supported with the EXCOR device fared much better. At 192 days, 91.7 percent of patients had been successfully transplanted or weaned and 8.3 percent of patients had died. Again, in contrast to the ECMO group, at 30 days, 96 percent of the EXCOR patients were transplanted or alive on device.

Here are the outcomes for both cohorts and their matched ECMO control groups. The rates of supporting the children to transplant or successful weaning ranged from 88 to 92 percent in the primary cohorts but 60 to 71 percent in the matched ECMO control groups. The difference in success rates at 30 days for Cohort 1 versus ECMO was significant, as well as the difference in success rates for 30 days in Cohort 2.

One of the secondary effectiveness endpoints evaluated in the protocol was support or functional status at various time points. This series of bar graphs depicts the patient's status from pre-implant to one month

post-implant. In Cohort 1, most patients were intubated and sedated prior to the EXCOR implant but by one month were awake and ambulating if old enough and eating. Please keep in mind that the median age of this cohort is 12 months. So not all of these patients would be ambulating or eating per se, although it is reasonable to infer that these infants would be receiving enteral nutrition.

In similar fashion, this series of bar graphs depicts functional status in Cohort 2 patients. These data emphasize the fact that in comparison to the severe limitations of ECMO, patients supported with the EXCOR device are able to be ambulatory, participate in physical therapy, and to receive meaningful enteral nutrition.

As you can see from these pictures, patients on the EXCOR device are able to function more like normal children. They go outside and, in many cases, are very active. This, of course, could never occur in patients supported on ECMO.

I'll now turn the podium back over to Dr. Canter.

DR. CANTER: Again, I'm Charles Canter from St. Louis.

The primary safety endpoint in this study was the serious adverse events over time spent on device. The endpoint was to show that the rate of serious adverse events were not greater than a predetermined success criteria of 0.25 events per patient day. This rate was set after reviewing the available serious adverse events in the earlier 2000 to 2007

United States EXCOR experience in coordination with FDA.

All SAEs for the children treated at the 15 IDE study sites were adjudicated and classified according to relatedness. The null and alternative hypotheses were that the SAE rate with the EXCOR was greater than or equal or less than 0.25 events per patient day.

The definition of success was that the SAE rate in the EXCOR group was less than 0.25 events per patient day, where significance was defined as the upper confidence interval of the Poisson confidence interval.

For Cohort 1, there were 96 total serious adverse events yielding a rate of 0.068 events per patient day. The upper confidence bound of that estimate is 0.083. For Cohort 2, there were 107 serious adverse events yielding a rate of 0.078 with an upper confidence bound of 0.094. Thus, the SAE rate per day in Cohort 1 and 2 are significantly less than the prospectively set rate of 0.025 proving the alternative hypothesis.

During the course of the study and analysis phase, we have realized that the use of ECMO prior to the implantation of the EXCOR device resulted in increased rates of serious adverse events compared to patients not supported with ECMO. In Cohort 1, those supported with ECMO pre-implant had twice as many events per patient day of support. For Cohort 2, those supported with ECMO pre-implant had one and a half times as many events per patient day of support. Please note that 28 percent of the primary study patients were supported with ECMO prior to receiving the

EXCOR device.

These two tables will summarize the serious adverse events in Cohort 1 and Cohort 2. The total number of events are listed and the percentage of subjects who experienced at least one of the events. The most common serious adverse events observed were major bleeding, which occurred in 40 to 50 percent in Cohort 1 and Cohort 2, hypertension, infection localized non-device, and neurologic dysfunction which occurred in approximately 29 percent in both Cohort 1 and Cohort 2. We will go into detail in some of the individual serious adverse events in a minute.

Of note, the next table shows other serious adverse events that occurred at lesser frequencies. Of note on this table is that the incidence of device malfunction was zero in both cohorts.

Anticoagulation therapy was an important part of the study. The protocol that the IDE sites followed contained separate anticoagulation guidance incorporating the following agents: unfractionated heparin, low molecular weight heparin, or warfarin and the antiplatelet medications dipyridamole and aspirin. Prothrombin times, INRs, partial thromboplastin times, and anti-factor Xa measurements were used to determine how well the anticoagulation was working. Thromboelastogram and platelet mapping were also used for additional information.

Centers were adherent to recommended anticoagulation guidelines as indicated by a means of the primary laboratory tests used to

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monitor anticoagulation. In looking at the neurological and bleeding events, as well as the values of pump changes, there was no difference in the intensity of the anticoagulation results at those time points.

In discussing bleeding adverse events, 22 of the primary cohort patients experienced at least one major bleeding event, and the rate was almost double when the child was on ECMO prior to the EXCOR implant. There were 37 bleeding events in the 22 patients at a median time of 4 1/2 days after implantation. Only 9 of the 37 bleeding events resulted in a reoperation, and there were no deaths related to a bleeding event.

In regards to infection adverse events, major infection occurred in 56 percent of the patients. Localized non-device infections occurred in 46 percent of patients. Site or pocket infection occurred in eight percent of patients. Sepsis occurred in 23 percent of patients. Infections were reported each time an antibiotic was started to treat an infection.

Infection SAEs appear to be related to issues of medical management of the critically ill child and associated with instrumentation violating host defenses rather than to implantation or use of the device.

No deaths were attributable to infection, and at no time patients were considered inactive for transplant due to infection.

Only one of the reported infectious SAEs could be attributed to use of the device, a drive line exit site irritation that resulted in breakdown of skin, colonization, and then infection with pseudomonas.

Neurologic events occurred in approximately 30 percent of Cohort 1 and Cohort 2. We will spend the next few slides discussing them in detail.

The PSOM was used to monitor neurologic status at pre-implantation and while on device. It is the standard clinical assessment for overt neurologic symptoms by neurology consultants per local institutional standards. Assessments occurred at one week, one month, three months, and every three months thereafter while on the device. PSOM scores prior to six months post-explant are likely not an accurate reflection of the true long-term outcome. Many factors, besides stroke or device exposure, would affect that outcome.

The clinical events committee reviewed clinical records and CT scan findings and classified each neurologic event and assigned relationships to device. The ECMO control group cohort lacked similar systematic neurological evaluation, but neurologic events were recorded in patients in the ELSO registry while they were on the ECMO device.

The PSOM was used in this trial as an exam recording tool and rating method to classify the findings of a typical standard, complete neurologic examination performed by a child neurologist. The final summary score ranges from 0, which is normal, to 10, abnormal.

We have stratified the final PSOM post-neuro events in the following categories: normal, a score of 0; mild, a score of .5 or 1.0;

moderate, a score of 1.5 or 2; and severe, a score of 2.5 or greater.

Stratification of PSOM score has not been studied. The stratification used in this analysis is based on consensus of child neurologists active in pediatric stroke research.

These next tables will go over the details of the seven patients in Cohort 1 and Cohort 2 who experienced a neurologic event. One patient experienced two ischemic events. Of the seven patients, one was withdrawn from support as a result of the neurologic injury. Of the remaining six patients, PSOM, pediatric stroke outcomes measure exams were performed post-explant. For the patients, one had no deficits 17 days post-explant. Two had mild deficits 23 and 221 days post-explant respectively. One had a moderate deficit 82 days post-explant, and two had severe deficits with PSOM scores of 3, 34 days post-explant, and a score of 4, 54 days post-explant.

This table demonstrates the PSOM at time of event, the highest score reported, and the latest score available for each patient. The Panel members should notice the columns on the table. It is notable in these columns where it shows these PSOM scores, how the overall PSOM scores improved over time in the patients reflecting the neurologic plasticity often observed in children after strokes. Also notable is that even children with mild deficits, as illustrated in the patient on the third row of the table, could ride horses and the patient with a severe deficit was doing well with

no focal defect 630 days after explant.

In regards to the seven Cohort 2 patients who experienced a neurologic event, two of those patients experienced both an ischemic and hemorrhagic event. Of the seven patients, one was withdrawn from support as a result of the neurological injury. Of the remaining six patients, PSOM exams were performed post-explant, and one had no deficit 50 days post-explant, two had mild deficits at 27 and 49 days post-explant, one had a moderate deficit 357 days post-explant, and two had severe deficits with PSOM scores 10 at 29 and 38 days post-explant. Many of these patients also exhibited progressive improvement in PSOM scores over time. Note then that even patients with mild deficits, notable the patient in the third row, had an average score on IQ testing and another one, the fourth one on the table with a moderate deficit attended school full time.

To summarize the previous two slides, the following table was constructed. The 14 patients who had a neurologic dysfunction event had the following outcomes at last follow-up which occurred at a median of 43 days post-explant. In Cohort 1, one patient was normal with no deficit, three had mild to moderate deficits, two had severe deficits, and one child had support withdrawn due to the insult. In Cohort 2, one patient was normal with no deficit, three had mild to moderate deficits, two had severe deficits, and one child had support withdrawn due to the insult. Therefore, the proportion of patients with severe neurologic dysfunction was 12.5

percent in Cohorts 1 and 2.

A summary of the rates of neurological serious adverse events over time on support shows that the primary cohorts had a 0.006 and 0.005 neurologic event per patient day. The recorded neurologic event rates in the match ECMO cohorts from ELSO registry data had more than double the neurologic event rate over the time on support of ECMO.

Concern was raised regarding the interaction between neurologic events and pump changes. In regards to pump changes, 25 of 48 patients had pump changes. Ten of those twenty-five patients had greater than or equal to two pump changes. There were 46 total pump changes. Forty-three of those were done for suspected thrombus. Thirty-eight were in LVADs, two were in RVADs, and six BVADs were replaced. The mean time to first replacement was 24.9 days.

Fourteen subjects in Cohorts 1 and 2 had neurologic events. Eight of these 14 had 17 pump changes with four patients having greater than one pump change. Eight pump changes occurred in five patients before the neurologic event. Eleven pump changes occurred in five patients following a neurologic event. In the primary cohorts, there was no association between pump changes and neurologic events. This was screened using both univariate and multivariate models.

Another secondary efficacy objective of the study was to determine the days of transplant eligible support. Transplant eligible means

the patient is actively listed for heart transplantation. Even though this is an efficacy endpoint, it is related to safety in that it shows that the subject will not be delisted even if experiencing adverse events. Only one patient in Cohort 2 was removed from the transplant list at some point during their support. That patient was first listed on the third day of support and then was delisted for 38 days due to a neurologic event. The patient was eventually relisted and transplanted successfully.

To address the HDE bar of probable benefit, we can see from this slide that 43 of the 48 patients supported by the EXCOR device were adequately supported to transplant or weaned successfully from the device. In conclusion, we contend that there's a benefit of this device to support sick children awaiting heart transplantation. The rate of serious adverse events seen in the trial was less than a third of the criteria set at the beginning of the trial to deem the therapy successful.

This table adds in the supportive groups from the compassionate use and the CAP cohorts for comparison to the ECMO control group. The overall success rate for the study groups is more than 80 percent, and the SAE rate is still well below the performance criteria. The success rate for the control groups is 65.6 percent, much lower than the success rate in the study group, and with an SAE rate well above that of the performance criteria in the study group.

The results in the compassionate use groups 3A and 3B, while

poorer than the study groups meeting inclusion criteria, compare favorably in terms of success and adverse event rate with the ECMO control group that excluded comparable patients to the 3A and 3B groups from the ELSO registry.

A summary of the neurologic events shows that even though 29 percent of the EXCOR children had a stroke, when looking at the time of support on the device, they had less than half the per day rate of neurologic events in the ECMO control groups because of the longer duration of support attained with the EXCOR.

A recent article published in *Circulation* last month also supports these high ECMO neurologic incident rates in children listed for transplantation while on ECMO.

Moreover, it is likely that the poor neurologic outcomes of the ECMO control group are underrepresented due to limitations of the ELSO database described earlier.

In summary, the trial showed that the primary efficacy measure of survival for patients treated with the EXCOR device was superior to the survival rate on ECMO from the propensity matched ELSO control group. Thus, the effectiveness objective has been met.

The trial also showed the serious adverse event rate per patient day of support for patients supported on the EXCOR was significantly less than the predetermined threshold of 0.25 events per patient day of

support. Thus, the safety objective has also been met.

We contend that we have proven probable benefit over the alternative ECMO support and that the safety profile is not unexpected given the medical issues the children face. Thus, we believe the safety and probable benefit stated as the requirements of the HDE application have been met.

As a pediatric heart failure and transplant physician, the trial results reassure me that the EXCOR provides a greater degree of efficacy and safety than ECMO support.

This map represents the pediatric heart centers where the EXCOR has been implanted. These stars represent virtually every pediatric heart transplant center in North America where they have already adopted this therapy in their management of children with end-stage heart failure awaiting heart transplantation. Considering this widespread use of the EXCOR via compassionate use regulations before and after this trial, it would be expected postapproval use to mirror preapproval use mitigating the need for a postmarketing study.

However, the Sponsor of the trial remains open to continued discussion in this area. Thank you for your attention.

DR. YANCY: Thank you. I would like to thank the Sponsor's representatives for their presentation.

We have a reasonable amount of time to proceed forward

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with clarifying questions to the Sponsor. I would instruct the Panel that we will have an opportunity yet again later in the day to raise questions to the Sponsor. So the focus of this round of questions should be for clarification of the data that have been presented.

Again, I'd like to thank the Sponsor as we are slightly ahead of schedule.

Let's begin with questions from the Panel. Yes, Jeffrey Borer.

DR. BORER: Thank you, Clyde. First of all, I have to say I'm very impressed with the design of this extraordinarily difficult study that the Sponsor and the FDA created. I don't know how you could have approached the problem in a more effective way.

I have two questions about which I'd like some clarification. The performance measure against which you compared SAEs was .25 SAEs per patient per day, and it was based as you said on U.S. experience. I'd like a little bit more detail about what experience and how that number was reached because all the groups did so much better than that. I'm wondering where it came from. So if I could have some detail about that, I'd appreciate it.

Number two, you've been performing this trial for several years. The follow-up we saw was actually much shorter than that, and I'd like to know, you may not have the data and the protocol may not have called for it, and that's okay, but I'd like to know if you have data about the

neurological status of these patients who came to transplant, post-transplant. Many of them had neurological events. They had a transplant. You mentioned that there's plasticity in the neurological system of kids, and I'd like to know if you know how they're doing later than the transplant.

So those two questions.

DR. CANTER: Okay. To answer your first question, one of the side effects of this trial --

DR. YANCY: I apologize. Just --

DR. CANTER: Sorry. I'm Charles Canter, St. Louis, Missouri. Sorry.

One of the side effects of this trial which had not been done before this trial was actually to quantify the serious adverse event rates on ECMO because it's a registry that had never been done before but was done as a result to compare SAE rates for children on ECMO compared to the EXCOR.

So when the trial was designed, back in 2005-2006, the EXCOR had just arrived in the United States and pediatric institutions were just beginning to get experience with it, and so that experience as it was evolving, over that period of time, was a review between the FDA and the representative, Berlin Heart. I think that in many ways, you know, not surprisingly reflects an initial experience, but that's when the rate was devised. That was what was going on at that time. FDA and the company

looked at it, and from that they said, here's what we're seeing. From this experience that we have now, we're going to design this threshold.

Now, obviously it's a lot better now and the trial then was then that likely it reflects learning curve and experience, but despite that, too, the fact that we're actually within this analysis to quantify the events, adverse event rates on ECMO, that's a very accurate reflection of what our patients experience when they're on ECMO, and it's a high even rate, and the EXCOR compares very favorably.

In regards to your second question, the last patient that was put in Cohort 2, the last patient in the trial, was transplanted in my institution in October of 2010. As you know, there are many things in a heart transplant patient the first year after transplant that can really affect quality of life and even neurologic events. There are many neurologic complications that can be associated with heart transplantation alone.

So at this point, there's really -- the trial in terms of one year post-transplant was really the time to evaluate those results is still ongoing, and we plan, of course, a major area of concern for those of us who use this therapy, and in transplantation, to do those assessments, they will come.

DR. YANCY: Dr. Somberg.

DR. SOMBERG: I too am very impressed with the quality of the design of the trial and its results.

I did notice from your presentation that there were, especially

in Cohort 1, a sizable number of patients who, because the cohorts failed essentially, were followed outside the trial. Is there any differences for both Cohort 1 and 2 with subsequent data that's been obtained, or has it been consistent throughout?

DR. CANTER: The CAP group, yes, the CAP group results are identical. There are some trends that are actually better than the initial Cohort 1 group.

If we could throw up the slide of the CAP results. I think if you can go back to the conclusion slides. There. No. If you look there, the CAP -- okay.

You can see there that actually if you look at the CAP patients, the extra 20 patients in the small size cohort, the one that continued the study, the overall success rate in those patients was 94.1 percent compared to 87.5 percent in the original small patient group, and that the SAE rate event per day actually decreased in the CAP patients. Again, I think that may just be due to chance. It also may reflect increasing experience in how we handle small patients on the device.

DR. ZUCKERMAN: Dr. Somberg, could I ask you to ask that question again after you hear the subsequent FDA Panel presentation which will include all the patient data. It's approximately 200 patients, and it is a point of concern.

DR. YANCY: Dr. Slotwiner.

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DR. SLOTWINER: I was just wondering if you could elaborate on the bleeding and infection complications a little bit, especially the infections. Did those require surgical intervention?

DR. CANTER: We're going to ask Dr. Cox, our infectious disease expert, to take the podium and address that question.

DR. COX: I am Elaine Cox from Riley Hospital for Children at Indiana University School of Medicine. I'm a pediatric infectious disease attending there.

We looked at every infection that was reported. The INTERMACS definitions, which are typically more liberal definitions for infection, were used in this study, and basically none of the infections seemed to be related to use of device except for one in the primary cohort. So that one was related to mechanical abrasion and superinfection of the cannula site.

Can we have the slide on the compassionate use?

So we adjudicated every event and then went through and reviewed the medical records. When we look at, like I say, Cohort 1 and 2, there were 59 infections in 27 patients, but only one was related to one cannula even though there were more than 130 cannulas employed in these patients.

Next slide, please.

If we look into the extended study groups of the

compassionate use and the continued access, we saw three infections there, two that mirrored the experience we had in the primary cohort with cannulation issues. So there were two cannulas that had some abrasion and then superinfection with pseudomonas in one and MRSA in the other, and there were about 170 cannulas employed in this group, but only two had issues.

The last infection that was considered and adjudicated for relation to device was a serratia blood infection that occurred within 72 hours of device placement, but that patient had been on ECMO for more than 30 days and ventilated prior to this procedure, which likely contributed.

None of these particular patients where we felt it was due to drive line had any reoperation or pump exchange due to that. There was one patient who had a pump exchange who had fungemia and the fear of seeding resulted in a pump change, but otherwise, there were no infections that required any surgical intervention.

DR. SLOTWINER: Thank you.

DR. YANCY: Dr. Lange.

DR. LANGE: Again, thanks for the presentation.

Just some things that would help me understand some of the points you made. For the patients who were on ECMO prior to the EXCOR implant, can you tell us what the timing of that? Were they transferred immediately from ECMO to EXCOR?

Second is, can you tell us a little bit about the anticoagulation protocol? Was it protocolized across all sites with respect to the type and also how it was monitored? I say that it's partly surprising that none of the neurologic events, either ischemic or hemorrhagic, were related to the intensity of anticoagulation. So I'll ask you to expand upon that.

And then, finally, the definition for transplant-eligible days. Was that a uniform definition? And what excluded people? For example, I'm somewhat surprised that children with active infections would be considered for transplant, and since infection was obviously one of the major SAEs, so if you'll expand upon that please as well.

DR. CANTER: In regards to your first question, one of the exclusion criteria was if patients were on ECMO for more than 10 days of support, so that to be eligible for Cohort 1 or 2, you could not have been on ECMO for more than 10 days. Some of the patients in the compassionate use group were patients who were on ECMO for greater than 10 days.

DR. LANGE: I'm sorry. In other words, were these people that were on ECMO and weaned off of it and later put on EXCOR or people that were transferred?

DR. CANTER: No. Patients who were transitioned from ECMO --

DR. LANGE: Right.

DR. CANTER: -- to the EXCOR.

DR. LANGE: Okay.

DR. CANTER: Okay. In regards to the definition of transplant eligible, it is what it is. Those people remained on the transplant list.

In transplantation of children, the decision to transplant somebody with an infection is often a day-by-day and hour-by-hour decision in terms of -- because of donor availability. So there are at times some children who are transplanted who've had a history of an infection.

For example, someone who may have had a sepsis event, say from a line infection, and they're on antibiotics, and they're in the midst of the event but it seems under control, if a donor heart is available, we know from experience it may never come again. So sometimes we will proceed with the transplantation, but again that's very, very, you know, patient-specific, doctor-specific, center-specific types of decisions. They're all incorporated in this trial and weren't standardized for the purposes of the study.

In regards to your question on anticoagulation, I'd like to ask Dr. Massicotte to step up to the podium and address that.

DR. MASSICOTTE: Good morning. My name is Patty Massicotte. I'm from the University of Alberta in Edmonton, Canada.

I was involved with facilitating the creation of the anticoagulation guidelines, and I do use the word guidelines. It is what we recommended. However, these patients were so complex that these were

guidelines only, and the individual treating centers had the opportunity to manage the patients as they best saw fit depending upon how ill the patient was and what their hemostatic condition was.

What I show you is what we actually developed for the anticoagulation protocol, and basically depending upon the day, the postoperative implantation day, and you can see that on the left-hand side of the slide, we varied and proceeded with our anticoagulation protocol in that on postop day 0 to 1, we really allowed for normal hemostasis to occur and no anticoagulation was recommended.

If the patient developed bleeding, the algorithm basically, depending on the amount of bleeding, we were to do basic hemostatic testing. If these results were normal, we would rule out surgical bleeding. If they were abnormal, blood products may be required to correct the hemostatic abnormality based on the results of those tests, and once the bleeding had resolved, we would then begin, and the platelet count was greater than 20,000, and we had thromboelastogram parameters which were also part of the equation, then unfractionated heparin began, usually about day 1 to 2 with no bolus and using a target anti-Xa level as our therapeutic anticoagulation goal.

If there was no bleeding, platelets greater than 40,000, and again meeting thromboelastogram parameters, we would add in the antiplatelet agent usually greater than day 2 or 48 hours, dipyridamole.

When the chest tube was removed and thromboelastogram parameters were again met, then we would add in the antiplatelet agent aspirin, and in children who were more than two days, who were stable clinically, we would transition them from unfractionated heparin, which as you know is administered intravenously if the patient was hemodynamically stable, and in children less than 12 months of age, we would actually proceed to the use of low molecular weight heparin with a target anti-factor Xa range, and the reason for using low molecular weight heparin in that group, as opposed to the agent warfarin which we used for long term in children greater than 12 months of age, is that warfarin, as you know, is a very narrow therapeutic index drug, and it presents a lot of challenges.

In the neonate, these children were on varying amounts of feeds which would really sort of challenge and really focus in on what a narrow therapeutic index drug warfarin was. It was extremely -- it should be challenging to maintain our target range, INR of 2.7 to 3.5.

We used primary and secondary monitoring tests with this anticoagulation protocol. Primary monitoring tests were INR if the child was on warfarin, PTT and/or anti-factor Xa level if the child was on unfractionated heparin or low molecular weight heparin, and then we used a thromboelastography with platelet mapping which is a way of actually looking at platelet function when the child was on an antiplatelet agent, as a secondary measure to give us more information about the hemostatic

system within the child that was being anticoagulated.

Can I have the next slide please, Mary Beth?

And this just shows basically again the agents used, the target ranges, and the primary and secondary measures of anticoagulation.

Can I have the next slide, please?

So as I said, these were merely guidelines which were recommended, but if we look at the adherence to the anticoagulation protocol, as reflected by the measure of how anticoagulated the patients were and our target ranges which were recommended in the guidelines, what we see is that across the patient groups, as we see on this slide, on the left-hand side of the slide, we see the group. So we see all IDE patients here which total 109 and, Mary Beth, can I have the next slide? Sorry. We'll look at the IDE patients.

Okay. So with the IDE patients which represents, of course, Cohort 1 and 2, as well as the compassionate release at the IDE centers and the CAP patients, and we see the actual measuring of hemostatic parameters of the child across the top of this slide that were used depending upon which agent the child was on, we see that with our ranges that we recommended, so unfractionated heparin of .35 to .5 units per ml, low molecular weight heparin .6 to 1 unit per ml, warfarin INR 2.7 to 3.5, percent platelet inhibition with the patient on aspirin using arachidonic acid of 70 to 95 percent, the PTT if it was used in the center of unfractionated heparin of

60 to 85, and then we have our thromboelastography parameters.

If you look within the IDE patients, we see that the mean of the complete study period, for example, of the anti-factor Xa on unfractionated heparin falls within the range that we accepted, and that occurs across all the other tests that I have mentioned depending upon which agent that the patient was receiving, and you can see that if you follow across, and that actually follows for Cohort 1 and 2 as well, that these means all are within the recommended range of guidelines.

DR. YANCY: Thank you. Dr. Page.

DR. PAGE: Thank you. I have two questions. First a follow-up in terms of the anticoagulation and antiplatelet monitoring and therapy. I'm impressed by the sophistication of the monitoring that was just shown to us. At the same time, there was inspection of the pump and lines for evidence of I guess visible clot, and can you explain what sort of protocol was undertaken to examine for this? It seems like a fairly gross examination, and is there a better or was there a protocolized examination of the lines and pump, and is there a better way somewhere between the lab exam and some sort of examination of the system, filtering or whatever, to see if a clot has been developed?

DR. CANTER: We'd like to bring Dr. Tweddel up to the podium to address that question.

DR. TWEDDEL: All right. Thank you. I'm Jim Tweddel from the

Medical College of Wisconsin, the Children's Hospital of Wisconsin.

The pumps are transparent, and they're inspected. Therefore, they're easy to inspect, and they were evaluated. Multiple people involved in the study were trained in evaluating the pumps, from nursing and staff, ICU staff and surgeons, and they were evaluated multiple times during the day by visual inspection.

When the pumps were changed, they were sent for pathologic examination.

If I could have slide number 10. The previous one.

So this is the photograph of the pump, and the location of the identified thrombus are shown. They were mostly in the areas of the valves, inflow and outflow valves. Fifty-three pumps from Cohort 1 and 61 pumps from Cohort 2 were examined, and the vast majority were not found to have significant thrombus accumulation.

DR. PAGE: Okay. So if I'm interpreting this correctly, the tubing typically did not have significant thrombus, but it was seen there at the inflow and outflow of the actual pump.

DR. TWEDDEL: Correct. Correct, and the valves for the device. There's a valve in this area, and there's one here. This is where the thrombi would be identified.

DR. PAGE: I see. And there were frequent examinations, but there was not a protocol, an hourly, four times a day. Who was held

responsible for examining that, or are you satisfied that enough examination was being performed despite the fact there was no schedule or protocol for examination?

MR. KROSLOWITZ: So the sites were -- Bob Kroslowitz from Berlin Heart. The sites were trained to examine the pumps at least every four hours. There was a flow sheet that was provided for them to document, explained exactly how to examine the pump and then to document if anything was seen on the pump in a uniform manner. All of the sites, essentially it was the responsibility of the bedside nurses who were trained exactly the same.

DR. PAGE: Great. Thank you. And one other question I had regarding the effectiveness as defined in the trial that included both transplant and weaning from the pump as I understand. In the slides that were shown to us, for example, the sixth slide after Dr. Fraser's title slide in his second presentation, looking at the effectiveness, it's called effectiveness endpoint and shows transplant at 87.5 percent, but underneath that it says transplant, 87.5 percent. Were all of those transplanted or were any of these individual children weaned without requiring transplant?

DR. FRASER: I believe you're asking about -- this is Chuck Fraser, Charles Fraser. I believe you're asking about Cohort 2. There was one patient weaned.

DR. PAGE: Actually just among all of them, Cohort 1 is shown

and then Cohort 2 is shown, and they both in terms of those graphs show -- they're just labeled as transplant, and I was just wondering. You partially answered my question. The majority of these individuals go onto transplant. There was this one patient who was weaned out of both Cohort 1 and Cohort 2.

DR. FRASER: In the primary cohorts.

DR. PAGE: So effectiveness basically translates to transplant?

DR. FRASER: Yes.

DR. PAGE: Great. Thank you.

DR. YANCY: We have approximately 12 minutes. I'd like to get as many remaining questions in. So let's have some brief questions and crisp answers. Dr. White, please.

DR. WHITE: Michael White, New Orleans. Actually if you'll bear with me, I have I think a very important question to ask.

Dr. Fraser, you made the point that the smallest patients are the ones that may gain the most benefit from this, and in looking at Cohort 1, most of the patients in Cohort 1, or the larger group, received the larger device. It looks as if only nine of the patients received the smaller device, the 10 ml pump, and one of those expired right away. So we had 8 patients with that 10 ml pump.

And the purpose in asking this question is that in the package insert under -- there's a warning, that under certain circumstances, the

message, and I quote, "left-right pump is not filling adequately," in some circumstances is not generated with the 10 ml EXCOR blood pump due to the low volume of air which is moved in the pump. Therefore, in pumps of this size, pay special attention to the movement of the membrane and ensure that each pump fills and empties completely.

My purpose in asking this question goes back to the idea of are we taking care of the coagulation problems adequately? And if you look at the PSOM scores -- and the FDA uses a different definition; they define greater than or equal to 1 is a poor outcome. I think you used greater than 1. If you look at those eight patients, one, two, three, four of the eight patients had PSOM scores greater than 1 at the last look and a fifth patient says unable when you look at the patient information sheets.

So is there a difference in the 10 ml pump that we ought to be paying attention to separate from considering in a group as Cohort 1 with the larger devices being implanted in the majority of those patients?

DR. CANTER: Could you -- can we pull up this slide?

Here this slide shows the efficacy and SAE rates stratified by pump size, and so you can see here in regards to your question specifically about the 10 ml pump. Patients with the 87, 7 of 8 patients placed on the 10 ml pump were transplanted or recovered, and the SAE rate was 0.066 events per patient day. And you can see overall the general trend, that there was a large degree of comparability at the younger patient size in

terms of efficacy and rates per patient day of serious adverse events.

DR. WHITE: Does this problem with the warning device have any bearing on the safety and efficacy of the device and the 10 ml pumps?

DR. CANTER: No.

DR. YANCY: Dr. Austin.

DR. AUSTIN: Two quick questions. Was surgical re-exploration required for any of the patients for bleeding?

DR. FRASER: We'd like Dr. Jaquiss to step to the podium and address that issue.

DR. JAQUISS: Robert Jaquiss from Duke University. Nine patients required re-exploration for bleeding. None of them required significant manipulation of device, generally for just excessive chest tube output in the first few days after surgery.

DR. AUSTIN: Thank you. The second question is help me with some confusion about the Kaplan-Meier in competing outcomes. If you could put up the first two slides with Cohort 1. The first one is the Kaplan-Meier, which I think is impressive to all of us, is the comparison of the two groups. But my confusion is related to looking at this where it looks like all the ECMO controls have died at 30 days, and if you go to the competing outcomes, which is the next slide, it shows that -- go back -- it shows that at 30 days death occurred in only 29 percent. So help me with that.

DR. FRASER: We'd like Dr. Naftel to address that issue.

DR. NAFTTEL: My name is David Naftel. I'm the statistician that helped with a bit of this. I'm at the University of Alabama.

So back up to the Kaplan-Meier curve, please.

So I'm glad you asked this question, and I know that we'll be discussing this a lot. This curve is the classic Kaplan-Meier depiction. You can think of it as survival while on the device, whether it's the ECMO device or the EXCOR device, and so what it tells you is if patients remained ECMO, that indeed the best estimate is what you see, that the survival really crashes. However, if a patient is transplanted, they're then censored at that point. So they no longer contribute to that. So it really is survival while on the device, and that leaves you a little bit asking for more information because you need to know what's really going on.

So if you go to the next figure. So that's the competing outcomes, which has become the standard way to present VAD data. So that gives you a better representation because it gives you the estimate, in this case with ECMO, it's the percent that went off ECMO. So they either recovered or were transplanted, and we actually don't know which from the ECMO registry, but it does tell you that by about 30 days, around 30 percent of the patients have truly died, and then around 70 percent have been explanted due to either recovery or transplant. Does that help some?

DR. AUSTIN: Thank you.

DR. YANCY: Dr. Augustine.

DR. AUGUSTINE: The first question is to ask you to clarify the column heading in the trial results, Cohort 1 neurologic status or Cohort 2, slide 63 or 62, I believe.

And then the second question is about how the timing of the neurologic events was determined. I'm specifically thinking about the subjects who had ECMO leading to implantation. For these children who would have been intubated and sedated and may not have had neurologic deficits evident until lightening of sedation, how was the timing of the event determined?

DR. FRASER: We'd like to ask Dr. Ichord to address that question.

DR. ICHORD: Rebecca Ichord, child neurologist, head of the Stroke Program at Children's Hospital in Philadelphia.

As part of the adjudication process, the adjudication committee members had access to results and, in fact, primary imaging, actual imaging of patients as part of the data that was submitted. We had access to all of the charts and progress notes, and so in the course of determining timing and potential relatedness, we tried to judge the age of an event, or the age of an infarct on a CT scan, since the protocol called for every patient to get a CT scan within 48 hours preferably before VAD placement, but also if not possible before, then very quickly after VAD placement. That would give us a mechanism for timing subsequent events if

they might occur.

So even though the neurologic exam would often be confounded particularly in the ECMO group by sedation and the like, we ultimately were able to rely on the timing of events relative to the findings on imaging to help us decide those events.

As far as your first -- could you restate your first question?

DR. AUGUSTINE: If you could just clarify the column headers on slide 62 and 63, particularly the second and third columns about neuro days post-implant and PSOM at the time of event. Is there a window, a time window for the PSOM at the time of the event and again column 2, exactly what do those days represents?

DR. FRASER: Those days represent the PSOM that was assessed at the time of the neurologic event and then after explantation. This highest PSOM score that was reported at any time during the course after the event and the latest one was the PSOM score that was recorded that was the latest after the patient was --

DR. AUGUSTINE: So the neuro days post-implant is what exactly?

DR. FRASER: That's the day the event occurred after implantation.

DR. AUGUSTINE: Okay. And then the PSOM at the time of the event, the days there, is that the number of days after the event --

DR. FRASER: Yeah, that's within the window of the event.

DR. AUGUSTINE: Okay. Thank you.

DR. YANCY: We'll take two more questions. One is from Dr. Weinberger and one from Dr. Jeevanandam.

DR. WEINBERGER: One general -- first a comment, a very nicely done study, a very difficult patient population.

But in order for me, as an adult cardiologist, to get my head around the value of this device, I have to understand a little bit more about the quality of life on device.

So we're given a composite safety measure called SAEs rates, and anytime you see the word rate, you've got to worry about the definitions. So that's the number of significant adverse events divided by the total number of days on the device.

And because these devices were implanted, the EXCOR device was implanted and kept in the patient much longer than the ECMO devices, the rates will appear to be much lower. So a much more meaningful measurement for me is the number of significant adverse events per patient. Do we have that data available?

DR. YANCY: If you don't have that readily available, you can present it this afternoon.

DR. FRASER: I think it's there. There. Here's the slide for the number with the events for Cohort 1 and Cohort 2. You can see that for

major bleeding in Cohort 1, it was 41 percent and 50 percent in the -- for example, neurologic dysfunction, it was 29 percent. These are the proportionate patients.

However, what's striking for us is the fact that while it's true that the longer you're on the device, the lower rate of the events, the relative rate of events have to be interpreted in light of how long you can stay on the device. Prior to availability of the EXCOR, the only device we had to maintain children for heart transplantation was ECMO, and ECMO as you can see, has a very limited time window of effectiveness.

DR. WEINBERGER: Just a clarification. On average, when I looked at these numbers, most kids seemed to have four to five major adverse events during their time on the EXCOR. Is that correct? I'm not interested in the breakdown. I just want to know if you look at all adverse events because that's a quality of life measure that we're going to be worried about.

DR. FRASER: That's correct.

DR. YANCY: It might be helpful for us to see that quantification if you can bring it forward later this afternoon. We don't need to do it now because I think what Dr. Weinberg is looking for is not an uncommon metric that says the number of events per person enrolled in the study, and I think it would be helpful. Dr. Jeevanandam.

DR. JEEVANANDAM: I think it's a great study because it's a

very difficult patient population after you study this, and I think what we need to appreciate is these pumps are really small pumps, and it's probably no way you're ever going to avoid having clots and CVAs with these pumps. These valves are, you know, milliliters, and so we need to accept the fact that they're going to have some events.

I think the amazing thing here is that you had a lot of events, and transplant basically rescued these patients. I mean this device got them to a transplant, but you transplanted people who had strokes, or babies who had strokes, and they actually seem to survive afterwards.

So I think somebody asked about, you know, what is the quality of life after they got transplanted? I mean you basically just stopped at a transplant but, you know, if they had had a stroke and been transplanted, it would be nice to know exactly how they did after their transplant.

Now, having said that, you know, it would be a good way if we could have a lot of good hemostatic data. Is there anything that chemically was triggered that could pre-stage or look at a thrombus before it formed? In other words, was there an infection event where then all of a sudden your parameters of hemostasis went up and then you formed a clot? Because I think that would be a much better way to look at clot formation than looking at it visually, and perhaps if you can predict that there's a clot going to occur, then you can heighten anticoagulation at that point to prevent the

clot from occurring.

And the other thing that I just wanted to bring up is, you know, the CVA, I realize it's hard to evaluate in a baby because they're sedated, but did these events occur more during implantation or did they occur as a period of time? In other words, were these ongoing events or were they basically a big spike in the beginning and maybe we didn't even know what the neurological status of the baby is before this device went in and then are we seeing it 10 days later because that's when the babies are being woken up?

And again I congratulate the Sponsor on the study. Obviously there's some safety concerns with stroke, which is the biggest thing in the transplants rescuing these patients, but is there any way that you think you may be able to predict when these strokes are going to occur from an anticoagulation point of view?

DR. FRASER: I'd like to have Dr. Massicotte address that question.

DR. MASSICOTTE: Patty Massicotte, University of Alberta, Canada.

As far as being able to predict events related to anticoagulation, I think it's difficult. I mean we made recommendations and had guidelines for anticoagulation for which I showed you that the centers were adherent, and I think that -- I mean I think certainly there's the

possibility, but I think right now we don't have a way to predict other than in our pre-implant blood work, we did some markers that are accepted within the literature as having hypercoagulability associated with them. Things like levels of inhibitors of coagulation, protein C, protein S, antithrombin, things like lupus anticoagulant, measuring levels of fibrinogen, and these were done with the knowledge that children are very different than adults, and they have very different normal values known as developmental hemostasis which progress over time to adult levels.

And so you can see that with our baseline information, Factor V Leiden prothrombin gene defect and anti-Fas lipid and antibody as well would be included in that, and so these were done and recommended, and these were done on a number of children, remembering that a lot of times at centers, even high powered centers, these results can take some time to come back, and so they often were not available prior to implantation.

DR. JEEVANANDAM: But were you able to go back in patients who had thrombus and go back and look at some of these values and see if they were abnormal, you know, coincident to an event, but granted it's retrospective?

DR. MASSICOTTE: Correct.

DR. JEEVANANDAM: No. Were you able to go back and see any differences?

DR. MASSICOTTE: I can bring back some of the pump change

data this afternoon after lunch and show you that within the pump change group, there were many children who had potential factors which would lend themselves to hypercoagulability.

DR. YANCY: The Chair has two comments. One, I'd like to thank the Sponsor for the clarity of your presentation and the resourcefulness with the answers.

Second, as you have a second opportunity to address questions, I didn't hear one of the Panel members bring forward the potential concerns you might have about outcomes, success outcomes in the compassionate use small BSA cohort, actually have an outcome similar to the ECMO control, and a little concern could be expressed that the compassionate use experience might be similar to the deployment of this device more broadly that is outside of the clinical centers, but we can address that later on this afternoon, but again, thank you very much for your clarity.

We will now take a break. I apologize if I didn't get to questions that all the Panel members have, but we will have an opportunity later to do that.

Let me remind the Panel that we refrain from discussing this meeting topic during the break. It is important that we stay on time. We will reconvene exactly at 10:15.

(Off the record.)

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(On the record.)

DR. YANCY: It is now 10:16, and I'd like to call this meeting back to order.

It has come to our attention by the biostatistician on our Panel that another request of the Sponsor is going to be made if you don't mind, and that would be to demonstrate a time to event with regard to stroke so that we can have clarity on that question. We can hope for that answer this afternoon. You don't need to respond at this moment.

DR. ZUCKERMAN: Could you repeat that again, please?

DR. YANCY: Let me defer to our statistician on the Panel.

DR. CONNOR: Jason Connor. I was just asking if it was possible to see a Kaplan-Meier curve from time to stroke after implant. Thanks.

DR. YANCY: Thank you very much.

Let us proceed now. FDA will give their presentation on this issue. FDA has 60 minutes as did the Sponsor have. The FDA presenters are Shreya Mehta, John Laschinger, Terri Johnson, Veronica Sansing, and then Shreya Mehta will close the presentation.

So we will begin with Shreya. Thank you very much.

MS. MEHTA: Thank you. Good morning, and thank you for attending this Panel meeting.

My name is Shreya Mehta, and I'm the FDA Lead Reviewer for

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this HDE premarket submission for the Berlin Heart EXCOR Pediatric VAD.

On behalf of FDA, I would like to thank the Panel for their time today and look forward to an active discussion of this HDE.

During this presentation, I will provide an introduction including a description of the device and the Sponsor's preclinical test descriptions. Dr. John Laschinger will then discuss clinical trial design and outcomes. Dr. Terri Johnson will then follow to discuss the statistical outcomes and challenges that were presented. Following Dr. Johnson, Dr. Veronica Sansing will provide postapproval study considerations. Lastly, I will provide a summary and FDA conclusions.

This presentation is not meant to be all inclusive of the information submitted by the Sponsor in their HDE application, nor is it intended to represent all of the information reviewed by the FDA with regard to this HDE.

Instead, our presentation will primarily focus on what FDA considers to be the key issues surrounding approvability of the device.

The indications for use proposed by the Sponsor is as follows:
The EXCOR Pediatric VAD is intended to provide mechanical circulatory support as a bridge to cardiac transplantation for pediatric patients. Pediatric candidates with severe isolated left ventricular or biventricular dysfunction who are candidates for cardiac transplant and require circulatory support may be treated using the EXCOR.

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FDA acknowledges the broad indications for use and will seek Panel input on any special clinical labeling to clearly identify any limitations.

The EXCOR Pediatric VAD consists of one or two extracorporeal pneumatically driven blood pumps (depending on univentricular or biventricular support), cannulae to connect the blood pumps to the atrium or ventricle and to the great arteries, and the Ikus driving unit. This unit provides the necessary controls for one or two pumps attached to the patient.

As the above figure shows, there are five sizes of pumps available ranging from 10 to 60 milliliters.

This slide provides a review of the regulatory history of the EXCOR device. In 1996, the EXCOR received CE mark allowing the Sponsor to market the device in Europe. In August 2000, the EXCOR emerged in the U.S. as an alternative for children requiring mechanical circulatory support via the compassionate use, CU, and Emergency Use, EU, provisions.

Under the CU guidelines, FDA approved patient implants in the U.S. on a case-by-case basis. Patients were implanted under the EU provisions under dire situations when there was not enough time for FDA review and approval.

In 2001, the Berlin Heart EXCOR received humanitarian use device or HUD designation from the Office of Orphan Products at FDA. Under this designation, the Sponsor would be able to pursue the HDE or

humanitarian device exemption marketing application.

From 2000 to 2005, the EXCOR continued to be requested for implantation under this CU and EU provisions.

FDA and Berlin Heart recognized the unmet need for this at-risk patient population and worked together toward an investigational device exemption IDE approval to begin a U.S. clinical trial.

On May 8, 2007, the EXCOR IDE was approved. Equipped with preclinical data from bench studies and clinical data from the IDE study, Berlin Heart submitted a HDE marketing application to FDA on February 6, 2010. The approvability of this application is the focus of today's Panel meeting.

The FDA preclinical review team consisted of the following members. Multiple engineers were involved in the review as well as an animal studies reviewer, a biocompatibility reviewer, and a microbiologist who reviewed sterilization, shelf life, and packaging data.

The Sponsor has conducted preclinical bench top tests and submitted the results of these tests to FDA in support of their HDE application.

A few bench top tests demonstrated structural integrity of the components, joints, and cannulae.

To demonstrate fluid characterization, the Sponsor conducted particle image velocimetry and mock flow loop tests which demonstrated no

areas of high shear or stagnant fluid flow.

Also, a host of biocompatibility tests demonstrated that the device is compliant with FDA-recognized international standards.

Test results demonstrated adequate electromagnetic compatibility and electrical safety of the entire system in the hospital environment.

Software verification and validation tests provided reasonable assurance that the software in the Ikus driving unit could consistently meet the specified requirements as intended.

All of these bench tests supported the anticipated and intended performance of the device in the clinical environment.

However, it is important to note that the device has not been subjected to tests for any external transport situation or the home environment. Although the Sponsor is not proposing at-home use, such conditions would warrant further preclinical testing.

Animal study data demonstrating in vivo experience with the EXCOR device were not provided for review.

At the time of IDE approval, FDA believed that implantation of this device in greater than 100 outside of U.S. patients and several patients in the U.S. under the CU and EU provisions was sufficient to initiate the IDE study.

FDA would like to point out that OUS data does not generally

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mitigate the need to demonstrate safety via an animal study prior to beginning a clinical trial on a new device. In this case, however, the clinical data available for the EXCOR at time of IDE approval was uniquely vast.

Furthermore, FDA did not believe that animal studies would likely provide any additional safety information that would not be available from the EXCOR OUS clinical experiences.

After these careful and deliberate considerations, FDA granted IDE approval to begin a U.S. clinical trial.

I would now like to introduce Dr. John Laschinger, a cardiovascular surgeon and our FDA Medical Officer, for this review. Dr. Laschinger will present the clinical trial design and outcomes for the study.

DR. LASCHINGER: Thank you, Shreya. I will now present the FDA clinical summary.

My name is John Laschinger. I'm a cardiac surgeon with both pediatric and adult cardiac surgical experience and also performed numerous heart and lung transplants during my career.

An outline of the FDA presentation is shown on this slide. We hope this will provide a coherent review of the data submitted for this HDE application. This presentation will primarily focus on what the FDA considers to be key issues surrounding approvability of this device.

The purpose of the EXCOR IDE clinical study was to

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demonstrate that the EXCOR Pediatric VAD or Ventricular Assist Device, merited approval by the FDA under HDE provisions by demonstrating a reasonable assurance of safety and probable benefit for the intended population.

The trial was a prospective, multicenter study, with single arm. Two primary study cohorts, Cohorts 1 and 2, were respectively divided based upon differential body surface area measurements. Statistical determination of safety was based upon a comparison to a performance goal and statistical determination of effectiveness was based upon survival rate comparison to historical extracorporeal membrane oxygenation or ECMO controls.

A third cohort of patients consists of those who were implanted under compassionate and emergency use provisions. These patients are intended to provide supportive data only and are not part of the primary study groups.

Patients in these groups were stratified by BSA and were implanted at both IDE and non-IDE sites. Additionally, a continued access protocol or CAP was initiated for small BSA patients at IDE sites after the maximum enrollment for Cohort 1 was reached. CAP patients met all eligibility requirements set by the study's inclusion and exclusion criteria.

The principal inclusion criteria are summarized on this slide. Age and weight appropriate patients with critical or worsening cardiogenic

shock were considered as were patients unable to be weaned from bypass or requiring mechanical circulatory support following corrective open heart surgery. Patients were required to have two ventricle circulations and listed for transplant to be included in the primary study groups.

Exclusion criteria were many, and the most important are summarized here. Patients on ECMO 10 or more days as well as patients with unfavorable cardiac anatomy were excluded. Intrinsic disease of other major organ systems, physiologic disturbances, malignant disorders, and stroke were also considered contraindications for inclusion in the primary study group.

Patient demographics for the primary study cohort is summarized on this slide. Patients were evenly divided by gender with age, height, and weight ranges being appropriate for each primary cohort assignment, which was based on body surface area. All patients in the primary study groups were in critical cardiogenic shock or exhibited progressive decline in their clinical status as defined by the eligibility criteria.

The following group of slides will highlight specific boxes in white and the data they contain, in order to highlight the differences that were present in the seven possible enrollment or implant cohorts in this study.

Between June 2007 and December 2010, a total of 204 patients underwent implantation of the EXCOR device. They were divided

into small BSA groups and large BSA groups.

The primary study group consisted of 48 patients equally divided based on BSA into two primary study groups, Cohort 1 and Cohort 2. Each of these primary study cohorts contained 24 patients.

A total of 109 patients were implanted in all cohorts at the 15 participating IDE sites. This included 48 primary study group subjects enrolled in Cohorts 1 and 2. Additional IDE site implants included the 20 previously described continued access protocol patients for small BSA patients. In addition, a total of 41 small and large BSA patients who did not meet eligibility criteria necessary for study enrollment at IDE sites were implanted under compassionate or emergency use provisions.

Patients implanted at the 27 sites that were non-IDE participants were by definition under compassionate or emergency use provisions, whether or not eligibility criteria would have been met. A total of 95 patients were implanted in these non-IDE cohorts and stratified into small and large BSA patients.

The objective of the study was to demonstrate that the overall survival and patients treated with EXCOR Pediatric was different from the survival and the historical control subjects treated with ECMO as a means of mechanical circulatory support.

The pre-specified hypothesis test for evaluation of the primary effectiveness endpoint was a comparison of the hazard ratios to one for the

EXCOR study groups and the ECMO controls.

Determining an appropriate comparator for effectiveness proved challenging with the design of this study. There were no approved VADs for pediatric clinical use and ECMO, although the standard of care for pediatric mechanical circulatory support has no approved or cleared devices and specifically is not approved or cleared for bridge-to-transplant indications.

Therefore, the historical control subjects to be used for survival comparisons were selected from the Extracorporeal Life Support Organization registry or ELSO, since this database was the best comparison available for determination of survival.

The control population used for primary effectiveness analysis for each primary study group consists of a matched set of 48 subjects who were treated with ECMO after the year 2000 and listed in the ELSO registry. Limitations of the ELSO registry for use as a historical control included the potential for inappropriate matching between patients. This is especially true in a small HDE study population such as this where patients with a wide variety of underlying conditions and co-morbidities are enrolled.

Further limitations specific to this study include the use of disparate definitions for outcomes and recovery for EXCOR and ECMO patients and the fact that ELSO does not capture events or outcomes other than survival post-explant. Details of the PSA matching, of the propensity

score analysis matching, will be discussed in the statistical review section of this presentation.

The survival time for this study was calculated as the interval from the initiation of support to when the patient reached an endpoint. Due to the nature of the ELSO registry, different definitions for the endpoint as well as recovery, success and failure were used for EXCOR and ECMO patients.

The underlying portions of the EXCOR definitions highlight the major differences in the definitions used for each treatment group. Although somewhat different, the use of these definitions was made necessary by the information available and do not hinder the final ability to make clinical decisions regarding the relative effectiveness of these devices.

Clinical survival and outcome data reviewed for determination of effectiveness included two sets of Kaplan-Meier curves and competing outcome curves based on how the cohorts were determined.

The first set was produced as previously described using BSA to determine EXCOR and ECMO Cohort 1 and Cohort 2 patients and will be presented by the FDA in the slides to follow. Recognizing the difficulty in obtaining suitable historical controls in HDE studies with small numbers of complex patients, the FDA requested a post hoc redefinition of the cohorts that were separated by age instead of BSA. This redefinition of cohorts did not change the composition of the primary study groups, but did result in

new ECMO comparator groups providing further data to aid in the assessment of clinical benefit.

This was the data that was presented by the Sponsor, and we will present the data based on the pre-specified cohort determination.

The pre-specified hazard ratio comparison was not submitted by the Sponsor. The FDA did conduct an independent analysis, and FDA's statistical reviewer will present FDA's analysis on the pre-specified hypothesis test.

This slide shows the respective Kaplan-Meier curves for percent survival on the device at various time points post-implant for Cohort 1 and ECMO control patients. The ability to achieve the long-term survival rate necessary for use of a device as an effective bridge to transplant was seen only in Cohort 1 patients.

Competing outcome curves for Cohort 1 subjects and their ECMO controls are depicted on this slide. Competing outcome curves allow unique visualization of patient outcomes over time since the cumulative sum of all potential outcomes at any point in time adds up to 100 percent. The ability to achieve the prolonged support time needed for successful bridge to transplant was clearly demonstrated in the EXCOR supported patients. The success rate of 87.5 percent was seen in Cohort 1 patients for bridge to transplant with support times up to 174 days being achieved. Since success was observed in 75 percent of ECMO patients, however, the longest support

time achieved was only 20.5 days.

This slide shows the respective Kaplan-Meier curves for percent survival on the device at various time points post-implant for Cohort 2 and ECMO control patients. Once again, the ability to achieve the long-term survival rate necessary for use of the device as an effective bridge to transplant was seen only in Cohort 2 patients.

Competing outcome curves for both Cohort 2 subjects and their ECMO controls are depicted on this slide. Once again, the ability to achieve the prolonged support time necessary for successful bridge to transplantation was clearly demonstrated in the EXCOR supported patients. The success rate of 91 percent, including both transplant and successfully weaned patients, was seen in Cohort 2 patients who were either bridge to transplant or underwent successful wean. Support times of up to 174 days were achieved in EXCOR patients. Success was observed in 66.7 percent of ECMO patients with the longest support time being 27.5 days.

Although the use of historical controls for primary effectiveness endpoint was problematic, the available relevant clinical data was sufficient to allow for clinical evaluation of the primary effectiveness endpoint. Based upon a review of the clinically relevant data, EXCOR provides clinically important benefits in survival rate and survival time versus ECMO, and these survival differences are critical for use of mechanical assistance for pediatric bridge-to-transplant indication.

There were two pre-specified secondary effectiveness endpoints that were presented with descriptive statistics only, and they include days of transplant eligible support and the ability to de-intensify concomitant hemodynamic support as judged by the parameters shown on this slide.

After thoroughly reviewing this data, FDA concludes that the Sponsor has also met these pre-specified secondary effectiveness endpoints. Patients remained actively listed for transplant for 99.3 percent of all days of support. However, there was no accounting for real or potential organ refusal due to changes in temporary clinical status. The ability to de-intensify concomitant hemodynamic support was observed with an overall trend towards decreased levels of support noted over time.

The paucity of available organs, especially in the pediatric population, leads to prolonged wait times for organ availability far in excess of the time provided by currently available methods of hemodynamic support for critically infants and children. Directly stated, there's a critical need for mechanical support devices for use in bridge-to-transplant indication in children with end stage heart failure.

In order to be effective, devices must provide the four key benefits summarized on this slide. The Panel will be asked whether the data submitted and reviewed regarding these four key features of primary and secondary effectiveness are sufficient for demonstration of probable benefit

for use of the EXCOR device for a bridge-to-transplant indication in children.

The primary safety objective of the study was to summarize the serious adverse event rates calculated as the number of SAEs per patient day of support while on the EXCOR Pediatric device. The safety determination was based on a comparison to a performance goal set at a level of serious adverse events per day typical for patients being supported by mechanical assist devices. The performance goal was set at 0.25 events per patient day of support.

As with the effectiveness endpoint, the determination of appropriate comparator for safety endpoint was difficult for many of the same basic reasons summarized on this slide. Direct comparison of individual SAEs with the ELSO registry is not possible since it is not adjudicated, voluntary, and uses different definitions for these events.

The INTERMACS registry cannot be used since it is comprised primarily of adult data. However, it did serve as a basis for standardized SAE definitions in study subjects.

Under the assumptions of the Poisson analysis, both the events per patient day of support and the upper bound of their 95 percent confidence interval were well below the pre-specified performance goal of 0.25 events per day of support.

Our statistical reviewer will show the results for more appropriate statistical analysis which also demonstrates that the safety

hypothesis was met.

Pre-implant ECMO had a deleterious effect on the incidence of SAEs, increasing it by a factor of 2.2 in small BSA patients and by a factor of 1.4 in large BSA study patients.

The data shows that the Sponsor has met the primary safety endpoint performance goal of a total SAE rate of less than 0.25 events per patient day of support.

The Panel will be asked whether safety sufficient for approval for use of the EXCOR device for a bridge-to-transport indication in children has been demonstrated.

Prespecified support of analyses were presented with descriptive statistics only and include transfusion requirements, EXCOR performance, neurologic status and quality of life, and neurodevelopmental assessments.

FDA acknowledges that the data shows transfusion requirements for all blood products were within expected ranges. In addition, the pump performed well providing excellent hemodynamic support for all sizes of devices implanted, and there were no failures or unanticipated adverse events.

FDA requested additional data from the Sponsor in the four key areas shown on this slide to further understand the risk/benefit profile for EXCOR. FDA will be seeking Panel input regarding each of these four

areas and their implications for approval, labeling for a broader bridge-to-transplant indication, requirements for training programs, and formulating appropriate postapproval study goals. Each of these four analyses will now be discussed separately.

The first is mortality data, and the implications for a broader bridge-to-transplant implication. The following groups of slides will highlight specific data regarding mortality and wean outcome data of the various patient cohorts as it was reviewed to show how clinical outcomes related to mortality and failure were determined.

There were 51 deaths in the 204 total patients implanted with the EXCOR device for a total mortality of 25 percent. In addition, four patients at IDE sites had unsuccessful wean, defined as death within 30 days of survival or an unacceptable neurological outcome. This yielded a total death or failure rate of 27 percent.

In addition, it must be stated that the mortality and failure calculations shown on here and all the calculations to follow are best-case scenario. The status of 6 patients weaned at non-IDE sites has not been recorded, and at the time of data log, 11 patients remained on the device. For the purpose of our mortality and failure calculations, all of these were counted as successes even though their final status remains unknown.

Three sets of observations made regarding mortality based on the data provided by the Sponsor.

The first summarized here is that low mortality was observed when the device is implanted at experienced centers using strict inclusion and exclusion criteria.

All patients in the primary study cohorts and continued access protocol groups were enrolled or implanted after strict eligibility criteria were met. In these groups, a low risk of overall mortality or failed weaning was observed at 8.8 percent.

Observation number 2 was that even at experienced IDE centers, failure to meet strict entry criteria resulted in death or failure rate that was substantially higher compared to patients who did. Additional analysis identified two possible predictors of mortality for patients implanted at experienced IDE sites, single ventricle circulations and any pre-implant use of ECMO.

The total mortality and failure rate for all patients enrolled and implanted at IDE sites was 18.3 percent. However, mortality and wean failure in patients not meeting strict criteria were substantially higher at 42 percent compared to a lower mortality and failed wean rate of 9.9 percent observed in patients meeting all entry criteria and implanted at these same IDE sites.

As noted, when pre-implant risk factors for mortality in IDE patients were examined, single ventricle circulations and pre-implant use of ECMO were identified as possible predictors of mortality.

The third observation regarding mortality was that for all compassionate and emergency use patients, the rate of overall mortality and failed wean was high and was not affected by the site of implantation, IDE versus non-IDE site. In addition, for compassionate and emergency use patients implanted at non-IDE sites, meeting all eligibility criteria did not result in a lower rate of mortality or failed weaning.

The total mortality and failure rate for all compassionate and emergency use patients was 36 percent and did not vary substantially between IDE and non-IDE sites. In addition, meeting eligibility criteria did not protect against mortality or failed wean in compassionate or emergency use patients.

The incidence of ischemic neurologic events was high. In Cohort 1 patients, 7 of 24 had an ischemic stroke with one additional severe global ischemic event for a total ischemic neurologic event rate of 33 percent.

The same incidence was seen in large BSA Cohort 2 patients.

Supportive data from both IDE and non-IDE site patients revealed a similarly high overall incidence of neurologic injury due to ischemic events. Although not directly or indirectly comparable for obvious reasons, it must still be noted that these rates of neurologic injury for pediatric mechanical support are approximately double the rate of pulsatile devices and six times the rate of continuous flow devices that are reported

for adult bridge-to-transplant patients in the INTERMACS registry, both in terms of the overall incidence rate and in terms of the events per 100 days of patient support.

For Cohort 1 patients, 17 of 24, or 70.8 percent, were alive and transplanted with good neurologic outcome as defined by the pediatric stroke outcome measure or PSOM score. Six patients, or twenty-five percent, had poor neurologic outcomes despite transplant, died or had a failed wean due to neurologic injury. One additional patient died of a non-neurologic cause.

For Cohort 2 patients, 18 of 24, or 75 percent, were alive and transplanted or successfully weaned with good neurologic outcome as defined by PSOM score, and 6 patients, or 25 percent, had a poor neurologic outcome despite transplant or died to due to neurologic injury.

Overall, 65 percent of the patients in each primary cohort survived transplant or successful weaning with no neurologic events, and 73 percent of all study patients were transplanted or successfully weaned with good neurologic outcome.

Over 90 percent of all adverse outcomes, including death, failed wean, and poor neurologic outcome were due to ischemic or thrombotic neurologic events. There are limitations with interpretation of these data, since these are only acute outcomes, highlighting the importance of the need for longer-term follow up.

Pediatric quality of life generic scale scores were also reported for primary study patients. Typical scores for a normal pediatric population averaged an 85 to 90 range out of 100, with higher scores indicating improved quality of life. Scores of children with chronic health problems such as cancer, asthma, diabetes typically ranged from 65 to 70. The range of PedsQL scores for EXCOR study patients varied widely but ranged from 20 to 65 for patient and parent/proxy reported scores. The minimal clinically important difference in PedsQL scores is defined as a change of one standard error of the mean or a change of 4.5 in the total PedsQL score. PedsQL scores in EXCOR supported patients were observed to be several multiples of the standard error of the mean lower than levels associated with chronic disease states in children.

Pump change due to thrombus within the pump is not regarded as an SAE. However, once detected, pump change is required. Thrombus is typically localized to the areas immediately adjacent to the inflow and outflow valves. Pump change due to thrombus was common, resulting in the average of 1.1 pump changes per patient in the primary study groups or 0.02 changes per patient day of support.

Noting the high incidence of the need for pump change due to thrombus, the FDA requested further analysis of the data to determine the potential contributory factors, including the effect on the incidence of SAEs, in particular thromboembolic complications and stroke, and the effect of

pump thrombus on late neurologic outcome.

The occurrence of pump thrombus was an ongoing risk with no identified relationship to any of the factors listed on this slide. Major infection was the most common clinical event noted to precede detection of pump thrombus.

For all IDE site patients, no effect was seen on the overall incidence of death or transplant with trends actually favoring those requiring pump change due to thrombus. Major infection rates, both device and non-device related, were higher in patients requiring pump change as well. Whether infection contributed to a hypercoagulable state or whether pump circuit manipulation resulted in a higher incidence of infection is not known.

The overall incidence of neurologic dysfunction caused by ischemic events were substantially higher in IDE site patients requiring pump change as was the incidence of arterial non-CNS thromboembolism.

For primary study patients, the average last PSOM score was higher in patients requiring pump change due to thrombus, signifying an overall worse neurologic outcome in these patients.

In addition, both the number of patients above the threshold of one for poor neurologic outcome and the mean scores of those patients were higher in patients requiring pump change due to thrombus.

Pump change due to thrombus is a frequent occurrence. Data

suggests that it is associated with a substantially higher incidence of ischemic neurologic events and overall poorer neurologic outcome as measured by PSOM, noting that these data were only obtained in the acute setting. In the absence of any identifiable clinical risk factors, the materials and design of the pump circuit and valves remain as a potential source.

Despite these findings, the overwhelming majority of patients were able to undergo transplant or successful weaning with either no neurologic events or good neurologic outcome.

In summary, the primary safety endpoint was met based upon the pre-specified hypothesis. EXCOR showed superior effectiveness based on submitted data with clinically important improvements in the ability to provide prolonged support. Pump performance was excellent with no device failures, and excellent long-term hemodynamic support that is necessary for use as a bridge-to-transplant device was provided. Concomitant support was able to be weaned in selected patients.

These results also indicated an increased mortality may be associated with broader clinical use for bridge-to-transplant indication and also when the device is used at relatively less experienced centers. Patients with single ventricle physiology and patients requiring pre-implant ECMO can also be expected to have higher mortality rates.

There are three important areas where the long-term results and effects remain unknown due to a lack of late follow-up data. These

include neurologic events and their effects on long-term outcome. The risk for these events is high, and acute neurologic or ischemic events are responsible for over 90 percent of adverse, early outcomes. However, the long-term effects of these acute events in surviving patients remain unknown.

Acute health-related quality of life data is also worrisome. However, the long-term data is essential for determination of final outcomes absent the acute alterations that may be present in patients requiring mechanical assistance.

Finally, both the causes and long-term effects of pump thrombus must be further delineated so that the incidence and consequences are mitigated and appropriate improvements in pump design and materials are encouraged.

I'd like to now introduce Dr. Terri Johnson, mathematical statistician at the FDA who will present the statistical review.

DR. JOHNSON: Good morning. I'll be presenting FDA's statistical review of the HDE.

I'll present sample size calculation and the primary safety and effectiveness evaluations and then end with a statistical summary.

Sample size of the study is driven by the primary safety endpoint. A sample of 24 subjects followed for approximately 100 days each would provide a power of 80 percent using the Poisson exact test for the

performance goal of .25 events per patient day, assuming .21 SAEs per patient day at a one-sided significance level of 2.5 percent.

With a sample size of 24 EXCOR patients, calculated based on the primary safety endpoint and 48 to unmatched ECMO patients will provide power greater than 99 percent under the assumption that the median time to death or recovery is 100 days for EXCOR and 4.833 days for the ECMO, with a two-sided significance level of .05 using a Cox proportional hazards regression.

Please note that the assumptions for the sample size calculation were applied to both Cohort 1 and Cohort 2.

Hypothesis for the primary safety endpoint was to show that the serious adverse event rate is no greater than .25 events per patient day tested at one-sided significance level of .025 using the Poisson exact method.

Here are the results for the primary safety endpoint for Cohort 1 EXCOR patients. The total time on device was 1,411 days. The observed SAE rate was .068 SAEs per patient day, and its upper 95 percent confidence interval using the Poisson method was .083, which is smaller than the performance goal of .25. Hence, the primary safety objective of Cohort 1 seems to be met.

The total time on device for Cohort 2 EXCOR patients was 1,376 days. The observed SAE rate was .078, and its upper 95 percent

confidence interval using the Poisson method was .094, which is smaller than the performance goal of .25. Hence, the primary safety objective for Cohort 2 seems to be met.

However, the implemented Poisson method for primary safety endpoint evaluation assumes that (1) within a subject, the adverse event rate is constant over time, and (2) among subjects in the study, the AE rate is the same. If AE rates are different between patients, the width of the confidence interval using the Poisson model would be narrower than it should be since the between patient variance is not considered in the Poisson model.

The FDA analysis showed that there was a significant over-dispersion indicating that additional variation exists in the data beyond the Poisson model. There are usually two approaches to account for the extra variation in the data, using a negative binomial model or a non-parametric bootstrap method.

FDA's analysis results using a negative binomial method showed that the upper limit of 95 percent confidence interval for serious adverse event rates were .144 events per patient day for Cohort 1 and .168 for Cohort 2, which were all less than the performance goal of .25.

Also FDA's analysis using the bootstrap method show that the upper limit of 95 percent confidence interval for Cohort 1 was .16 events per patient day and for Cohort 2 was .15 SAEs per patient day which all were less

than the performance goal of .25.

Another statistical issue relates to the evaluation of the primary effectiveness endpoint using the propensity score method. Propensity score calculates a probability of a patient receiving one treatment over another treatment given certain baseline and demographic characteristics. Propensity score method attempts to mimic a randomized trial when historical control data are used.

Please keep in mind that the propensity score method can only adjust score imbalances in observed covariates and cannot adjust score imbalances in unobserved covariates. If there are differences between the two treatment groups that are explained by an unobserved covariate, then the propensity score analysis will lead us to a biased estimate of the treatment effect.

Hence, it is important to pre-specify all the relevant covariates in the propensity score analysis.

For this study, the propensity score is a probability of a patient receiving EXCOR over ECMO. Covariates built in the current propensity score model include age, weight, primary diagnosis, prior ventilator, prior inotrope use, and history of cardiac arrest.

It should be pointed out that BSA, which is an important covariate that might affect treatment outcome, were not included in the propensity score model. This is a serious concern regarding the

appropriateness of the propensity score model using this HDE.

You recall that the ELSO registry was used to select two propensity score matched controls for each of 24 EXCOR patients for Cohort 1 and for Cohort 2 separately. There were 747 patients in the registry who received ECMO; 640 patients were eligible for propensity score analysis for Cohort 1. Please note that the patients who were older than 10 years of age or weighed greater than 40 kilograms were excluded for matching to Cohort 1. Two ECMO patients were matched and selected to each EXCOR patient as controls.

This is a box plot showing the distribution of propensity score for treatment and control groups. There is not much overlap in propensity score distribution between the two groups. Nonetheless, 48 reasonably matched controls can be found for Cohort 1.

This table provided by the applicant compares the distribution of pre-specified propensity score covariates between Cohort 1 and its matched ELSO controls indicating balances were achieved for those covariates using the propensity score model.

You recall that the pre-specified primary effectiveness hypothesis was to test hazard ratio of EXCOR relative to ECMO using a Cox proportionate hazard regression tested at two-sided significance level of .05.

The unadjusted hazard ratio is problematic since the correlation among the matched triplets is not accounted for. FDA's analysis

show that the hazard ratio after adjusting for the matching design was .099, and it was significantly lower than 1. Hence, the primary effectiveness objective for Cohort 1 seems to be met.

For Cohort 2, the Sponsor has failed to provide sufficient information on the matched controls selected using the propensity score method. Therefore, FDA performed its own analysis trying best to recreate the results in the HDE. The FDA analysis shows that 682 patients were eligible for propensity score analysis. Please note that all patients including those who were considered for Cohort 1 match were included in this analysis since it seems that the applicant has done the same.

On this slide is a box plot showing the distribution of propensity scores for Cohort 2 and its matched control group. Similar to the propensity score distribution comparison between Cohort 1 and its matched controls, there's not much overlap between the two groups. However, 48 matched controls can be found according to the distribution also.

This table provided by the applicant presents the comparison of the distributions of the pre-specified propensity score covariates for Cohort 2 and its matched ELSO controls. Please note that age and weight seems to be still different between the Cohort 2 EXCOR patients and the matched ELSO control patients. There were 8 patients in the ELSO control group who were younger than 2 years of age and weighed less than 10 kilograms whereas there were no such patients in the EXCOR group. This

implies that the implemented propensity score model was not appropriate and would not adequately adjust for biases between these two groups.

As a result, the primary effectiveness endpoint for Cohort 2 cannot be evaluated because analysis that appropriately adjusts for matching design cannot be performed since data were not provided. Also, the statistical results for the primary effectiveness endpoint for Cohort 2 in the HDE may be biased and not interpretable since the implemented propensity score method failed to achieve balances in the observed covariates.

In summary, the primary safety objective was met. The primary effectiveness objective for Cohort 1 seems to be met. However, the results may still be biased due to imbalances in omitted important covariates such as BSA from the propensity score model.

And the primary effectiveness objectiveness for Cohort 2 is inconclusive since imbalances in observed covariates in addition to imbalances in omitted covariates still exist.

A clinical judgment is needed for the study inference on the primary effectiveness objective.

That concludes the FDA's statistical review of the HDE.

I would like to introduce Dr. Veronica Sansing, our epidemiologist from the Division of Epidemiology in the Office of Surveillance and Biometrics.

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DR. SANSING: Thank you, Terri. Good morning. I will now present the postapproval study considerations.

Please note that the slides I present today are slightly different than those that are in front of the Panel. This is due to the receipt of the updated information from the Sponsor. Today's slides will incorporate these updates.

Before we talk about postapproval studies, please allow me to clarify a few things. The discussion of a postapproval study prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting the device's safety and probable benefit have been established. The plan to conduct a PAS does not decrease the threshold of evidence required by the FDA for device approval. The premarket HDE data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and probable benefit.

The reasons for conducting postapproval studies are to gather postmarket information including longer-term performance of the device, data on how the device performs in a broader population that is treated by physicians with varied experience as opposed to highly selected patients treated by investigators in the clinical trials, evaluation of effectiveness of training programs for use of devices, evaluation of device performance in subgroups of patients since clinical trials tend to have limited numbers of patients or no patients at all in certain vulnerable subgroups of the general

patient population, monitor adverse events especially rare adverse events that were not observed in clinical trials. In addition, postapproval studies can also address any other issues that may be identified by Panel members based on this expertise.

Postapproval studies should contain a fundamental study question or hypothesis, safety endpoints and measures of assessments, acute and chronic effectiveness endpoints and methods of assessment. The PAS should also specify the duration of follow-up.

Should the HDE be approved? The FDA review team identified the following postmarket issues for this device.

First, there may be a learning curve associated with device use. Studies in adult populations using LVADs have shown that learning curves must be evaluated for patient selection, surgical procedures, both implant and explant and postoperative care, operators within the IDE study who have had experience in performing these procedures. However, as the device is made available to a wider range of patient populations and surgeons, there may be a learning curve associated with device use.

Another important consideration is the long-term effect of device exposure. This device is first of a kind in the pediatric population. The IDE study followed patients until transplant or recovery and one-year post-explant collecting information regarding clinical, neurological, and quality of life status. This short timeframe may not capture the full

spectrum of adverse events associated with the device. A greater follow-up period post-transplant or recovery may be needed to better capture unexpected adverse events. Studies in the U.S. and outside of the U.S. have followed pediatric populations for an average of 5 to 10 years post-explant.

Berlin Heart proposed to conduct the EXCOR Pediatric VAD postapproval study to fulfill postapproval study requirements.

This table presents an overview of the proposed postapproval study to evaluate the device's safety and probable benefit. The EXCOR Pediatric VAD postapproval study is a registry of the first 24 patients implanted with the EXCOR Pediatric VAD per device labeling.

The sample size was based on the safety endpoint. A sample of 24 patients with approximately 100 days of follow-up provides greater than 80 percent power to conclude that the serious adverse event rate is less than .2 events per patient day, with a one-sided alpha of .025. The number of sites were not specified though the Sponsor expects to enroll three sites per month.

Follow-up duration will be from implant until transplant or recovery, with scheduled contacts at two, four, and six weeks, three and six months, and every three months while on device support.

The Sponsor anticipates that it will take 12 months to complete the study.

Primary effectiveness hypothesis states that the survival to

transplant or recovery rate for the EXCOR Pediatric postmarket is not equal to that of EXCOR Pediatric premarket. The Sponsor will compare the postapproval study survival to transplant recovery rate with the data from Cohorts 1, 2, and 3 combined in an IDE study in order to evaluate postmarket performance. Neither power or sample size calculations were provided for this hypothesis.

The primary safety endpoint measuring adverse events will be calculated as the number of serious adverse events per patient day while on support of the device. The Sponsor hypothesizes that the rate of serious adverse events will not exceed .25 events per patient day. The Sponsor will present a list of the detailed serious adverse events.

The secondary objective will capture device malfunctions and will be descriptive in nature with no specific testing or analyses. Device malfunctions will be classified according to pump failures and non-pump failure.

The PAS includes a training program but does not assess a possible learning curve associated with the implant and explant of the device. Studies within the adult population for other marketed VADs have shown that a potential operator learning curve should be evaluated for VADs. It is not clear whether the learning curve exists within the pediatric population. Operators within the IDE study will have had experience in performing these procedures.

However, as a device is made available to a wider range of patient populations and surgeons, an assessment of a potential learning curve with respect to patient selection and implant and explant procedure, related adverse events, for example, thrombus, may be necessary.

The FDA would like to see the PAS include a formal evaluation of a potential learning curve.

The EXCOR Pediatric VAD has been used in the pediatric population in both the U.S. and outside of the U.S. for several years with studies reporting long-term follow-up beyond explant. As previously stated, patients' health status and neurological outcomes are not followed beyond recovery or transplant under the current proposal.

The review team would like to see long-term follow-up beyond device explant. An appropriate length of follow-up would be approximately five years or more.

The PAS should also include an assessment of quality of life metrics.

I will now hand the presentation over to Shreya Mehta for the conclusions.

MS. MEHTA: Thank you, Veronica.

I will now provide an FDA conclusion. First, however, FDA would like to remind the Panel about the approval requirements for a HDE marketing application.

Prior to HDE submission, the Office of Orphan Products, OOPD, first evaluates the device. The device should be intended to benefit patients in diagnosis and/or treatment of a disease or condition that affects or is manifested in fewer than 4,000 individuals per year in the United States. After OOPD review, the product may be granted humanitarian use device or HUD designation.

This evaluation by OOPD is not an assessment of the device's safety or probable benefit.

After HUD designation is granted by OOPD, the Sponsor may submit an HDE marketing application to the Center for Devices and Radiological Health, CDRH, at FDA. CDRH reviews the applicant's HDE and considers the totality of the data submitted. It is important to note that HDEs are exempt from statutory effectiveness requirements. Instead, under HDE provisions, the Sponsor must demonstrate safety and probable benefit.

FDA encourages the Panel to assess the device's probable benefit in the intended patient population and to determine whether these benefits outweigh the risks all while taking into consideration the other approved and available alternatives for this patient population.

Turning back to the specific application, I'd like to outline the following points.

The Sponsor's preclinical test information adequately demonstrated safe use of the device in the clinical environment.

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Based upon the Sponsor's pre-specified hypothesis of less than .25 serious adverse events per patient day, they have met the primary safety endpoint.

The primary effectiveness objective was to demonstrate that overall survival of EXCOR was likely to be superior to ECMO. Based upon clinical interpretation, FDA believes that the primary effectiveness objective was also met.

Secondary effectiveness endpoints provided by descriptive characteristics included days of transplant eligible support and the ability to de-intensify concomitant hemodynamic support. The Agency believes that these outcomes were supportive of the clinical effectiveness determination.

Despite these positive results, FDA has concerns with regard to certain clinical outcomes. Specifically, FDA noted higher mortality with the expansion of device use to patients who did not meet the strict eligibility criteria of the study, such as those with single ventricle physiology and pre-implant ECMO, and those who were implanted at relatively less experienced centers. Furthermore, FDA noted the high incidence of neurologic dysfunction seen in these patients and its effect on outcome.

Also the health-related quality of life data in this study does not seem sufficient to determine the long-term neurological effectiveness of the device.

Lastly, FDA believes that the incidence of pump thrombus and

its effects on neurologic injury and outcome are cautionary.

The Agency seeks Panel discussion regarding these noteworthy clinical outcomes and how they may reflect on the safety and probable benefit of this device in the intended patient population.

FDA also seeks Panel input regarding how the following issues may be addressed via postapproval study should the device be approved.

Outcomes of the trial demonstrated that statistical challenges exist when historical control data are used as a comparator with the device.

FDA seeks discussion from the Panel with regard to utilizing a different control for studying the PAS patients.

Additionally, the long-term effects of the device, specifically with regard to neurological outcome, remain to be seen. Incorporating long-term follow-up for the postapproval study patients may help elucidate these longer-term effects.

Furthermore, the Agency believes that the data from Cohort 3 and CAP patients suggests that there may exist a disconnect between the primary cohort data seen in this study compared to what will be seen with broader bridge-to-transplant patient use.

To address this discrepancy, the FDA proposes that adjustment for learning curve and adequate training protocols be incorporated into the postapproval study protocol.

Thank you very much for your attention. The FDA looks

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forward to Panel discussion and deliberation regarding the key issues we have presented, and we would be happy to answer questions you have about our presentation.

DR. YANCY: I would like to thank the FDA speakers. You had three seconds left. So you got it all done within the designated time, but your presentations were quite clear. So thank you.

Does anyone on the Panel, as we did before, have any clarifying questions or concerns to be raised now for the FDA? Please remember that the Panel may likewise readdress the FDA in the afternoon. So this is the first of two opportunities. I think the first hand was Dr. Barrett -- Mr. Barrett.

MR. BARRETT: Mr. Barrett. Excellent presentations. I have two really quick questions.

This morning, we, the Panel, we had some excellent training from the FDA about how HDEs work, but I have one clarifying question that came to mind as I listened to your presentations. To get an IDE, you have to have a hypothesis or has to be something you're testing, but from a regulatory point of view, is it absolutely required that the Sponsor conduct all of the IDE specified analyses or even meet the primary efficacy endpoint for there to be a finding of reasonable benefit? Maybe Dr. Zuckerman, or I'm not sure who.

MS. MEHTA: I'd like to defer that to Dr. Zuckerman.

DR. ZUCKERMAN: Sonna, why don't you come up to the Panel also.

MR. BARRETT: Because we did see that there were some analysis that either weren't able to be completed or weren't completed, and this is in the PMA, and so I'm just seeking some clarification there.

DR. ZUCKERMAN: Okay. And I think you know the answer to that question. Certainly it makes it much easier and effective for looking at a clinical trial if we pre-specify certain hypotheses, and at the end of the day we have the data to look at those pre-specified hypotheses, but we have a saying here that this Advisory Panel only gets the difficult applications, and these are the data, and what we're going to be doing today with the help of our Advisory Panel and our FDA questions is, given these data, have we been able to determine safety and probable benefit.

And so I'm not going to bias this Advisory Panel, but I am going to indicate that this Advisory Panel has an important mission today, and they will do their best efforts to put together the available datasets and analyses and come up with an answer.

MR. BARRETT: All right. Thank you. And that leads right into my second question, and I'm guessing I know the answer to that already, but in the conclusion of the clinical review and in the overall conclusion of the FDA presentation, there were positive statements about effectiveness. In the statistical review, there were again some things that couldn't be

completed.

My guess is you have a clinical dataset and you want to apply the best available tools and techniques and analyses for lack of a better term, a PMA-like analysis, just because that's the state of the art and that's the best way you can look at the data, but again just because the statistical analysis couldn't be completed, it didn't prevent you from concluding clinically what you concluded. So am I understanding the dynamic correctly?

DR. ZUCKERMAN: Okay. I'm going to ask Dr. Connor also during our Advisory Panel meeting this afternoon to comment on this, but as you again point out, Dr. Johnson is an expert mathematical statistician. Statistics is a branch of science that depends upon a rigorous application of mathematics specifically looking at random probability distributions and making certain conclusions, and Dr. Johnson is operating from that vantage point.

However, there is a practical reality also that these are the data, and we can make decisions that incorporate a statistical model which may or may not be flawed and still come out with a decision at the end of the day because we live in a binary world, and I think the Advisory Panel is more than capable of doing that.

Also, the statistician for Berlin Heart may want to, in their comments this afternoon before the exclusive Advisory Panel discussion, respond to some of Dr. Johnson's comments. If Dr. Naftel wants to prepare

some slides during lunch, that's perfectly acceptable.

DR. YANCY: Let's continue with our Q&A. Dr. Connor.

DR. CONNOR: Jason Connor. This will be a question for Dr. Johnson. First I have a yes or no question and then a larger question I guess.

So did I understand correctly that all the ECMO patients had treatment initiated in 2007 and before and all the EXCOR patients were March 2007 and after?

DR. JOHNSON: I think Dr. Laschinger knows, can answer that question better.

DR. LASCHINGER: I'm not 100 percent sure of the 2007 cutoff for ECMO because those patients may have been identified at the end of the study. So I'm not sure about the last enrollment date for ECMO.

DR. CONNOR: Okay.

DR. LASCHINGER: But it was patients after 2000. I know that for sure.

DR. CONNOR: Okay. Because my concern, and this is my larger question for propensity scores, is the ideas that we want to take observational data and make it like a clinical trial which, you know, if you want to compare smokers to non-smokers, we try to identify people with the exact same probability of smoking given job and drinking and how often you go to church and all this stuff, and that way we're comparing exact same

people who did and did not smoke.

So I thought I heard that the ECMO patients were actually 2007 or before. So the fact that there wouldn't be overlap, meaning there wouldn't be patients who some docs put on ECMO and some docs put EXCOR, leaving to ask the question, why was the propensity score analysis even appropriate or why were propensity score patients included before 2007?

For instance, the first question you answer is what is the probability someone gets EXCOR? Well, if you know they were 2005, that probability is zero. And so it seems like we're ignoring something we know that should go into there, and so why is this propensity score analysis actually answering the question we want to answer?

DR. JOHNSON: I think that's an excellent question. There were a lot of limitations to actually finding appropriate historical control data, and that is actually one of the limitations of this study using the ELSO registry as a stable control.

And as you mentioned, even if we, you know, I'm not exactly clear how we would use that, like, you know, time that the patient received the device even to build in the propensity score model if there's absolutely no overlap at all or, you know, it may probably even make the -- even less overlap on the distribution propensity score. I mean you already, even without the ELSO, there's a lot of -- there isn't a lot of overlap. So we know

that these two groups are very different. However, you know, we try to do what we can do, best we could do basically looking for historical control data.

DR. YANCY: Dr. Jeevanandam.

DR. JEEVANANDAM: I have a couple of comments. First of all, thrombus and pump exchange is not considered a serious adverse event. I mean it's an expensive event. It seems to be serious because it is associated with the high incidence of CVA. So I want to know why that's not considered a serious adverse event. I have other questions, but go ahead.

DR. LASCHINGER: It was just not pre-specified a serious adverse event. Once we looked at the data, we examined it more carefully, but as one of the pre-specified serious adverse events, it was not considered when the trial was designed.

DR. JEEVANANDAM: So it was not pre-specified. So it's not an event. I mean we need to consider that, I guess.

DR. LASCHINGER: Yes.

DR. JEEVANANDAM: And then my next question is, you know, you did say that you stopped this mining of data for ECMO patients in 2007. I mean since 2007, there have been newer ECMO cannulas and newer -- not cannulas, but oxygenators and pumps. For instance, there are magnetically levitated pumps now that are available. So the technology has changed with ECMO as well. So by stopping at 2007, we may not be getting the latest

technology in ECMO for comparison. Just a comment. I don't know if you can answer that one.

And then, you know, there's this concern about non-IDE sites having a worse result. I mean I think one of the things that's very important here is the aggressiveness of the transplant programs. I mean transplant is clearly rescuing these patients, you know, whether they're infected or they have CVAs, and not all programs will go ahead and transplant somebody who's had a CVA, and that may be one of the bigger differences that we're seeing in terms of non-IDE sites versus IDE sites.

And I guess my last comment is about, you know, we are looking at safety. It's safety compared to ECMO. I guess the other, you know, we're probably not going to have a super safe device because I don't think you can have a device that small with that little flow that's not going to have complications, and I guess the thing we have to kind of balance is do you have a transplanted patient who's had a stroke versus a person who's dead? And so I guess that's the thing that we need to consider.

DR. YANCY: Dr. Jeevanandam, you do bring up a good point with your first question because if thrombus observation and pump exchange is excluded from a significant adverse event and as an in -- to the calculus, it might be a reasonable question to look at a post hoc calculation that does incorporate the visualization of thrombus and pump exchange. I mean there seems to be a margin between the pre-specified 0.25 events and

the observed events, but nevertheless it would be more transparent and more clarity if that was incorporated into the calculus.

Dr. Hirshfeld.

DR. HIRSHFELD: Yeah, this is I think intended to be sort of a context setting comment for how we think about the rest of the data as we discuss it this afternoon.

I think, first of all, it's clear that all these patients who are in the protocol would die without mechanical circulatory assistance. And I think it's been pretty clear to me from the data we've heard this morning that this device allows people to be supported for longer periods of time than ECMO permits. It's also clear that this is extraordinarily complex and very resource intensive in order to maintain these children on this device.

And I think in trying to understand this, we need to take a slightly different slant on how we look at complications and outcome. I don't find this serious adverse event rate per day to be a very useful parameter to look at, and I gather this was the parameter that was agreed upon when the trial was designed, but I don't find it to be very useful.

I think what's much more important is either the occurrence at any time of an event that either requires a major response, such as surgical re-exploration, or an event that leaves the patient with a permanent injury or permanent disability. And I think in survival to the end, free of those events, is a more useful parameter to look at in terms of judging the efficacy

of this device.

And that's related also to outcome. I mean we are using as an outcome parameter survival to transplantation, but we all know that the story's not over for these children at that point, and we also know that there are children who were counted as survival to transplant who have impaired neurological function who are counted as survivors and successes but who have had impaired neurologic function.

So I think we really need to focus ultimately on what long-term quality of life is achieved for these children, and I heard some hints this morning that those data at one year are not available, that the Sponsor does not have those at this point. I'm very interested to know what fraction of these 48 children have good quality of life a year after they went on the device.

DR. YANCY: Thank you, Dr. Hirshfeld. Dr. Moon.

DR. MOON: I have a couple of issues or questions, one specifically looking at the two factors you found to be more associated with a poor result with previous ECMO and single ventricle. The previous ECMO I'm not too concerned about because that is a logical bridge in a patient that you haven't decided is really a transplant candidate quite yet.

But the other issue is a single ventricle. Were these single ventricles that had been surgically corrected? And if so, was it patients that were immediately postop that couldn't be failed from wean during surgery

and therefore had to put on the device emergently versus a patient with a single ventricle who had a slow deterioration that was developing end stage heart failure symptoms that was put on more electively? I think it probably makes a huge difference in the predicted success.

DR. YANCY: In addition to the FDA response to that question, if the Sponsor could address that question this afternoon, we'd appreciate it.

DR. LASCHINGER: Yeah, I think that's probably the better alternative because we don't have the individual patient data to be able to answer that effectively.

DR. MOON: That's what I thought. And one other thing, there was no animal data required before the study. Now that we've seen a whole bunch of thrombus in these patients in these devices, wouldn't it be logical to require some animal study postapproval in order to figure out why clots are developing in these devices at certain locations? It would be better than testing it in people.

MS. MEHTA: Is Mike John here? I think that -- I'm not sure from a Government perspective or regulatory perspective how much preclinical data we can ask in a postapproval study, but Mike John might be able to elaborate a little bit on what type of additional thrombus data we could get from an animal study.

MR. JOHN: Thanks. Mike John. I was the animal studies reviewer on this file.

So one of the difficulties with assessing thrombus, particularly in sheep studies in VADs, is that the sheep like all ruminants are notoriously difficult to anticoagulate. So it's difficult to assess what is sort of background thrombus, what might be related to the device. When we looked back at the data, we essentially came to the conclusion that there was a significant amount of clinical data already available, so much so that there weren't any additional specific biological questions that thought more testing could answer.

I think that the thrombus issue, you know, again because these devices are all going to be explanted at some point, could be assessed grossly at explant and probably would not be useful to be tested in additional animals.

DR. MOON: One last quick thing is in the presentation this morning, it was suggested I think 86, 87 percent of the explanted devices had no clot in them at all when they were inspected. So I'm wondering whether those devices were explanted inappropriately maybe, and who determined whether there was really a clot that required an explant?

MS. MEHTA: So I think that the ones that had observed thrombus were explanted from patients who were ultimately transplanted. I think one of the things that Veronica, Dr. Sansing brought up for the postapproval study was possibly looking at explanted pumps in patients who did experience thrombus.

DR. YANCY: Dr. Connor has a follow-up question.

DR. CONNOR: Yeah, I have a comment to Dr. Moon --

DR. ZUCKERMAN: Before get to that question, I think that Dr. Laschinger had some important additional questions --

DR. LASCHINGER: I'm sorry.

DR. ZUCKERMAN: -- a key question asked by Dr. Moon.

DR. LASCHINGER: Yeah, we thought that was a key question also and asked the Sponsor to elaborate on the data they presented, and from their response, we gathered that most of the explanted devices that were examined were those that were removed from transplanted patients.

Also the way that the devices were handled once they were explanted were that they were washed out and intra-pump thrombus was hopefully collected in a gauze for I guess weighing and measurement and things like that. So I'm not sure that we're precise. The Sponsor will have to comment on how precise their measurements were and how precise their efforts were as far as examining pumps that were replaced for thrombus.

DR. YANCY: Dr. Patel, did you need to comment?

DR. PATEL: Sonna Patel-Raman. I'm Team Leader for VADs at FDA.

Just in response to your question about the additional animal testing, something that we have considered is adding at explant a formalized or protocolized explant analysis in the postapproval study as part of the

device evaluation.

DR. YANCY: Dr. Connor had a follow-up question.

DR. CONNOR: Just a comment to Dr. Moon. I think, and I couldn't find the slide here from the Sponsor, but it didn't say there was no clot. It said no significant clot because I remember thinking at the time what is the definition of significant? So it doesn't mean there's none at all, I think.

DR. YANCY: Let me have our Patient Representative, Dr. Posner, speak.

DR. POSNER: Yes, thank you. I have a relatively naive question. I know we're dealing with the pump and the catheters for the pump, but is there any consideration of an outflow thrombus filter since so much problem seems to be focusing on stroke and CVA?

And then the other question is, I haven't heard anybody talk about hemolysis problems, which used to be the problem with almost every pump. So those are my two questions, one about filtering and one about hemolysis.

DR. LASCHINGER: From the hemolysis, the data submitted do not suggest there was any significant hemolysis problem.

For the filtering, when you have small pumps that have relatively small flows, any kind of filter would add an additional afterload to that that would prevent effective function of the pump in certain circumstances. So overall I think the risk of that would greatly outweigh the

benefits and might actually make the pumps not effective, although the Sponsor can comment on that more directly this afternoon.

DR. POSNER: Because you've got the pre-pump filter --

DR. LASCHINGER: Yeah, same comment about pre- and post-pump filters, yes.

DR. YANCY: Dr. Somberg.

DR. SOMBERG: Thank you. The FDA review is most helpful, and I'm glad they were insightful to put together the entire experience, not just the IDE, which is an important aspect.

With that said, on page 18, you talked of the total mortality of failed weans and all, about 25 percent which is a significant number, but we don't have anything to really put that in context. Can you or have you done any work to look at the registry that was used to compare the ECMO data and to say what is the overall mortality there so we have some comparator in some way? Because the IDE has a comparator. This has just a statement and, in fact, some of these subsequent statements are quite concerning as well about the overall outcomes, but how can we put that in some context? Have you given that any thought?

DR. LASCHINGER: You're asking about the overall mortality in ELSO registry patients. Is that -- am I understanding?

DR. SOMBERG: Yes.

DR. LASCHINGER: Okay.

DR. SOMBERG: And the overall failure rate and things of that nature. So we have some sort of context.

DR. LASCHINGER: Yeah, I don't have the data in front of me, but from looking over data from the ELSO registry, I think the overall mortality for all comers is going to be in a range of 50 percent, but that includes people that are put on there for non-cardiac indications and other things. So I don't have a fast and hard number for cardiac indication ECMO from the ELSO registry.

DR. SOMBERG: So if you were trying to make a comparator like they did for the IDE study, you would try to go back to the registry and exclude those people. So out of the 700, maybe you'd reduce it to 600 or 500 or something like that, maybe not to try to do a paired match, but to do something. Did you try to do anything like that and try to say, well, you know, overall we have an adversity of mortality of 25 percent. What would that be comparable in a similar population in the registry and for ECMO?

DR. SANSING: Yeah, that's a good question, but FDA has not reviewed that data. Perhaps the Sponsor may answer that better.

DR. YANCY: Dr. Nykanen.

DR. NYKANEN: I just have one question. I echo Dr. Hirshfeld's comments on the complexity of these patients and the complex systems that need to be in place to look after them.

We've talked a little about the so-called learning curve. Was

there any evidence in the data that was presented from the cohorts that there indeed was a learning curve? Because presumably these organizations and the study sites had these systems in place prior to the heading in. So is the data able to discern whether there's a learning curve or not given the relatively small number of patients?

DR. SANSING: For the premarket study, you noticed that there was a difference between survival, between Cohort 3. Cohort 3 was the patients who did not meet all the inclusion and exclusion criteria, and therefore these are -- this is the cohort that most represents possible defaults in patient selection. That was one indication, that there may be a learning curve indicated with patient selection.

The second hint was that the non-IDE sites had performance that was less than those of the IDE sites. That's an indication that there may be a potential learning curve associated with the implant and explant of the device, and these are all concerted potential.

Therefore, within the postapproval study, we are proposing that there be two forms of a potential learning curve, indications for patient selection as indicated by Cohort 3 and then implant/explant as indicated by the non-IDE sites.

DR. YANCY: Dr. Hopkins.

DR. HOPKINS: Thank you. I'd also like to compliment both FDA staff and the Sponsor for a set of very clear presentations, and the

solution to some potentially, what I would have thought 10 years ago would have been almost insurmountable problems in design.

My question is a clarification problem, a clarification question for the Panel, probably Dr. Laschinger. John, you can probably answer this.

We're being tasked specifically to think about the transition to the real world, which every one of these Panels I've been on for 20 years has been asked to contemplate. The universe of that world is at least initially going to be limited to pediatric transplant centers. How many of those are there in North America? And what is the median in range of transplants being done per year by those centers so that we can at least contextualize what the universe of the real world will be?

DR. LASCHINGER: I'm not sure --

DR. HOPKINS: If you can respond to that.

DR. LASCHINGER: I think Chuck actually presented those numbers in his presentation, Dr. Fraser, and so other than those numbers, I don't have those numbers in front of me right now.

DR. HOPKINS: Is Dr. Fraser still here? Yeah. Do you know those numbers offhand?

DR. FRASER: (Off microphone)

DR. HOPKINS: The number of pediatric transplant centers and the average number of cases that they do.

DR. FRASER: (Off microphone.)

DR. HOPKINS: Okay. So this is a potential question for the Sponsor. Maybe the Sponsor could give us that number after lunch because that really defines the universe.

DR. YANCY: Well, we did see in the opening presentation by the company representative approximately 300 pediatric transplants being done per year. What the denominator is for that in terms of number of centers, I don't know that information.

DR. HOPKINS: But my question is in context, Dr. Yancy, with the learning curve. I mean if we're talking about 25 centers, that's one thing. If we're talking, you know, when you talk about stents and valves, you're talking about hundreds or even thousands of learning curves. So there is a context there that at least is useful to me.

DR. YANCY: It's a very important question because again when you look at the compassionate use and emergency use data, you see very different outcomes.

DR. HOPKINS: Correct.

DR. YANCY: Dr. --

MS. MEHTA: I'm sorry. The Sponsor is estimating about 50 centers.

DR. YANCY: Dr. Kato.

DR. KATO: I don't know if this is helpful or not, but there was a study published in the *Pediatric Cardiac Surgery Annual*, a single center

study in Berlin on the Berlin Heart, and it was a 15-year experience, and they only had 68 cases. So that's, you know, roughly 4 cases a year for 15 years.

DR. HOPKINS: My current recollection is that the average transplant program does about six or seven transplants a year. So it's an important context.

DR. YANCY: It is 11:45. So I'd like to take just a few burning questions so that we can have time to gather our thoughts at lunch and check out. So I think Dr. White's hand was first and then Dr. Augustine and Dr. Lange.

DR. WHITE: Just very quickly, I think Dr. Hirshfeld made some interesting comments about the fact that these are patients that we are presumptively expecting to die. It's we do this or they're going to be dead, and I'm not sure that that's absolutely true. And I think one of the problems we have when we're looking at the difference between ECMO and the difference between the use of this device is that when we use ECMO, almost always, I would propose to you, it is an emergent situation. The patient we know is going to die. We put it off until the very last second, and very frequently we are putting very critically ill children on ECMO.

When one looks at using a device, one is looking at a critically ill child who we expect to die at some point but we also are at fear of waiting too long and having a child that we can't rescue by putting the device in. And the difficulty in looking at the two sets of data may lie in our

intent to treat and the way we approach the two patients before we make that selection.

So I would propose that a lot of what we need to do in our considerations is to look at the data alone for the devices, which is would you feel that a 31 out of 3 -- chance of survival for your child despite a 30 percent chance of bad neurological outcomes, et cetera, et cetera, et cetera, is that acceptable for this device considering it's the only one?

So the analysis has been excellent. The data that's been presented has been excellent. It's been presented in a very clear fashion, but I'm not sure that we can still make that comparison in a reasonable way.

So the data for the device probably needs to stand alone, and we need to consider it in the context of this is a device, presumptively you're going to die if you don't use it, and are we willing to accept this level of serious adverse events, whatever poor outcomes, whatever measure you choose, in this context? Thank you for the time.

DR. YANCY: And so we'll have a chance to deliberate this in the afternoon, but the other important proviso here is under the definition of the HDE. And so if we accept that the bar is probable benefit and reasonable safety in the context of the clinical scenario, that frames the discussions that we need to have later on today, but thank you for your point, Dr. White. Dr. Augustine.

DR. AUGUSTINE: Another learning curve question, and I'm

wondering if there are analyses available that take a look, not so much at IDE versus non-IDE in terms of differential performance, but number of patients enrolled in terms of high enrollers versus low enrollers. I look at the study site enrollment, and there are some Cohort 1 and 2 sites that have 13 subjects, but there are others that just have 1. So is there evidence when all inclusion of criteria are adhered to? Is there still some differential performance by number enrolled? And does this get to an experience kind of issue versus something intrinsic to being an IDE site in terms of adherence to protocol or other factors that might be considered?

DR. LASCHINGER: That data is in particular very hard to do because a lot of the centers had one or two implants, and so if you compare somebody who had one implant that died versus a center that had, you know, six or seven and, you know, five of whom lived, it's not a very fruitful comparison. So we were curious about that, too, but I don't think there's any real way to get at that.

DR. ZUCKERMAN: Okay. But maybe we can ask the Sponsor during lunch to try to group it into a few buckets and see what they can show us after lunch. Is that understood, Dr. Naftel, what we're asking for?

DR. AUGUSTINE: And also if you could include even a simple average number of patients enrolled for an IDE site versus non-IDE.

DR. LASCHINGER: Yeah. In particular, there were four centers that implanted most of the devices. So if we look at those four centers

versus everybody else, that might be the most helpful.

DR. YANCY: And you did share with us data that demonstrated that there wasn't a difference between IDE versus non-IDE whereas the larger difference was compassionate use or emergency use.

Dr. Lange.

DR. LANGE: Just two things I'd like the Sponsor to clarify over lunch. One is, I'm still confused about the 87 percent didn't have clot. There were 114 devices in that study and 48 patients. So if they didn't have clots, I'm not sure why they're being -- the whole thing's just confusing. So if we could clarify that, that would be great.

And the other thing that would be helpful with regard to anticoagulation is rather than saying the average INR was 2.7, what I'm interested in is what percentage of the time were the people subtherapeutic or supratherapeutic, and does that relate to the incidence of bleeding and/or thrombotic complications?

So if we could do that, it would be great.

DR. YANCY: Very quickly, Dr. Nykanen.

DR. NYKANEN: Just one quick question maybe for the Sponsor, is if I could have some indication as well as to during the IDE, how many patients or a sense of how many patients you felt would have been screen failures? In other words, you're thinking about putting them on, but for some reason or another they didn't meet inclusion criteria. I didn't see any

numbers with respect to how many patients were turned down because of exclusion criteria.

DR. YANCY: Let me bring this question and answer period to a close and thank the FDA again for great clarity.

I think this morning we have covered some significant ground, and I would like to once again thank the Sponsor and the FDA for their clarity.

Before the Sponsor disbands, I'd like to just summarize the questions that that Panel would like for you to address as we reengage with you this afternoon. This is in no order of priority but just the way they've been captured.

We'd like to know more about the patients who had single ventricle support and their characteristics.

We'd like your perspectives at least on why there were differential outcomes, and if you have descriptors of why there were differential outcomes for those that received a device either for compassionate use or emergency use.

If there could be some additional calculation of the significant adverse events expressed as per patient.

If we could have some description recording time to stroke event, that would be helpful.

If you've got any data at all regarding longer-term follow-up to

address a concern that a Panel member raised.

Regarding thrombus, we raised questions about your definition of thrombus since it didn't appear to be an absolute definition. We'd like to know precisely what were the number of devices that were truly clot free.

And then the last question regarding the adequacy of anticoagulation, and then finally a question regarding the outcomes in centers that were more experienced versus less experienced.

Overall, I think we've captured some important themes today. We're dealing with a critically ill population, not just of patients, but of children. We are dealing with a device for which there really is very little alternative. We recognize we have a very compromised comparator, wouldn't even call it a control group. We have a registry that intended to just capture the events during the implantation of ECMO, and so that gives us some difficulty. And then we are trying to put in context a different cohort with small numbers. This is buffeted against a threshold of probable benefit and reasonable safety. So those are the things that we'll need to seek clarity on this afternoon.

We will reengage at 1:00, and I thank everyone for respecting the time and having such focus and interest. Thank you.

(Whereupon, at 11:55 a.m., a luncheon recess was taken.)

AFTERNOON SESSION

(1:00 p.m.)

DR. YANCY: I'd like to resume the meeting. It's now 1:00 p.m., and we need to come to order. If I can have the Panel members reconvene around the table. FDA is present. Hopefully the Sponsor is present with responses to some of the inquiries. Thank you. Thank you.

I would like to resume this Panel meeting. We will now proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda.

Mr. Swink, our Designated Federal Officer, will now read the Open Public Hearing disclosure process statement.

MR. SWINK: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency 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 relationships 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 this meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. Thank you.

DR. YANCY: Thank you, Mr. Swink.

We have had four requests to speak. We ask that each of you speak clearly into the microphone, which will allow the transcriptionist to provide accurate recordings of this meeting. Again, you'll need to identify yourself and give us any sense of affiliation you might have. Please also respect our time situation and keep your comments relatively brief and straightforward.

We have five speakers, four that were pre-approved and one that has presented today.

The first speaker is actually a group of two, Mrs. Angie McGraw and Bailey Hunsberger.

MS. MCGRAW: We have no financial relationships.

MS. HUNSBERGER: Hi, my name is Bailey Hunsberger, and this is my mom, Angie McGraw. We're from Indianapolis, Indiana. I'm 19 years old and a sophomore at Indiana University.

I was implanted with the Berlin Heart EXCOR Pediatric device in 2005. In the year before, when I was 12 years old, my heart began to fail

because of scar tissue that prevented the normal growth of my left ventricle. My heart failure was very severe, and I was rapidly deteriorating. I would mostly likely not have been able to survive the time it could have taken for me to be transplanted, and because of the condition of my lungs at the time, I not only needed a heart transplant, but I needed new lungs as well.

There was a small window of time that was available for me to be transplanted, which led my healthcare team to decide with the use of a machine to aid my heart would be the best option for me to have a chance not only at transplant but survival.

I was very small for my age. I was 12, yet my physical appearance would lead any person to believe that I was actually 7 or 8 years old. Because of my small stature, the adult size devices here were out of the question, which left nothing available to me in the United States.

This meant that my doctors would need to go across the Atlantic to a company in Germany called Berlin Heart that was building child-size assist devices. This company offered hope that I would be given a chance at life. The doctors at Riley Hospital were granted permission for compassionate use by the FDA and started working to have the machine brought over from Germany.

They succeeded, and I was implanted on January 31, 2005. The urgency and necessity for the device was proven to be overwhelming, evidenced by the turn for the worse that my health was taking.

In the 30 days between the decision to use the Berlin Heart and the actual implantation, I gained one-third of my body weight in fluid due to my severe heart failure.

I was implanted with the Berlin Heart, and within the first month, all my extra fluid was gone, and it lowered the pressures in my lungs making it possible for me not only to be transplanted but to need only a new heart. I was on the Berlin Heart for about six months, living at the hospital, waiting for a heart to become available. My doctors routinely ran tests to make sure that I was functioning well with the device, taking measurements, and studying how my body was reacting to it.

During the months of June and July, the tests became more frequent until one day at the beginning of July, the doctors came into my room to tell us what they had found. What they told us, they never expected to say, and we most certainly never expected to hear. My heart function had increased during the time on the Berlin Heart to a level that surpassed everyone's expectations. The doctors told us that the risk of a transplant would be higher than the risk of being explanted and keeping my own heart.

I was taken off the Berlin Heart on July 18, 2005, and was sent home a week later with my own heart.

Being told at the time that all of this occurred, I didn't understand the significance of what had happened, and I wasn't sure what it

meant to be on this device called the Berlin Heart, but what I did know was that after living my whole life with heart problems and being barely able to function in the year before the implantation, the Berlin Heart made me feel better than I had felt in a very long time.

MS. MCGRAW: Bailey was born in aortic stenosis. Her defect was so severe that she wasn't expected to live past infancy. By the time she was 12, she had already undergone two open heart surgeries both on the leading edge of medicine.

When her medical team met with us and told us about her urgent need for a VAD, I remember being stunned and confused. It was difficult to process that there wasn't a VAD available here to help Bailey. We make them for adults, just not for kids. With lots of prayer, and a little time on our side, Bailey was able to give her medical team the 30 days they need to complete the legal and logistical process of getting approval to use the device and to have it shipped to Indianapolis from Germany.

To this day, I can't keep myself from thinking about those babies and young children who don't have the luxury of time to allow the process to be completed. There is a need for a child-size assistant device here in the United States.

When Bailey was on the EXCOR, she felt great. We took walks all over the hospital. She made birdhouses, Shrinky Dinks jewelry, and even sold her jewelry to poor unsuspecting hospital staff. She kept up with her

studies and never fell behind in school. She has since received her driver's license, graduated high school with her peers, has a summer job at a local retail store, and she and I both crew for a hot air balloon pilot who raises money for sick kids.

Not only did the Berlin Heart save Bailey's own heart, her own lungs, and her life and kept our family together, it has also given the medical world valuable opportunities to study the path of a rare survivor of a severe congenital heart defect.

Thank you very much for your time, and we truly appreciate what you're doing today.

DR. YANCY: Thank you very much. Bailey, we are delighted that you had such a good outcome. It takes a lot of courage to come in front of a bunch of strange, mean people and tell your story. So thank you for being here and, Angie, most of us are parents, and we understand your emotions. So thank you for coming forward.

MS. HUNSBERGER: Thank you.

MS. MCGRAW: Thank you.

DR. YANCY: The next public speaker will be Joe Basta, and I think Tim will accompany you. Yes.

MR. BASTA: Good afternoon. I'm Joe Basta and this is my son, Tim. We wish we could have our daughter here today, but she's at the hospital right now. She's pretty feisty. She wanted to come here. I asked

her if I could tape her to show the group, but she was mad. She said, no, I wanted to go down there myself. So Tim and I are representing our family today.

We're here today to share our ongoing experience with the Berlin Heart VAD. Timmy wanted to come with me today as he knows how important this device is for his sister, Josephine. Josie is currently -- excuse me. Josie is currently a patient at A. I. duPont Hospital in Wilmington, Delaware. She's quickly approaching 10 months in the cardiac ICU, 9 1/2 with the support of the Berlin Heart device. This is really a good story. I'm sorry if it's just a little emotional.

We're patiently awaiting for the perfect donor heart to become available so Josie can come home and we can be a family of four again living under one roof. Can you pass that picture of Josie around to the committee?

Timmy's going to pass around, or you could pass around please the picture of our daughter, Josie. This is on her first day of school in September of last year. Josie was a very typical, healthy, happy seven-year-old girl and was in school in first grade for about a month until she fell ill on the 2nd of October to what my wife and I thought was your standard, run-of-the mill GI bug. Within the next two days, she went from the emergency room, I'm sorry, in Chester County Hospital onto A. I. duPont Children's Hospital being diagnosed with heart failure.

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We were told that her condition was most likely caused by a virus, but none was ever identified really.

Josie was a fighter through her first week at duPont but her heart continued to weaken and she required more supportive measures. Her worst night came when she awoke from a deep sleep when she looked at her mom in horror, she took a deep gasp, and immediately coded. Miraculously, again, this is a good story, she was resuscitated twice that evening, one with regular CPR and one with a defibrillator. During the following week, her precious heart weakened further. We were told by physicians that the heart was very sick, and she needed to be listed for a heart transplant.

The words transplant, very sick heart, and Josie all in the same sentence just were beyond any nightmare for my wife, Marjorie, and I.

In the meantime, Josie required greater aid to bide her necessary time until this gift of a heart arrived. Her surgeon, Dr. Christian Pizarro, recommended that Josie receive the Berlin Heart as a bridge to transplant. Marjorie and I are typically very methodical people and we take a lot of time in making any decision, but we quickly signed that seven-page authorization as tears streamed down our faces.

We were told that this device was not FDA approved and required goodwill approval before we could proceed. To this day, this still shocks us every time we look at this amazing device that's sustained Josie's

precious life for almost 10 months now.

As Josie awaited for approval and receipt of all the Berlin Heart's components, her condition unfortunately worsened. Her organs began to show signs of failure and her blood pressure became unstable. A decision was made to place her on an ECMO device for life support as Berlin Heart had not yet arrived in time. To make matters worse, weather-related storms delayed the final receipt of all components required for the Berlin VAD.

Josie underwent surgical placement of the Berlin Heart on the evening of October 14th. Thankfully all went well and Josie's vital signs stabilized. Her heart rate, blood pressure, and respiration slowly began to improve. Doctors were now able to register a pulse in her legs that was not present only days earlier.

We couldn't be more grateful to Dr. Pizarro, his team, and this amazing heart machine that Josie has affectionately called her helper heart.

In the nine months following Josie's Berlin Heart operation, the following fantastic progress has occurred. Josie was brought out of her medical coma. She's regained her ability to speak. She's regained her ability to walk. In fact, we've been keeping track of how far Josie has walked with her Berlin cart, and just to let you know, I'm a mathematician, so I like measurements, one loop around our CICU is about 20th of a mile. Josie has recently passed the 26.2 marathon mile mark walking with her Berlin cart,

that is 524 loops, and I know she put in 5 more yesterday.

She's increased her weight since being admitted. She was pretty weak and light when she went in. She even lost more weight prior to the Berlin Heart, but she was admitted at 40 pounds, and since that time, she's up to 62 pounds, and she's also grown 2 inches during this time.

Another milestone is that we've had several heart offers in the last two months, but when our surgeon went out to look at the hearts, we found they were not of the quality that Josie needs.

So our Berlin Heart has also given Josie the chance to wait for that perfect heart for her, the best one that's out there to give her the best chance for her future.

Some other noteworthy milestones, while in the hospital, included an outside visit from her dog, Tara, that she misses so much, and a pie-throwing contest as Timmy's going to pass that around and show you a picture of that. It was a fair that went on at the duPont Hospital. As those of you can see, she hit me pretty well in the face with that pie, something I would have never expected or let her do unless she was in the hospital.

She also celebrated her eighth birthday last month with five of her best friends and her brother, Tim. Tim, if you want to pass this picture around. That picture was taken of Josie on her birthday with Timmy and Josie walking around hand-in-hand in the CICU, and that's probably another thing that doesn't happen very often between brother and sister, holding

hands and smiling together. She looks great, doesn't she? She's pretty happy that day being with her brother.

To say the least, Josie's not only survived, but she's thrived with her Berlin Heart. Words cannot express our gratitude. We live in era of great advancements in heart surgery and technology, and thank God that Josie is the recipient and proof of this.

From the pictures I've shown you and the stories I've shared, I hope you've seen that our baby girl is one spunky fighter. I'm positive she's alive today due to the assistance of this lifesaving Berlin Heart VAD and the excellent care of our doctors and nurses at A. I. duPont Children's Hospital.

As with all medicines and devices, we know there are risks and side effects. In our eyes, the advantages of the Berlin Heart far outweigh the risks. All children and parents should have a second chance at life available to them.

I came here today to share Josie's story with you not only because I know the Berlin Heart has saved her life, but it's also because I want this to save countless lives of other children. It has given Josie the best chance of survival until her new donor heart arrives, and it will. I'd love to see this VAD readily available on the shelf of every children's hospital in the United States so that valuable time is not lost in saving their lives.

We lived the ticking clock scare of our lifetime. We'd love to see this obstacle removed from this gut-wrenching experience.

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Please consider our wonderful success story in your decision today. Thank you for listening to our story and giving us a chance to talk.

DR. YANCY: Mr. Basta, thank you for bringing forward your story, and we really do hope that Josie proceeds and does very well. Maybe one day she can actually run the marathon. That would be a great way to get this resolved.

We have another speaker, Gil Wernovsky.

DR. WERNOVSKY: Good afternoon. Thank you very much for the opportunity to present to the Panel. I'm actually here as a member of the public, although I am a pediatric cardiologist, and I work in cardiac intensive care.

I do have to give you just a few disclosures, and I hope you don't mind, I did bring a few slides to make my points. I don't have any financial conflicts of interest. I need to be very clear that I've not been involved in this study nor in the study in any way. I just work at an institution, and I've used this device for many years now. All the photos that I'll show you are with parental consent.

I'm clearly biased. I've worked at two large children's hospitals, one in Boston and the Children's Hospital in Philadelphia for the past 16 1/2 years as a cardiac intensivist.

What I deal with is critically ill children with heart disease, and my research interest is in long-term school performance and long-term

outcomes. I've been particularly interested in the neurologic effects of cardiopulmonary bypass as well as extracorporeal circulation. I'm certainly available to answer any questions that the committee might have. And I've been the director of the cardiac ICU and now run the neurocardiac program. So I hope that my insights are helpful to the Panel in this regard.

My patient population is skewed toward the stories you've just heard, which is two young children that are critically ill. If you look at our 26-bed ICU, it's very similar to the units around the country. This is the age distribution that you can see here, and the overwhelming majority have no mechanical support options with the limitations except for ECMO.

These babies are critically ill. They have many difficulties. If they need extracorporeal circulation, this is what they look like. They're on these tubes and wires and they have multiple suture lines that can be bleeding.

The mechanical support of the failing circulation in children in the short term can be used for a variety of reasons, such as following CPR and fulminant myocarditis, but as a bridge to transplantation or destination therapy, ECMO is just not a solution.

Many of you have heard this term, babies are not small adults. These are kids right next to each other in our unit.

So this is just not an option. This is what ECMO has -- I think many people think ECMO looks like. That's a baby on respiratory ECMO.

They're not even connected to a ventilator. But this is what our patients look like, and the complications of extracorporeal support as used with ECMO increase exponentially beyond about one to two weeks of its use.

The complications from ECMO include bleeding, renal failure, stroke, and brain death, and that's what we have as a basis of comparison for these children that need extracorporeal support. It's an inadequate solution.

I'll start with the story of a little girl named Rose who passed away recently, a patient I followed for 10 years who went into fulminant heart failure and died waiting for a Berlin VAD to become available.

The problems we have waiting for transplantation is the waiting time, the malnutrition, the physical condition, and renal dysfunction. The Berlin Heart obviates many of those situations. It's a necessary component in our intensive care units for comprehensive therapy of heart disease. It is an unmet need. I can't imagine working in our ICU taking care of babies with heart failure without this device.

Its efficacy in my opinion has been proven, and its safety, although it does have its issues, is significantly better compared to any alternative that's around.

In terms of bleeding, it's far superior to ECMO, and although there's no trials that go head-to-head in terms of the risk of stroke or other central nervous system abnormalities, it is certainly superior to ECMO or the

natural history for many of these babies which is death. And importantly, it allows nutritional and physical rehabilitation during the wait.

This is a little boy named Zion. I was going to bring him with us, but he was too busy playing with his friends. This is how it started. He tended to put his macaroni and cheese on the Berlin Heart device. It was a little bit difficult for us to sometimes get to the settings. He was originally resuscitated and went on ECMO and then was implanted with the Berlin Heart. I have a couple of videos to show you of him walking around with the Berlin Heart and cleaning all the nurses' stethoscopes. It's an amazing way to rehabilitate these babies before they get their heart transplant.

And I'll close with Sarah. Sarah lives about 20 miles from here and was in our hospital about seven months waiting a heart transplantation. This is the day that she finally got her offer, and she had been on the Berlin Heart for about six months. She was going to join us today. She really tells a wonderful, wonderful story, but unfortunately the committee had booked this during their annual vacation, and she's now out on this boat.

So I'll summarize, and I'll be happy to answer any questions you might have, but this is an essential device. I cannot see, as I mentioned before, running a cardiac intensive care unit without this device for young children. It's the only mechanical support system we can use for these kids. It has extensive experience now throughout the country and throughout the world and importantly allows rehabilitation like the stories you've heard

today. It allows the kids to survive.

I also am a father. I can't imagine what this would be like for the families that come here. So thank you very much for your time.

DR. YANCY: Thank you very much. We appreciate it, Dr. Wernovsky.

We have one more scheduled speaker, Henry Walters; Children's Hospital in Michigan I think is your attribution.

DR. WALTERS: Distinguished members of the Panel, thank you for the opportunity to speak. My name is Henry Walters. I'm Chief of Cardiovascular Surgery at Children's Hospital of Michigan in Detroit, Michigan. I'm here on my own volition to speak in favor of approval of the Berlin Heart EXCOR Pediatric Ventricular Assist Device. I have no disclosures. I've received no compensation from Berlin Heart. Children's Hospital of Michigan has paid for all my travel-related expenses to this meeting.

Children's Hospital was one of the non-IDE sites that used Berlin Heart EXCOR Pediatric VAD under the compassionate use regulations. So perhaps some of our data might be of interest to you.

This represents our entire experience, the good and the bad, and it's not protocol driven. I've excluded no patients.

Occasionally there are times when medical therapy fails to maintain a stable hemodynamic state, and mechanical stabilization is required. At Children's Hospital of Michigan, we've been faced with this

situation 18 times in the last 12 years, since the inception of our pediatric cardiac transplant program, during which time we've performed 87 pediatric cardiac transplants.

Before the availability of the Berlin Heart, we were forced on four occasions to adapt an adult ventricular assist device to our pediatric patients. We struggled with this. Trying to adapt an adult device to an adolescent, to a young teenage cardiac patient, and in at least one of these four cases, we realized the death related to the size mismatch between the adult pump and the pediatric recipient.

Also because of the lack of pediatric size pumps and cannulae, we were totally unable to apply this adult ventricular assist device to any of our infants or neonates. We simply did not have a ventricular assist device for these, our smallest patients. We needed a device that was designed for and not adapted to the pediatric population.

The availability of the Berlin Heart was a welcome and much anticipated step forward in the treatment of our pediatric patients with intractable heart failure because of its unique advantage of being developed and designed to serve the pediatric population.

Since its availability to us in September of 2005, we've inserted 14. These 14 patients had nowhere to go. Cardiac transplantation was their only chance for survival, and none of them were stable enough to wait for a donor heart on medical therapy. The severity of their cardiac illness of these

14 patients is underscored by the fact that we were forced to place 11 of them on ECMO support as a prelude to inserting the Berlin Heart because of an acute and profound deterioration in their clinical condition before the Berlin Heart could be inserted.

ECMO, though originally designed for mechanical pulmonary and cardiac support in children, is at best only a very short-term solution. It is a poor bridge to cardiac transplantation because the patient must remain heavily sedated and intubated, and after one or two weeks, the complication rate progressively becomes prohibitive.

The Berlin Heart is the only true pediatric ventricular assist device available in the United States. Ten of our 14 patients survived cardiac transplantation, and nine of these are alive and thriving today, a result directly attributable to the efficacy of the Berlin Heart.

Now, these nine survivors ranged from 6 months to 13 years of age, with a mean age of 4.4 years when the Berlin Heart was inserted. Those are the survivors.

The five patients who did not survive in contrast were much younger. They ranged in age from 1.2 months to 6 months with a mean age of 3.5 months, and two of them required biventricular support.

In our experience so far, it's this neonatal age group and the need for biventricular support who are our highest risk group. The hospital stay of our survivors after insertion of the Berlin Heart range from 23 to 137

days. This could, depending on one's perspective, be considered relatively short given the severity of the cardiac illness, the associated co-morbidities, the unpredictable time in hospital waiting for a suitable donor heart, and the incredible complexity of these cases.

Once a donor heart was implanted though, the ventricular assist device was removed and the mean hospital stay was only 27 days.

We follow all of our patients frequently and very closely at our own institution, and the quality of life of our nine survivors have been unequivocally excellent.

None of our total of 14 patients experienced a wound infection or mediastinitis. We did require re-exploration for bleeding in three patients. This complication was clustered in our earliest experience and has not plagued us for the last 10 implants.

We've changed the pump five times in five patients because of the development of deposits around the valve leaflet commissures, and as we've gained experience and confidence in using the Berlin Heart, we've lowered our threshold for performing pump changes because it's a quick, technically easy procedure that may reduce the incidence of strokes.

Of our nine survivors, two patients experienced embolic strokes while on the Berlin Heart. Both of these patients, after cardiac transplantation, have recovered complete function without any neurological sequelae.

But of the five patients who died in our series, one death indeed was attributable primarily to an embolic stroke and one to a hemorrhagic stroke. In the remaining three patients who died, one probably died of an inborn error of metabolism, not fully recognized at the time of the Berlin Heart insertion. One neonate on biventricular support died of sepsis with multiorgan failure related to her underlying condition, and the final patient died primarily of donor heart dysfunction after transplantation.

Our experience with the Berlin Heart has been unequivocally favorable. As our experience has grown, we've become confident with the techniques of insertion because the components are sized to accommodate pediatric patients. They're well designed, and they yield consistent surgical results. With each new insertion, we now have a reasonable expectation of a successful outcome even in the sickest patients.

The Berlin Heart representatives have been responsive to our requests for product, for support. The corporate investment in terms of on-site personnel, postoperative follow-up, and assistance in the management of clinical issues such as anticoagulation has been consistently detail-oriented and superb.

The Berlin Heart stands alone in filling a tremendous void in the field of pediatric cardiac failure. I can honestly say that of our nine survivors, eight were too small to have possibly accommodated any of the available adult ventricular assist devices, and therefore for these patients,

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the Berlin Heart was truly the key for their survival.

Finally, for those babies in our series who for some reason did not survive, the Berlin Heart at least offered a reasonable hope for survival for which I believe their parents were uniformly and extremely grateful.

Thank you very much.

DR. YANCY: Thank you, Dr. Walters.

Is there anyone else in the audience who would like to come forward during this public comment period? Yes.

MR. SMITH: My name is Rich Smith. I'm the Director of the Artificial Heart Program in Tucson, Arizona, and I've been dealing with devices for 25 years. My surgeon is Dr. Copeland, and we have a tremendous amount of experience with all different types of devices with kids.

One of the areas that we haven't really talked about is recovery here, and we were the first ones to bring in the Berlin in 2000, and over that 10-year period of time, we learned to look for recovery, and we just published a paper recently in *ASAIO* that says up to 70 percent of these patients that are under three years old, we can expect recovery, and we've followed some of these patients up now 10 years.

So I think one of the things that's key is once Berlin I believe is in the closet ready to use, that the key is unloading the left ventricle. And so having this device in the closet even for bridge to transplant, I think we will

develop techniques to look for recovery which is even better than going to transplant in these types of cases.

Thank you.

DR. YANCY: Thank you, Rich. I appreciate your perspectives.

Is there anyone else who is here this afternoon who would like to speak during this Open Public comment session?

Hearing no response, I will now pronounce that the Open Public Hearing is officially closed, and we will proceed forward with the rest of today's agenda.

Before proceeding forward, I really want to again speak to all of those who came forward, the physicians, the Basta family, Bailey, Angie, it takes a lot to do this, but it really helps us to hear your perspectives. So thank you for having taken the time to do this.

We will now begin the Panel deliberations. Although this portion remains 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 requested to speak will identify themselves each time they happen to speak as this will help the transcriptionist identify the speakers and capture the comments correctly.

Before we interrupted our day for lunch, we articulated seven areas of query that we wanted the Sponsor to address plus other areas that

you thought would be helpful to answer some of the concerns and curiosities expressed by the Panel. Is the Sponsor prepared to respond to the questions and concerns from earlier this morning?

Thank you for coming forward. Let me review how we'd like to do this. It is 1:35, and we need to get through sufficient time for you to respond to the questions and have more Q&A with the Panel, but I would like to see this part of the discussion curtailed at approximately 3:00 p.m. So we have a fair amount of time to listen to the responses and engage in more queries which will allow us then after a short afternoon break to go forward with the FDA questions.

So with that having been said, I'll let the Sponsor begin. Do I need to rearticulate those seven areas or do you have them?

DR. FRASER: I think we have them, Mr. Chairman. This is Charles Fraser from Houston, and if it's agreeable, we'll just go down the list and --

DR. YANCY: Please.

DR. FRASER: Yep. So first we would like to call on Dr. David Naftel to speak to the propensity analysis and various other statistical issues that were raised.

DR. NAFTEL: Thank you. So I am David Naftel.

So first of all, I'd like to say that we really appreciate the excellent statistical review from Dr. Johnson. A lot of really good points, and

we paid attention and took notes, and I'd like to say upfront that we essentially agree with everything that she said and presented. There are a few areas where we have small quibbles, but I think the important thing is that whether we look at it our way or her way, that the differences are very small, and none of them lead to any differences in conclusions or any of the major points that we have made or that FDA has made.

I'd also like to thank Dr. Zuckerman for putting perspective on the role of a statistician, and I see that so well that the statistician is here to think about all the formal clinical trial rules and try to apply them and to follow the statistical analysis plan.

And I think it would be great if Dr. Johnson and Dr. Connor and I could sit down and talk about these points, but I think there's very little to involve you with at this point.

I do want to spend a little time though on the propensity analysis because that has come up, and I think it will continue to come up. So let me just go over a little bit of that, and I'll try not to drag this out or make it too dry. That's not possible.

DR. YANCY: You are a statistician.

DR. NAFTEL: My mother loves me. (Laughter.)

Please show the first slide.

So I want to show you exactly what we're dealing with. With the ELSO patients, there were 747 patients that were filtered from the

registry as you heard earlier, and then if you look to the right, you see the Cohort 1 and Cohort 2 patients and their ages, and in just a kind of square comparison, shows that there's a very different distribution of ages between ELSO and each of the cohorts. So our job is to look at age and weight and several other variables and see if we can, through propensity analysis, get a group from ELSO that better matches the EXCOR patients.

Next please.

So weight, there was quite a difference in the original 747 patients, and when you look at primary diagnosis, you'll see there really is quite a difference with the ELSO patients having a very high proportion of congenital heart disease, higher than either of the cohorts in the EXCOR patients.

So here is the statistical analysis plan for propensity matching. It was stated upfront that the variables to be included in the model, and it's a logistic model, the variables were to be age broken down according to four groups, weight according to three groups, then use of inotropes, ventilator support, and cardiac arrest prior to device placement and then those categories of diagnoses, and it's actually a total of 18 variables that the statistical analysis plan said must be forced into the model regardless of statistical significance.

So at the request of FDA, Berlin Heart was asked to engage an independent statistician to perform the propensity analysis, and that's when

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they came to me to ask me to do that and, of course, I was quite happy to do it.

At that time, I had not seen any of the trial data. I had not been involved in the plan. So I truly was an independent statistician.

We were very careful that the datasets that were provided to me, both the ELSO and EXCOR, contained only those variables in the statistical analysis plan but had no outcome data whatsoever so that, you know, whatever I was going to do, it would in no way be biased by the actual results.

And just a rule of thumb, if you think of each analysis, you think of the event being, did the patient receive the EXCOR? So that would be 24 events, and it's a little interesting, with 24 events, there are various schools of thought, but most people, statisticians would say maybe 3 to 5 variables is all you could look at, and yet I was asked to look at 18.

So from our usual perspective, we rarely would break age down into groups. We would just enter age as a continuous variable, same for weight. For the diagnoses, the only one that really occurred at a very high frequency was dilated myopathy. So all the variables in gray are the ones I proposed to look at. I asked Berlin Heart about this, and they ran it past FDA, and I believe there was agreement.

So here is the model for Cohort 1. So all variables are in there. Interestingly, the significant ones are age and weight and dilated myopathy.

The other variables, while forced in, really didn't have much to do with whether or not a patient received an EXCOR in Cohort 1.

So forgive me for this, but this is the actual result of the propensity analysis, and if you look at the ELSO curve, that's the percentile or the cumulative numbers for the actual propensity score, and what that is telling you is most of the ELSO patients, almost 90 percent, have a score near 0, that is a 0 probability of receiving EXCOR because they were just so different.

But we did the matching anyway and let me just go straight -- the Panel will be able to see that better than everyone else, but this is a plot of the ELSO 48 patients, of their propensity score plotted against their matched EXCOR patient, and you'll see it falls pretty much in a straight line with a very high correlation and that's what we're looking for.

Now, in Cohort 2, we performed the same analyses, and this time interestingly, age and weight didn't matter in these older body surface area patients. Ventilator status was important, and you'll see the dilated myopathy was important. And I'll pass that.

And now this scattergram is not as good and just as Dr. Johnson pointed out, the matching was not as good. Even though there were a lot of ELSO patients, there weren't that many who actually were appropriate for matching. It's not bad, but it's not fantastic.

So here's what happened when we finished. When you looked

at the 48 matched patients, and I'm just working on Cohort 2 because that's where the questions came up, you'll see that there's some ELSO patients below two years that did indeed get matched to Cohort 2 patients, and the overall distribution is significant.

Now, if you just compared the mean ages, interestingly, it was not significant. So it says on the average, the ages are about the same but the distributions are not similar, and that's just the way it is from the propensity analysis. It's okay maybe but not so good.

Same with weight. We're a little bit off, but let me get to perhaps the more important ones.

In ventilator status, looking in these Cohort 2 patients, the ELSO patients matched the EXCOR quite well for ventilator status, also for inotrope use, 83 percent versus 88. For prior cardiac arrest, they matched very closely, and finally when you look at diagnosis, they match very closely.

So what that led us to say to ourselves is we thought the matching worked fine. We, you know, to be realistic, this is two groups of 24 patients, and what we've said is we have a good set of matched patients, but we think of it more as a reference group or a benchmark group, and the statistics that you've seen, we think they're good. You see how the survival differs, and we think of the ELSO group, the ECMO group as a good reference point to help you judge just where do the Berlin Heart results fit in. Thank you.

DR. LANGE: Dr. Naftel, as a non-statistician, I would say after your careful explanation that your mother doesn't love you. She has the propensity to love you. (Laughter.)

DR. YANCY: Dr. Connor, did you want to comment on David's presentation?

DR. CONNOR: Yeah, maybe I have one question. So, and I don't want to belabor this, but I still don't think this is what propensity scores were made to do, and I'm not sure how it accomplishes the goal.

So maybe my simple question is why were propensity scores used in the first place versus some other just matching techniques where they would give you, you know, the whole ELSO dataset and the baseline characteristics for these 48 patients and to go in and figure out, you know, maybe who the best matches were without using propensity scores? Why does this improve that versus, you know, there's a rich literature on the best way to match patients?

DR. NAFTEL: Yeah, that's a very good question, and I do not want to fall back on that defense that I wasn't there when this was built but, in fact, I wasn't there when this was built. (Laughter.)

So I agree with you. There are a lot of other ways to match, and this really -- and I appreciate your comments. This is over different time periods, and it really becomes more of a matching strategy to find the nearest person with these key elements. So I can't argue with you, and I

agree that there are other ways to do this.

DR. CONNOR: Right, because it seems, you know, the problem is this is a matching strategy and it turned out not to be a great one because we had very divergent ages, for instance, and there were very young patients matched, versus a matching strategy would have had ages matched maybe exactly or much, much closer, and so, you know, and again I don't want to belabor the point, but it seems like, you know, some other matching strategies may have been much better.

DR. NAFTEL: Yes, and we analyzed it after the fact looking, you know, we did all the scattergrams, age versus age, and when we did the nearest matching for propensity, and we looked at how it brought age along, I was truly disappointed. I thought with 700 patients I'd be able to match just right on but, in fact, I wasn't. So the data, the patients just weren't there.

DR. YANCY: For the Panel, any other questions for David Naftel?

Yes, Dr. White.

DR. WHITE: Michael White, New Orleans. Just very quickly, that one chart you showed, you said that the likelihood of any of the ECMO patients receiving an EXCOR was practically zero. Is that similar to intention to treat for those of us who are not statisticians? Would that fit that definition?

DR. NAFTEL: I would not say so. That's a group of patients who were just so different from the EXCOR, and if you think of it, in the matching strategy, most of those had diagnoses that were not either congenital or dilated cardiomyopathy. There were a lot of real young patients. So they were just totally different.

DR. CONNOR: And isn't it a fact that I mean, I don't know if 600 out of these 670 ELSO patients could not have received EXCOR because it wasn't available, and so that's going to affect this dramatically.

DR. NAFTEL: Yeah, absolutely.

DR. YANCY: Is the Panel satisfied with what we've seen?

Dr. Zuckerman?

DR. ZUCKERMAN: Yeah, Dr. Connor, just to put this in perspective, I do think that Dr. Naftel used the right word for the pound of liberations as a reference point because this whole idea of matching in the LVAD space is actually a challenging one and needs further statistical work.

I can tell you in a general context that the use of propensity score analysis, even in our adult LVAD examples where it should be easier, hasn't been a success in that certainly from a FDA perspective, we're going to need to go back and reexamine how we're finding controls, but the data are the data for today's deliberation.

DR. YANCY: Dr. Fraser, proceed.

DR. FRASER: I believe the next focus of questioning was on the

outcomes, difference in the single ventricle in compassionate use patients, and Dr. Canter is going to speak to that.

DR. CANTER: Yes, Charles Canter from St. Louis. First slide. Do you have the clicker? I'll just stand.

So this represents the distribution of the single ventricle patients in the various cohorts within the study. As you can see here, that generally the single ventricle patients were younger and smaller and that there was actually only one older patient, a single ventricle patient implanted in both the 3B IDE site groups and the 3B non-IDE site groups. So 12 of the patients were younger patients within IDE sites, 7 were in non-IDE sites, for a total of 21 patients.

So I will now present to you the largest worldwide experience with bridging single ventricle patients to transplant with ventricular assist devices, whether it be infants, children, or adults.

There is a recent review article in a surgical journal that clustered a fewer number of these patients, all collecting the case reports in the literature prior to this date, and they are less than 20. So this is the worldwide largest experience in utilizing any ventricular assist device for supporting single ventricle patients to heart transplantation.

The median age and weight of this group is 29 months and 11 kilograms. None of the patients were placed on the device for the use of heart transplantation as primary therapy, nor were they placed on device

after initial failed cardiomy for failed surgery. Forty percent were placed on the device after it failed initial palliation, either a Norwood procedure, a pulmonary artery band, or Blalock-Taussig shunt. Another 40 percent were placed after heart failure associated after the second stage of palliative therapy, which is the bidirectional Glenn shunt, and 20 percent were placed on after the Fontan.

You can see the outcomes here. There were nine deaths. Seven were transplanted. One was a successful wean. One was a weaned failure, and three were on device.

Thus, this represents the first attempt to apply any long-term mechanical circulatory support technology to single ventricle patients.

In other patient children that we have used the Berlin on, we, of course, have been able to use the experience in our older patients, where adult VADs can be used and the adult, accumulated adult experience in many, many patients, to assess how to best use circulatory support in two ventricle patients.

For single ventricles, there is none.

This is the initial step, and as everyone knows, it will become an issue in the adults. The largest number of congenital heart patients in the United States now are adults, not children. The outcomes of single ventricle patients who are in heart failure is increasing. There is actually, as some of you may know, the first trial that's been registered out in Tacoma

for destination therapy with the HeartMate II for a Fontan patient that has one participant.

So this whole area of support for this particular type of heart failure, with this particular type of heart defect, is in its infancy, and how it will turn out remains to be determined.

DR. YANCY: Any other questions from the Panel?

Yes, Dr. Page.

DR. PAGE: So of this group, seven were successfully transplanted?

DR. CANTER: Yes.

DR. PAGE: And one successfully weaned.

DR. CANTER: Yes.

DR. PAGE: What do you think the survival would have been without this device in these 21 patients?

DR. CANTER: Personally, if they were put on ECMO and we got a heart before two weeks, we may have been able to transplant them. ECMO for this type of patient is just like two ventricles. It's often a two-week therapy.

DR. PAGE: I understand that this is just conjecture, but who better to at least estimate of these 21 individuals with 8 surviving with the Berlin, clearly the mortality is higher than the rest of the series we looked at, but in this high risk group, how many of this 21 do you think would have

survived?

DR. CANTER: In this group with small children, I don't know, two or three in St. Louis. We might be lucky to get a donor in the first 14 days after listing them.

DR. PAGE: So two or three. So a --

DR. CANTER: That would be my guess.

DR. PAGE: -- three or fourfold increase in survival from the Berlin device --

DR. CANTER: I would be skating on very thin ice to make that, you know, make that --

DR. PAGE: Obviously this is back of the envelope, but I think the point is important because this is a very high risk group that I don't think should necessarily be a contraindication for use of device if you're providing a chance of survival that would not otherwise be realistic.

DR. CANTER: I would agree with that statement, and the other point I would like to make to the Panel is I am not sure that in trying to judge the efficacy of the Berlin experience in this group, you can't solely judge it on the basis of the EXCOR device. There's no comparison group in the adults to see how, you know, continuous flow VADs do in a single ventricle adult patient.

This is a mechanical device applied to this very unique physiology, and what we're seeing here, trying to separate out what's the

effects of the EXCOR versus what's effective with a ventricular assist device in general at this point, with these small numbers, were impossible.

I was just handed a note to say on our 21, 10 of those were on ECMO prior to placement on the Berlin. So even further complicating matters.

DR. YANCY: Additional questions? Dr. Lange.

DR. LANGE: It appears you have a competing outcome plot. Could you just throw that up?

DR. CANTER: Sure.

DR. LANGE: Thanks.

DR. CANTER: This represents a competing outcome from an analysis that was in *Circulation* published June 29th of last month, showing competing outcomes for one ventricle circulation on ECMO derived from a combination of the UNOS and ELSO registries. The first author was Christopher Almond, and you can see there that he dragged his competing outcomes out to 90 days, and you could see in that group 35 percent were transplanted, 47 percent were dead by 90 days of support with a recovery rate of 8 percent. This perhaps again is sort of the same registry, but that's what the current experience is with ECMO.

Now, I don't know the distribution of those cases, how they compared to our groups as well, how many are in Fontans or not, but you need outcomes, and that's the best one available in the literature.

DR. YANCY: Any additional questions for Dr. Canter?

Dr. Fraser.

DR. FRASER: I believe the next area of questioning was about the learning curve and the differences in outcomes between IDE and non-IDE centers. I believe we have some slides reflective of that.

Basically we do agree that there is an element of a learning curve if you will, but perhaps the learning curve is not the right terminology. These are operations that are being performed in complex centers that do complex pediatric heart surgery and, in fact, the operation is not particularly difficult. It's the context in which the patients are being cared for, and we think that the outcomes are reflective of an institutional commitment to the care of children with heart failure.

I also wanted to comment on the question that Dr. Hopkins raised about the number or the denominator or the potential denominator. There are actually 50 centers performing pediatric heart transplants in the United States, and roughly half of them performed between 10 and 20 transplants a year over the last decade and less, much smaller numbers.

So these slides demonstrate outcome differences between the -- and this is the aggregate data for all sites, between sites implanting more than four devices and less than four devices, and there is some degree of difference.

Next slide.

This is the IDE site as I believe was pointed out by Dr. Laschinger, a bit more comparable results between the IDE and non-IDE sites, and then the last slide. And the non-IDE sites, a bit of different outcome.

I thought Dr. Walters who rose and spoke during the public forum session really spoke to this quite well about how results do improve over time and articulated very well the institutional commitment necessary for improving results, but all together we would agree that, you know, continuing support from the company and education about implanting the devices is important.

DR. YANCY: I think these data are quite responsive to the queries the Panel had. If you would just revisit these three slides for the Panel so that everyone can take yet another look, I think it would be helpful.

And there's a question from Dr. Posner.

DR. POSNER: Yes, I had a question about the learning curve. When I think of learning curves, I think of hand-eye coordination, but from what I've seen here, it seems like there's a large difference in learning how to handle the hematology and also the inspection of the pumps. And what's your feeling about the learning curve? Is it an implant problem or is it inspection of the pumps, or is it the various different formats for monitoring the hematology?

DR. FRASER: Well, I think it's a very insightful question and

observation. Having put these pumps in and with all due respect to the whole process, the sewing in the pump is not the hard part. The hard part is deciding who to put it in and then taking care of them afterwards.

And, yes, I think we need very focused commitment from hematology, from our intensive care team, from our transplant medical team, and our experience or our ability to manage these pumps does improve with experience.

DR. YANCY: If you would go forward to the non-IDE.

DR. FRASER: Unfortunately my advancer is not working. Can you -- the non-IDE, yes.

DR. YANCY: Thank you. Additional questions from the Panel?

Dr. Page.

DR. PAGE: Are we convinced that the non-IDE patients are similar to the IDE patients? One could hypothesize that these represent patients who have gotten sicker and then they have to have the device acquired for their institution which may delay availability. Do we have an idea of the time between identification of the problem or just how sick these kids are at the time they have the device because that could certainly skew the results for them looking like it's a learning curve, and actually it's a different population receiving the device.

DR. FRASER: I believe we do have data to support that.

Charlie, do you have the compassionate use slide? I think we have data to

support that contention.

DR. CANTER: Charles Canter from St. Louis. So, this slide begins to represent the breakdown of the non-IDE sites in terms of the large children B and small children 3A, and the volume they did. And you can see that actually it's very similar to the IDE centers as you remember from our slide this morning in that a number of sites did a very few number, the pointer isn't working, and there were some that were relatively high enrollers, mainly the Children's Hospital of Michigan. Thank you. Got the pointer. There you go.

So some were low, 1 or 2, but some, Children's Hospital of Michigan did 10. Children's Medical Center in Dallas did seven. The Children's Hospital of Philadelphia has done seven where Dr. Wernovsky came from. Here's the rest of the sites. The girl who's waiting in Delaware have done four in the study. Pittsburgh did seven and then became an IDE center. These represent the time when they weren't part of the IDE study. So you see a wide variety of use, but also of note is how many of these -- if you look down the roster of these, this is pretty much the roster of pediatric heart transplant centers in the United States.

I've got to go for the slide advancer here. This isn't working.

Okay. So this will show why in the non-IDE compassionate use, why eligibility wasn't met. You can see that for 10 of them, they run ECMO for greater than 10 days, of note that 14 of them had evidence of hepatic

disease. Only one had evidence of renal disease, and one was on peritoneal dialysis.

So for the most part, they missed the inclusion criteria because they were either on ECMO for greater than 10 days, which may address availability of the device issues you brought up, and they also had evidence of liver disease.

Next slide.

In the IDE compassionate use group, a large proportion of the ones that are in 3A and 3B simply represent patients who were put on the device prior to IRB approval at the site, that they actually met the inclusion criteria in the trial, but the site did not have IRB approval for the trial at the time they were implanted on the device. So by default, they had to go into Cohorts 3A and 3B.

Aside from this issue, really the majority of patients otherwise were because, as we just showed, single ventricle circulation. There was one patient who had hepatic-induced thrombocytopenia. There were seven patients again that were supported on ECMO for greater than 10 days. So that for the most part, in the IDE sites, it was because they're waiting for IRB approval, they had single ventricle circulations, or they had been supported on ECMO for greater than 10 days.

Next slide.

If you look and break out the transplanted and weaned rates,

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among the sites, you can see that overall, they are relatively comparable, with the IDE sites having a little better transplant and wean rate to the non-IDE sites. The SAE rates may look reversed, but they're relatively comparable. Whether these are statistically significant, I don't know if they are or not.

Next slide.

You can see here that the mortality of the IDE primary imports that met entrance criteria, the mortality was 7.9 percent versus 0 that didn't meet the entry criteria. So total mortality is 7.4 percent. If you look at, compare the IDE sites who are in 3A, the mortality was 15 percent that met entrance criteria versus 32 percent that did not, for an overall mortality of about 27 percent and the non-IDE sites, it was higher.

Next slide.

For the patients who met entrance criteria, this is the data. Here again, overall the IDE sites' performance was a little better than the non-IDE sites, but some of that may reflect the fact that those patients at the IDE site would have met inclusion criteria but just didn't get their IRB yet with relatively comparable SAE rates.

Next slide.

So on the outcomes and summarizing, these are the outcomes for the file, just to summarize. This is what we have on the basis of -- this is the compassionate use group.

DR. YANCY: Thank you, Dr. Canter. Questions from the Panel?
Dr. Moon and then Dr. Hirshfeld.

DR. MOON: I saw on there that there were six patients that weren't transplant candidates when the device when in. Do you have any insight into that? How could that be rationalized? Because what's going to be done with the patient who's got a device in them who is not a transplant candidate?

DR. CANTER: Mr. Kroslowitz will --

MR. KROSLOWITZ: Bob Kroslowitz from Berlin Heart. I believe the patients that were not transplant eligible or listed for transplant at the time were not single organ transplant candidates, that they had some component of pulmonary dysfunction and needed to be listed for two organ transplants, and then with the device, they'd become transplant eligible.

DR. CANTER: So, in summary, one of the patients like that would have been the little girl from Delaware that came in today, who, not knowing the individual case, it sounds like her pulmonary resistance was too high for a heart only transplant, was put on the device, listed as a heart-lung with follow-up. This is often done with adult devices. You know once they go on it, in the adult world, if you go on LVAD, your resistance will drop. Her resistance dropped. She was allowed to be listed for a heart only and got a heart only transplant. We've had similar experience with that in St. Louis that we published in 2007 in *Circulation*.

DR. YANCY: Dr. Hirshfeld.

DR. HIRSHFELD: Yeah, I think these are very illuminating data, and I think it would be appropriate to recharacterize the learning curve to an ongoing team experience. I think ideally when you consider the complexity of managing a patient on this, an ideal center would have one or two patients on this device in their unit at all times, so that they would maintain the expertise of the team continually rather than we did one three months ago and, oh, we're going to do one now, and let's see if we can all remember how to take care of these patients.

And I think this has implications for how this device might be ruled out in terms of, you know, where it would be available and so forth because I think it would be optimally used by centers that would have large numbers of patients who were eligible for the device.

DR. FRASER: Might I comment on that observation?

We at Texas Children's would completely agree with that contention. In developing a freestanding ventricular assist device program in a Children's Hospital, we have found that it is a very resource intense proposition, and there is sort of a baseline level overall heart failure treatment that one must have to have all of the elements that we've essentially recapitulated in our expert Panel here today. So we would agree with that contention.

DR. ZUCKERMAN: Dr. Fraser, that's a very nicely stated expert

opinion, but could we have the Sponsor also comment on Dr. Hirshfeld's suggestion. What is the Sponsor's response?

MR. KROSLOWITZ: Again, there's a lot of resources that are required for use of the device in an institution. I think that we have a number of non-IDE centers that are very committed to this technology and have put resources where they were not to take care of a small number of patients.

I think that this discussion is not something that is just an issue with us in the pediatric community. I mean this is a discussion now in the adult VAD community whether there should be Centers of Excellence, only a small number of centers putting that in, and I don't know how you would ever make a decision as to where you would limit the device, the technology, somebody would die and not get the device because of where they were.

DR. YANCY: Dr. Connor.

DR. CONNOR: So along the lines of, you know, I certainly understand that the learning curve is center-specific. It's not about, you know, the dexterity of a particular surgeon. It's something like the standard of a valve might be.

Do I understand right that there are really only 12 additional places in the country that this would essentially be being used at? So we don't have to worry about the cardiologist on the corner. It's really just educating 12 sort of virgin centers?

MR. KROSLOWITZ: So there are approximately 50 pediatric cardiac transplant centers in North America. We showed you that 38 of the centers have implanted.

The remaining 12 centers, I can tell you for sure, have already spoken to us and are interested in the device and have either identified a patient that either was transplanted before we got there or died before we got there, but I can't imagine that there's another center that we have not at least spoken to that has interest in using the device, but that would be correct to say that there are only 12 centers where we have not implanted.

DR. YANCY: So with that in mind, and in keeping with Dr. Zuckerman's question and Dr. Hirshfeld's comments, back to the Sponsor.

For those 12 sites, or other sites that might become interested, is there a standardized protocol arrangement and training scenario? Maybe Dr. Fraser might want to comment on that as well.

MR. KROSLOWITZ: Yeah, so we have some slides that we can put up. We are very serious about our training. We do have a training program. Right now we provide implant support. The company policy is that you must take our clinical assistance for the first three implants. At the time that we provide the support, we are on site for three to four days, providing pre-implant training, implant training, and then post-implant bedside training in all aspects of patient care, et cetera, of the device.

We have subspecialty specific training. So we train the nurses on specific things, the hematologists on specific things, the surgeons on specific things. We have training modules, if you could go back just for a minute, on theory overview, device product overview, patient selection, implantation techniques, and then practical, with the device, hands on of the system components, operation troubleshooting, preparing the pumps, et cetera.

Next slide.

Here you can see some of the minimum required training modules that we have. We train the surgeon on the overview, implantation, anticoagulation therapy, measures required, daily wound care, et cetera. So we do have what we believe is a quite comprehensive training program in place.

DR. YANCY: Dr. Zuckerman, is this responsive?

DR. ZUCKERMAN: Yes, thank you.

DR. YANCY: Dr. Lange.

DR. LANGE: Thank you. I would note that, as Dr. Fraser stated, getting people through the operation is pretty easy with a talented surgeon, experienced surgeon, and it's the postoperative care where a lot of the complications happen.

I'm interested in the Sponsor's stance that a postmarket analysis or study would not be beneficial, and that I assume that when the

Sponsor takes that, they would assume that all that's to be known about this topic is already known, that nothing could be gained more, and that registry and looking at sites and what goes on over the next year and two and three years past 24 patients wouldn't somehow provide insight on how to lower the complication rate.

MR. KROSLOWITZ: I'll just comment, and then I think Dr. Fraser has a comment.

So we believe that a postmarket study is to gain the initial look at the device in real life use, what it's going to be like, and I'm not saying that there's not things that would be learned. I don't think there's ever in medicine not something to learn, but I think that the purpose of the postmarket study, to see how the initial widespread use of the device will be, has already happened.

We had 48 patients enrolled in our primary study, yet presented data on more than 200 patients, compassionate use and from all these other sites that have already implanted the device.

So the purpose of the postmarket study is to see what it's going to be like. The initial use of the device in the real world, that's already happened.

DR. LANGE: So your stance is that all the knowledge to be gained from those has been gained and an additional registry or study won't gain any more information. That would be the stance. That's what you're

staying.

DR. FRASER: I don't want to speak for Mr. Kroslowitz, but I don't think that's what he's saying. I personally think that a continuing registry is critical going forward. I think all these patients should be in a registry and followed longitudinally and, of course, examined in the context of the heart transplant community. We have much to learn about the long-term outcomes of these patients.

DR. LANGE: I know you can't speak for the Sponsor but that would be --

MR. KROSLOWITZ: We agree.

DR. LANGE: Okay.

MR. KROSLOWITZ: A registry would be appropriate.

DR. LANGE: Thank you.

DR. FRASER: I would just like to add my support for that, but the issue here in postmarketing or increased experience in children is it's a paradox, and we have the only -- of the EXCOR, but we as pediatric heart failure physicians and surgeons are learning when we can and can't apply mechanical support to our very unique patient population, and what we do in children will likely overflow into what happens to adults with congenital heart disease in this area as well.

So I think there's a critical need for ongoing, you know, organized assessment of mechanical circulatory support in children and in

pediatric heart disease. How that translates to an individual company or device doing a postmarketing study, I think that's a big issue that has to be dealt with in one way.

DR. YANCY: Dr. Borer.

DR. BORER: Yeah, I was going to save the comment about the postmarketing study until the question for that, but since it's been raised, I think that while Dr. Lange is absolutely right, one reason to look and see what happens is to determine if there is some evidence or information that can allow you to avoid problems as this technology is used further, but that's not the only reason.

To me, right at this moment, the primary reason to do a postmarketing study, and I mean a postmarketing study of the type that's been recommended by the FDA, is that I don't know what happens to these people after they have the therapy that this device has bridged them to, and I think that's crucial information. We need to know whether the hoped for benefit of getting the several months to find a donor heart is actually worth it. Do they have a reasonable quality of life? Does the plasticity of the nervous system of children allow them to overcome the strokes that some of them have and live reasonable lives? I think we need to know that, and we're not going to know it unless there's a nice, rigorous follow-up for several years.

None of the doctors sitting in front of us are saying you

shouldn't do that, and I don't even think the Sponsor is saying you shouldn't do it, but I'm saying you should do it, that it's absolutely essential.

DR. YANCY: One of our queries before the break was, in fact, whether you had at least some anecdotal information about quality of life on longer-term outcomes. I don't know if you've gotten to that part yet or not, Dr. Fraser.

DR. FRASER: Dr. Ichord will address that.

DR. ICHORD: Dr. Ichord speaking now. I think for answering that specific question, if you advance to --

DR. YANCY: Dr. Ichord, if you can just give us your attribution again.

DR. ICHORD: Dr. Rebecca Ichord. I'm the Head of the Pediatric Stroke Program at Children's Hospital. I'm a neurologist.

While I'm on the topic of neurological dysfunction, I can go ahead and give the data that was requested earlier regarding time to stroke. So go ahead back to that.

So we were able to collect and summarize the time from implant to time of identification of neurological dysfunction event.

DR. CONNOR: In days.

DR. ICHORD: This is in days. This shows Cohort 1 and Cohort 2 with the size of the cohort, the number of patients who had an event. This shows you the mean time in days from implant to the identification of the

event. In Cohort 1, it was 27 days, and in Cohort 2, it was 12 days as a mean. This shows the median, 20 days and 12 days respectively with the range.

The next slide shows this same data in a Kaplan-Meier curve, summarized for both cohorts, and what you can see is that most of the events occurred within the first two to four weeks, and thereafter, patients maintained on support at later time points didn't experience these events. So the highest risk period as best we can tell from these data for having a neurological event is in the first two to four weeks after implant.

So before I go onto the more broad question of what's the long-term picture of these patients, are there any other questions related to this data?

DR. YANCY: Dr. Ichord, this is quite informative. I think there's some Panel members that had questions about this. Dr. Weinberger.

DR. WEINBERGER: I'm a little -- I'm missing something here. So if the time to average first neurological event is about a month, why don't we keep seeing events in the same patients, or are these patients not making it? What's going on here? I mean if you've shown that you've had a neurological event on the average of 1 month, and these people are staying with these implants for 6 to 12 months, how are they being protected?

DR. ICHORD: I don't have an answer to that. We don't know why. Our data and our data collection wasn't designed to address that question.

The Kaplan-Meier curve is going to be affected by censoring of patients who get transplanted. So the number of patients represented, but I don't know the answer to that.

DR. YANCY: Dr. Connor.

DR. CONNOR: So in particular the median here is 12 or 20, and if you go to the next slide, that curve never gets to 50 percent, which is to say there isn't a median. So these two -- the curve and the chart don't really jive with one another.

DR. ICHORD: I'm going to defer to Dr. Naftel to answer that.

DR. NAFTEL: You know, that's always sort of a bad way to present data. Those statistics -- can you back up one slide?

So that's among the events, that's the mean time to the event among the people who had the events. So there's some information but the Kaplan-Meier curve, go to that please, you need to keep in mind that's time to the first event, and once a person has the event, you know, the second event isn't accounted for. So it's just time to first.

DR. YANCY: Additional questions? Dr. Connor again, and then Dr. Kato.

DR. CONNOR: So, you know, maybe in conjunction with the learning curve idea here, it seems like the hazard, which is measured by the slope of this curve, is clearly the highest from, you know, around two weeks. So do we know better now how to avoid that, how to make that hazard go

down? It would seem like, you know, maybe I would expect something right after surgery, but that's not when we're seeing it. So do we know better how to make that less steep now with the better experience?

DR. ICHORD: Again, I don't have the answer to that, and the study wasn't designed to answer that question. One would hope that over time and with more experience among sites and with ongoing studies of the risk factors for these events, then that kind of information would become available, but our study wasn't designed to address that.

DR. YANCY: Dr. Fraser.

DR. FRASER: Charles Fraser. Again, this is opinion not based on data, but it's an intuitive observation.

There's a lot going on in these children's lives between day 0 and day 30. They're on the ventilator. They're on multiple inotropes. Some of them have been on the ECMO. They haven't been feeding. They're getting ramped up on anticoagulation. Their feeds are changing. There is a tremendous amount going on, and that they're in a great state of daily medical fluctuation and thereby that risk is compressed in the first 30 days seem to be intuitive to me.

DR. YANCY: Dr. Kato, my apologies for mispronouncing.

DR. KATO: Just one, and this is going to take you away from the neurologic events, but I'm just curious. You said before that the average time to transplant was about 119 days, and yet some of the patients that

have been here talking about their experience have been on this device for months, 10 months, 12 months, you know, this is a fairly long time.

What is your anticipated time on the device if you start to roll this out? Given the fact that it's a limited donor pool, how is this going to change that wait time? Because I've got to presume the wait time is going to really increase and that some of these events are going to be increasing in frequency.

DR. CANTER: Well, that will be interesting to see how it affects it, you know, and I think that's -- I would like to -- answer the question and try to answer Dr. Borer's question as well.

I think that we're very interested in what's going to happen or what the purpose of this device is get the child to a transplant. How routine use of an assist device as we go forward, as they're becoming more routine, will affect outcomes in children with a relatively limited donor pool remains to be seen. You can already see some effect, I think, in the story of the person from duPont, how the surgeons there who it sounds like they would have already transplanted somebody, you know, but they're waiting for the perfect donor. Now, everybody's idea of a perfect donor is patient-specific and often doctor-specific. So, you know, I think how that's going to interact is a very interesting question that we're going to have to wait and see.

But I'd like to -- if I could step back and answer Dr. Borer's question. I think it's very important for the Panel to realize that a pediatric

transplant recipient is not a normal child. We always tell the patients in St. Louis, when we list them for transplantation, that they are exchanging a fatal disease for a chronic disease. Living with a heart transplant and getting to a heart transplant is a chronic disease. Pediatric heart transplant recipients, there is very little actually true quality of life data for the entire group for how their outcomes are with regulated instruments unfortunately because of the lack of funding that one gets for what is truly a rare disease.

What there is, it's quite clear that they remain abnormal in a number of key neurodevelopmental outcome measures. So when we assess the effect long term at one and five years, especially at five years, trying to tease out the effects of a specific intervention, which is being on a VAD, compared to the whole -- that can affect these neurodevelopmental outcomes, will be tremendously challenging, is not as simple as it might be to think about it, in trying to design appropriate comparison groups, and now there really isn't even data in those comparison groups to make a comparison to.

DR. BORER: Clyde, may I just follow that up?

DR. YANCY: Dr. Borer.

DR. BORER: I agree and that's very helpful. I wasn't suggesting that you could tease out what the contribution of the VAD is. What I was asking really is what are we getting for what we're putting in? We'll get to this discussion later, but let me just presage by saying that it seems to me

that you're allowing kids to survive a lot longer than they otherwise would so that many of them will be able to get to transplant when they couldn't before, and I just think it's important that we know for that resource input what we're getting at the other end, and we won't know unless somebody looks. It's not the VAD that's doing it. It's, you know, what are we getting for this strategy?

DR. CANTER: I think it's our obligation as the pediatric heart transplant community to give the public that information. That's our obligation. Study, postmarketing study, or not.

DR. YANCY: Additional questions? Dr. Moon.

DR. MOON: Just briefly. Are we sure these strokes all occurred at these days or they were recognized at these days? Could they have been intraoperative strokes that weren't identified until the patient woke up at 10, 12, 14 days?

DR. ICHORD: Dr. Ichord again. Yes, you raise a very good point. The date of the event is the date that it was recognized to be clinically evident, and in our adjudication, we made a rigorous effort to and determine roughly the timeframe so that we could then adjudicate causation and contribution, but it's quite true that the date is not, can't be assumed to be exactly precise on that specific day. It could have been plus or minus a day. Generally these patients came to attention because they had a clinically recognizable symptom, and so if they were immediately post-op

and deeply sedated, they would not be able to be recognized as having that deficit.

DR. MOON: Did you think they were all embolic or the great majority were embolic or malperfusion?

DR. ICHORD: It's not really possible. I don't think to say, I think most of the events that I was involved in, and I was involved in adjudicating all of them, they looked on imaging to be consistent with an embolic process. So, yes.

DR. YANCY: Dr. Augustine.

DR. AUGUSTINE: Two questions. It was brought up earlier the difficulty of evaluating this data in a vacuum so to speak without a comparator, and I'm wondering if Dr. Ichord can talk about generally accepted frequency of stroke in patients on ECMO.

My other question is about outcomes, looking at PSOM scores in terms of greater than/equal to one being a poor outcome. What is your interpretation of the premonitory status of these patients prior to implantation and how that might be impacting later outcomes?

DR. ICHORD: Yes, in answer to your first question about what's the expected rate of stroke in the ECMO populations, I think we've learned in the course of this study that there is very little, almost no data published that is done in a well-performed prospective cohort study. So the answer is we have very little data that's informative of this particular

population.

I think just in reference to some of the other comments made, that comparing our stroke rate with that in adults, that the stroke rates reported in our group were higher than that reported in the literature. I think I would say that our population is very difficult to compare to adult populations because of the different disease and different illness states. So I would just raise a precautionary note that comparing these two patient groups is limited.

DR. YANCY: Dr. Ichord, if you would, if you can answer the broader question --

DR. ICHORD: Yes.

DR. YANCY: -- that we had asked to start with.

DR. ICHORD: So the other question about the PSOM and kind of broader picture, we have a couple of slides to put up for that.

DR. YANCY: While that's occurring, Dr. Zuckerman had a question.

DR. ICHORD: I'm sorry. What was other question?

DR. ZUCKERMAN: Could we just go back to the Kaplan-Meier just for the record? Where the Kaplan-Meier starts to get flat, do you know how many patients there were for evaluation at that point? Were there one or two? Excuse me.

DR. ICHORD: We have that information --

DR. ZUCKERMAN: Excuse me. To Dr. Connor, if you could help us out here because we're learning a lot about methodology today, and some of these patients are going to have multiple strokes. So you pointed out the limitations of Kaplan-Meier; it only includes the first stroke. Would a better way to present these data in the future just be a cumulative incidence curve of stroke?

DR. CONNOR: I think I like this way better because, you know, it's really, you know, and I guess there are going to be more severe strokes that are subsequent, but I think this is good.

In terms of the other question, I think I see tick marks, right, they're really small.

DR. ICHORD: Yes.

DR. CONNOR: But if I count those, it looks like there's still at least 10 or more patients left at 60 days where it flattens out.

DR. ICHORD: I was just told that there's nine patients at that point where it flattens out.

DR. ZUCKERMAN: Okay. Thank you.

DR. YANCY: If you would proceed now with the broader question, Dr. Ichord.

DR. ICHORD: Okay. Next slide.

So many questions have been raised about what is the -- what can we say about the quality of life and neurological functional outcome of

our patients in this cohort? It's important for us to comment on the significance of the PedsQL or the health-related quality of life data that was presented and collected in the study.

As it turns out, the available data for the PedsQL computations was extremely limited due to small numbers, and by virtue of the fact that the way that the data were expressed and collected in the database is not comparable to the way it's reported in the literature. So the comparison that was made in the FDA presentation is actually not valid, and the way that our numbers were expressed were in terms of the absolute numbers of the total scores whereas the values that are presented in the literature are expressed as percentages of the number of questions answered, and we did not collect that data. So, in fact, the data that we have on PedsQL is really inconclusive because of the way it was expressed in the low numbers.

So moving on, the neurocognitive assessments are ongoing, and we have again limited data interpreting limited numbers of patients' data on neurocognitive assessments across a broad range of ages, using different instruments for different ages. It becomes very complicated. So the data that we have is really not of a type that can really be used to draw firm conclusions.

So the best that we have is the PSOM post-explant, and I've presented here in a table the latest PSOM for those patients in the cohort that had no neurologic event, and those that had at least one neurologic

event adjudicated. And what we have here is the latest, the number of patients in each of those groups that we had data, and the time of their latest PSOM after explant. Sorry. This is the time after explant. So we have a mean of 47 days and a median of 32 days. These are the PSOM numbers. The mean for the non-neurologic event subgroup is 1.1, and the median is 0.5, and the range of 0 to 10. In those that had at least one neurologic event, the mean, the latest PSOM was 2.8, and the median was 1.3.

Now, before you really think about what this means, I need to tell you more about what a PSOM actually means, and this is in answer to Dr. Augustine's question.

Next slide.

The PSOM is a way of scoring the results of a standard neurologic exam. The final summary of impressions is determined by the neurologist doing the exam. They formulate a score, it's a Likert type of scoring, where you can only assign a 0, a .5, a 1, or a 2, and each of these domains of the neurologic exam is assigned a score along this Likert system, and you get a total that ranges from 0 to 10, where 0 is normal on all domains and 10 is 2 on all domains.

Next slide.

So what we did in dividing up the final total PSOM score was to stratify into multiple categories of severity what has been referenced in the FDA report as a single binary division into good and poor and, in fact, the

field of childhood stroke has not studied this approach, and there is no agreement in the published literature about how to stratify PSOM scores.

So we did this division based on data that was in part derived from a study as well as consensus, and if you go to the next slide, I'll show you what I mean.

In a study where we used the PSOM concurrent with another outcome measure called the KOSCHI -- the KOSCHI is the King's Outcome Scale for Childhood Head Injury. It's similar to Glasgow Outcome Scale -- it gives you a similar five point division of severity of outcome as you might see in a modified Rankin or Barthel or a similar instrument, and this is really the only existing published data that gives you any sort of comparison or context as to what a PSOM score means relative to a broad functional category.

And what we found in this group of 22 patients is that a PSOM score of 0 to .5 corresponded to a very good recovery on the KOSCHI. A score of 0.5 to 2.5 corresponded to a moderate disability. A score of greater than 2.5 corresponded to severe disability. And so the intuitive classification that we came up with was supported by this type of classification.

So really the decision or the determination that a child has a poor outcome is of limited utility unless one has a more graded way of describing outcomes as is done in the standard way in clinical trials of stroke in adults, and it makes much more sense and it's much more standard to divide up outcomes, not into a binary good versus poor, but rather into at

least a multiple layered degree of severity.

And so that was the basis for our finding that only 12.5 percent of our IDE cohort had an impairment that was in the severe or worst category, I think.

I hope that answers the questions that people have. That's the data that we have on outcome to date.

DR. YANCY: And we appreciate the effort. We know it was short notice. We have two questions from the Panel. Dr. Nykanen.

DR. NYKANEN: I just wonder if you could comment on, I know that this was a score that was designed for patients who had had stroke, but what's your sense of the background of the patient who is on cardiopulmonary bypass for congenital heart disease? Would their PSOM scores be 0 given the incidence of neurocognitive developmental issues, behavioral problems, and language difficulties in the cardiopulmonary bypass group that have not had a stroke? Could that be interfering with some of the background here that we're seeing?

DR. ICHORD: Yes, I think that's correct, and I think that influence of many different factors affecting the outcome and not just the stroke and the underlying disease is reflected in the data that -- yeah, go ahead and display this here.

As you can see here, this shows the patients who did not have a stroke or a neurologic event, and their latest PSOM score was not normal.

At the same time, it was only in the mildly impaired range with only a -- well, including some that were more severe, but on average, they do have mild impairment, and a very critical caveat to all of this data is a point that's been raised by Panel members as well as acknowledged by our own presentation, is that these data are at a very early time point, a median time of 47 days, I'm sorry, 32 days post-explant.

In the field of stroke research, we wouldn't consider that you would have a reasonable estimate of their long-term outcome until you've got to at least three months and really more appropriately at one year, and as you saw in the data presented earlier by Dr. Canter, many of these children started out around the time of their event or at the worst of their deficit with scores in the five to six range and improved over a matter of even a few weeks or a couple of months down to scores of one.

So this is a very dynamic group because they're recovering from disease and because they're growing the plasticity. So these data need to be viewed in mind with the understanding that this is still very early in their course and that continued recovery and improvement can be expected.

DR. YANCY: Dr. Posner.

DR. POSNER: Yeah, basically I had the same question, and that was all the confounding variables that are there that I think need to be taken into account when you actually do design the study. I know Shands which had 8 of the assist device users, which is my old hospital, about 30 percent

of our patients are migrant farm workers' children, and they also have their surgeon's children and judge's children. And so again, if you're going to be looking at it for one year out, or two years out, the migrant farm workers' kids are going to be going from Florida to Louisiana to Texas to North Carolina and back to Florida, and the neurosurgeon's kids are going to be in daycare in Gainesville.

So I think when you design the study, I think it's critical that the study be done so you can give informed consent to the patient's parents as to what to look forward to. You really need to design it with all these confounding variables as to patient population.

DR. YANCY: I think we've heard quite a bit about the complexity of the special population. Dr. Ichord, thank you very much for your comments.

Dr. Fraser, there's one large area that we've not addressed yet, and that's the thrombosis issue. If we can spend the last 15 minutes reviewing that as there were a number of questions there.

DR. FRASER: Yes. Charles Fraser. I believe there were two broad categories. One was the pump thrombi and the assessment of them, and the other was the anticoagulation range. Am I correct on that?

DR. YANCY: Yes, sir.

DR. FRASER: Okay. I think we'll first ask Dr. Jim Tweddel to come up and speak to the pump change information.

DR. TWEDDEL: Thank you. Jim Tweddel from Milwaukee.

Could we -- I think it's the last several slides in this. We can start here, yes.

The first thing I'd like to emphasize is that I've heard the term explantation used but, in fact, these pump changes are really very straightforward procedures as Dr. Walters discussed earlier. They're done at the bedside. There's no escalation in support required during the pump change. If the patients are extubated or intubated, they just get a little extra sedation.

The pump itself is very simple to prime and de-air, and you simply clamp the cannulas, remove the gun ties and remove the pump, implant the new pump, and secure it and de-air it and turn it on. It takes about almost as long to do it as I've just spent explaining it. And there's really no substantive interruption in mechanical support during that period of time.

Now, if we can go maybe towards the end. The other questions concerned the examination of the pumps after they were explanted. That one.

The explanted pumps from the Cohorts 1 and 2 were examined by Dr. Fred Clubb. He's a cardiovascular pathologist at Texas A&M University, and he has been involved in the explant of pump examinations on multiple other assist device studies, I think almost every assist device

study, and they were sent to his lab.

These are the definitions of the deposits he identified on the devices.

Can we go to the next slide, please?

And at the bottom are the size determinants. So none is no deposit identified, and then minimal and mild, moderate and large are shown there, and then the actual size of the deposit is listed. So large deposits were greater than five millimeters, and small deposits were less than two millimeters. I'm having a hard time reading that myself.

Go to the next slide, please.

These were the regions of the pumps that were specifically inspected, and deposits in these regions were noted.

Next slide, please.

And these are a little hard to read. I apologize. They're from the pathology report. So the first -- Cohort 1 is on the left. Cohort 2 is on the right. This is the effluent. So the fluid inside the pump was drained out and examined, and you can see here they're mild, and none are the bars on the left that are none and mild rather are the bars on the left that have any significant numbers.

Next.

These are the inflow regions. Again, the vast majority of the pumps had no deposits, and these incorporate those regions identified in

the diagram.

Next slide, please.

And these are the outflow regions, again not very many deposits identified.

So why is that? Well, one, because the pumps are very easy to change, there's a very low threshold for pump change-out, and the deposits we're seeing by visual inspection are very small.

The pumps themselves are transparent. You can see through them. You can identify these deposits pretty easily, but obviously you can't see through the blood. So you don't know what's just beyond those little specs you're seeing within the pump housing itself. So any sort of deposit would cause some concern and might reach the threshold for pump change.

The pumps themselves were then sent for examination, but when you're doing the pump change-out, obviously the patient getting a new pump implanted is the primary priority and getting that old pump, making sure that it doesn't slosh around or anything is less of a priority at that point. So it's possible that some deposits or thrombi were lost in that process.

DR. YANCY: Dr. Lange, I think you had questions about this area.

DR. LANGE: So -- and I'm just trying to clarify. These pumps were removed because there were something visible in them or were these

pumps removed at the time of transplant? In other words, I'm just trying to reconcile. We heard some data --

DR. TWEDDEL: Right.

DR. LANGE: -- there's 1.1 pump changes per patient.

DR. TWEDDEL: That's correct. If I can go to the first slide of this set.

That's right. There were -- that one. Next. Okay.

So 25 of 48 subjects had at least 1 pump change. Ten of those 25 had greater than two pump changes, and they were -- 43 of the 46 pump changes were for suspected thrombus and one was due to a fungemia. One was due to an embolic stroke that occurred, and so the pump was changed, the consequence of that, and the other one was due to positive blood cultures as well.

DR. LANGE: I was just trying to reconcile that with the slide that said 87 percent of pumps were thrombi free. I was just trying to see what --

MR. KROSLOWITZ: Bob Kroslowitz from Berlin Heart, if I can just add to that.

All of the blood pumps, so those that were exchanged for thrombus, suspected thrombus formation and those that were explanted at the time of the transplant for all IDE patients were evaluated by the pathologist.

DR. YANCY: Dr. Ferguson.

DR. FERGUSON: Just to follow up on what Dr. Lange asked earlier. Do you know anything about the therapeutic anticoagulation level in these patients at the time the pump is removed or how often they had been subtherapeutic?

DR. YANCY: Actually, Dr. Fraser, that allows us to segue to this part. This should be the last part of what you need to do.

DR. FRASER: Yes, and if I can go to that slide. And maybe I can ask Dr. Massicotte to join me.

MR. KROSLWITZ: I believe Dr. Massicotte was going to speak to that issue --

DR. FRASER: Okay.

MR. KROSLWITZ: -- if that's okay.

DR. MASSICOTTE: I believe the Panel requested to look across the range of the study from the point of view of anticoagulation, the adequacy of that. By looking at the particular patients that were on the particular agent, so unfractionated heparin, low molecular weight heparin, or warfarin, and whether the patients fell below the recommended therapeutic range, within or above the range, and the numbers that I'm going to give you are the numbers that are available that have been entered into the INTERMACS database for these patients.

And so what we've done is, if you look at this slide, we've

actually combined unfractionated heparin and low molecular weight heparin under the umbrella of heparin, albeit they do have different ranges, but this statistical sort of lumping takes into account those different ranges, and what we see is not unexpected from what we see in the pediatric literature for the complexities of using these drugs in children.

We see in Cohort 1 and 2, with a child on either unfractionated heparin or low molecular weight heparin, that 41 percent of the values were below range, 46 percent were within range, and 13 percent were above range.

Equally for warfarin, using the INR as the measure of whether the drug was therapeutic, and again this is not unexpected because this is what's purported in both the pediatric and the adult literature, that we see patients about 64 percent of the time below the range, 18 percent in range, and 18 percent above range.

And, again, just to reiterate, what the Panel knows from the various comments, these are a very complex population of different ages of children. They have different hemostatic parameters as they age. They have different pharmacokinetic and pharmacodynamic parameters as they age, and so that really affects both dosing and clearance and metabolism of these complicated drugs.

So the drugs in themselves, we see different bioavailabilities, and we also see the challenges of a narrow therapeutic index, warfarin,

which is affected by multiple factors, nutrition, genetics, and how ill the child is. Thank you.

DR. YANCY: Any additional questions here? Dr. Borer.

DR. BORER: Before you sit down, that's very helpful. One thing you didn't tell us is when were these determinations made? If these kids had very recently had these devices implanted, then there would be the usual tendency of the implanting surgeon to run the anticoagulation low to avoid immediate bleeding problems. So I'd like to know when these were done?

The second point though is that even if some of the numbers were low, it's not true, and you can speak to this much better than I can, it's not true that because a number like a INR is below the stated therapeutic range that there's no protection against coagulation. That's not true. There's often a great deal of protection against coagulation. So when were these done, and how do you put -- I think you already said it, but how do you put these numbers into context of the illness and the nearness to the operation?

DR. MASSICOTTE: The actual guidelines that were developed which I showed this morning, and I'll show you again, actually gave the centers guidelines as to when to do actual hemostatic testing as well as guidance as to when to start the agents. And so you can see the hemostatic testing that was done. If the child was on unfractionated heparin daily, if

the child was on enoxaparin or warfarin, because remember those were the stable patients, two times a week for four weeks and then once a week, which is actually more than probably you would do on other children that are on these drugs.

Platelet mapping which involved thromboelastography, and looking at platelet inhibition if the child was on an antiplatelet agent, again you can see that it was quite frequent and then became less as the child became more stable or explanted.

Any anti-factor Xa basically is the same, a little less than unfractionated heparin because the bioavailability is much better than unfractionated heparin.

Could I have the actual protocol which is slide 9?

And so basically those were the tests we recommended, and those were the timings of the tests.

As far as when the anticoagulation started, we actually recommended that for the first 24 hours because many patients were still bleeding post-implantation, that you try to -- that the centers achieve normal hemostasis, and so for the first 24 hours, we really recommended no anticoagulation.

At that time, after 24 hours, a reassessment was done and hemostatic measures were done within this 24 hours. If there was still bleeding, again more than 10 ccs per kilo per hour, that hemostatic testing

panel was repeated. If it was normal and the child was bleeding, surgical bleeding was ruled out. If it was present, obviously the child went back for another look in the operating room, and if there were abnormalities that could be resolved to resolve the bleeding, then blood products were given depending upon what the hemostatic testing showed.

If there was no bleeding at that point, and the platelet count was greater than 20,000 and the thromboelastogram had parameters that were recommended acceptable, then unfractionated heparin was started, and it was started specifically with no bolus because we didn't want to incite any bleeding and we wanted to sort of trial and test, and also we equally started it with half of what would be considered therapeutic age-based dosing. And within a six to eight hour period, if there was no further bleeding, we would increase up to therapeutic anticoagulation to achieve the target value of .35 to .5 units per ml, and again from there we carried on. If there was bleeding and platelet counts changed, then the recommendations would be to decrease the dose or to stop.

And, again, these are guidelines, and so individual physicians would manage patients within these guidelines as best they could to be safe for the patient.

DR. YANCY: Jeff, is that adequate?

DR. BORER: Yes.

DR. YANCY: Dr. Fraser, I think you've been quite responsive to

our questions and concerns.

Before we take a break, let me see if there's some additional questions. Dr. Slotwiner.

DR. SLOTWINER: I just had one more question about the thrombi that appeared to form on the pump. Does it seem that they form within a certain time period after it's placed, or is that for the duration of the implant or of the use of the pump?

DR. TWEDDEL: I think slide 4 is the answer to that, 3. That will work.

Is there a time course of the pump thrombus?

DR. SLOTWINER: Yeah.

DR. TWEDDEL: The average time to first replacement was 25 days. So it doesn't seem like there's a particular time when they're at greatest risk.

DR. SLOTWINER: Okay. Thanks.

DR. YANCY: I see three more questions. The first one was Dr. Austin, and then Dr. Page and then Dr. Connor.

DR. AUSTIN: I don't think this was indicated, but was there a correlation between the appearance of thrombus and the below or the low levels of anticoagulation, temporal correlation?

DR. MASSICOTTE: Patty Massicotte from Edmonton. I don't think we have that data. I don't know. We don't have above range, in

range, and below range. What we have are what I showed you this morning, from the point of view of adherence to anticoagulation, and that is medians with ranges as far as the actual recommended ranges.

DR. YANCY: Dr. Page.

DR. PAGE: I notice you're using dipyridamole in your algorithm. Any consideration of other antiplatelet agents? Obviously the Panel's concerned about the stroke risk here, and maybe there's literature and experience in this sort of situation, but what about Plavix, that sort of thing.

DR. MASSICOTTE: Unfortunately most of the drugs, in fact, I think all of the ones are off label. We have very few paucity of studies with any of these agents, and we have very few studies, in fact, if any with Plavix or any of the other antiplatelet agents.

There will be studies coming, at least another pediatric populations with the new antiplatelet agents, but again it's programs that will take five years to complete.

DR. YANCY: Dr. Connor.

DR. CONNOR: So I think it would be interesting if the FDA, you know, after today, would request sort of the same Kaplan-Meier curve for time to first pump exchange due to thrombus because it's interesting that there are no ischemic events after 60 days, and it would be equally interesting if there were never a need to exchange a pump due to ineident

thrombus after 60 days. I think that would educate us toward the device.

The second comment I wanted to make, I wanted to maybe better answer the last question Dr. Zuckerman directed to me regarding the Kaplan-Meier curve for stroke. I think maybe as a parent who understands data analysis really well, the difference from zero to one stroke is a much bigger deal to me than the difference between one stroke and two strokes. So five children having one event is far worse to me than one child having five ischemic events.

So in terms of thinking about what best should go on the label, the Kaplan-Meier curve would seem to convey the best information to me for a clinician to discuss the risk/benefit tradeoff of the device to a parent. So that's aimed at your previous question.

DR. ZUCKERMAN: Thank you. And can we just ask the hematologist one additional question? You've taken us through a very complicated scenario, and the summary slide of percentages within predefined bounds is low for a variety of complex reasons, but if you were to change the anticoagulation and protocol going forward in several ways, would there be some suggestions?

DR. MASSICOTTE: I think that's a very difficult question because we have no reason to suspect the current anticoagulation protocol, from the point of view of outcome events, and so I think that's a very challenging question which we need to pay attention to as we go forward.

DR. YANCY: Before we allow the Sponsor to complete this section, are there any new areas or new questions or unaddressed concerns that any Panel member has for the Sponsor?

Yes, Dr. Ferguson.

DR. FERGUSON: I just had a question about the DeBakey heart. I mean it's already been approved. In children, granted it's a larger size of children, but you mentioned that it hadn't been more widely adopted, and I was wondering why you felt that was and how this device represents an improvement over that one?

DR. FRASER: Well, I believe that we -- this is Charles Fraser again.

I believe that we at Texas Children's had the largest single center experience with the DeBakey child VAD, which was admittedly seven or eight patients, but unfortunately the performance of the device was suboptimal. We had several pump stoppages from thrombus, and the therapeutic profile was very, very challenging. And as you alluded to, it's not at all suitable for smaller children. It's really, you know, for adolescent size patients. So --

DR. YANCY: Dr. White, please.

DR. WHITE: I'm not sure if this is the appropriate time, but we are being asked for suggestions on the package insert. Is that correct?

DR. YANCY: It is, and we will discuss that later this afternoon.

DR. WHITE: Thank you.

DR. YANCY: Additional questions? Anything that's been unaddressed?

I think you've satisfied the Panel. Again I appreciate your clarity and your responsiveness to a number of areas. So thank you very much.

It is now 3:08, and so we will take a break until 3:30. I would request that the Panel members take a fairly close look at the prepared package from the FDA that says Final FDA Questions for Circulatory System Devices Panel, Berlin Heart EXCOR Pediatric Ventricular Assist Device. This is a subject that will occupy the rest of our afternoon, and taking a moment to preview these questions will help us move more smartly through the next segment.

We'll reconvene at 3:30.

(Off the record.)

(On the record.)

DR. YANCY: It's presently 3:30. We need to start to reconvene. If the Panel members would come to their places, please. If FDA can be available for any additional questions and if the Sponsor can reconvene, we'll get started just as soon as possible.

The purpose of this afternoon's session is to specifically review the several FDA questions. Each Panel member has a copy of those

questions at their place. I'll give everyone just another minute or less to get situated.

We're still waiting for two of our Panel members, but we will go ahead and get started in the interest of time.

At this time, it is the responsibility of our Panel to focus on the FDA questions. Copies of these questions are in your folder. We prompted you before the break to take a look at those questions so that we can move through this afternoon's session with our thoughts very clear.

I would request that each Panel member identifies himself at the time that you speak to facilitate the transcriptionist just as we've done all day.

I need someone from FDA to project the first question, please.

Question 1a appears before us. While that question is highlighted, let me call your attention once again to the document which reads Final FDA Questions for Circulatory System Devices Panel. There's some language that I need to read so that it can be appropriately entered into the record.

This is Question 1 that addresses the Primary Effectiveness Endpoint Results.

An HDE application must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health

outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. The Sponsor's pre-specified hypothesis test for the primary effectiveness endpoint was to compare the hazard rates of the EXCOR treatment group to the ECMO control group.

The Sponsor seems to have met the pre-specified primary effectiveness endpoint. The hazard ratio for the Cohort 1 comparison (unadjusted for matching) was 0.043 (p-value = 0.004); and the hazard ratio for the Cohort 2 comparison (also unadjusted for matching) was 0.02 (p-value = 0.004). However, these results, as pointed out by FDA, may not have sufficiently adjusted for differences between the EXCOR and the ECMO patients.

There is a table that is at your place on page 1 of 4 of this document. I won't go through the table, but you can read it. Let me just highlight that Cohort 1, intention to treat, had an 87.5 percent survival. The ECMO control group had 75 percent survival. Cohort 2, intention to treat, 24 subjects, 91.7 percent. ECMO control group, 66.7 percent.

Let me also remind you that the pre-specified secondary endpoints include days of transplant-eligible support and ability to de-intensify concomitant hemodynamic support by analyzing the subject's status with respect to whether the subject is awake, ambulating, sedated, intubated, on ECMO or another assist device, and eating.

This then gets us to the question as projected before you; this is Question 1a.

Please comment on the difference in duration of support and success rates (survival to transplant or successful wean) between patients treated with the EXCOR and ECMO.

What we'll do is field the responses from the Panel. When we have a sense that the Panel has reached a consensus opinion, I'll do my best job to rephrase that and present it to Dr. Zuckerman, and he will let us know if the response is responsive and adequate.

So let's begin with Question 1a. Dr. Borer.

DR. BORER: Okay. We've been reminded that our standard is whether benefit is probable and, of course, whether it balances risk, but here we're being asked about the benefit part. And I would say that we've seen observational data, and even if it's only for a subset of the universe of the patients that might be at risk, these data show that this device gives many months of survival during the search for the very rare donor.

The alternate therapy from the data we've seen allows less than a sixth, or maybe less than a tenth, of the amount of time that this new device allows.

We don't have a rigorous comparison, the matching may not be perfect, but we have the best data we're going to get, and unless ECMO has improved dramatically since 2007, and I know that it has not, the lack of

the most rigorous statistical comparisons notwithstanding, it's my strong opinion that the Berlin LVAD is more likely to allow a child to come to transplant than any other alternative. There are things I don't know, but I think that the comparison here really in my intuition, without the rigorous statistical analysis that we like, is very much in favor of the new device.

DR. YANCY: Jeff, that's very good. Let me see if I can paraphrase this for the purposes of the group, and say that your answer to Question 1a is that the EXCOR provides significantly more time by at least an order of magnitude and with regards to probable benefit, that you believe that that is significant by a clear margin.

DR. BORER: Yes.

DR. YANCY: Dr. Jeevanandam.

DR. JEEVANANDAM: Yeah, I confirm, I think from an effectiveness point of view compared to ECMO, it is clearly an effective device to bridge a patient to transplant. There's no other device that can achieve what this does, which it gives mobility to the patient as opposed to ECMO, which basically makes the patient completely in bed. Conceivably these patients at some point may even be able to go home. So I think from an effectiveness point of view, this has passed its test.

DR. YANCY: Thank you. Dr. Somberg.

DR. SOMBERG: I agree with both my colleagues and want to go just a little bit further because everything I've heard today besides the

very concise and limited cohort, when you expand it and you take all 200 patients, all the numbers I've heard is there's reduced mortality. So you're on this thing longer, and you have a better chance of the rescued transplant, and at the same time, you seem not to pay for that with, in fact, you get the dividend of less mortality. It may be by half if these numbers are correct. So that impressed me very much.

DR. YANCY: Dr. Nykanen.

DR. NYKANEN: Just speaking practically as a pediatric cardiologist who looks after these patients, this is just one of the many therapeutic options that may be available for somebody as part of a heart failure program or heart failure management. I don't work in a transplant center, and currently my biggest difficulty with parents is the decision to put somebody on mechanical circulatory support either with an active pump or on ECMO with passive drainage because the duration that a patient can survive to transplant in that situation, I really wonder sometimes if we're using ECMO or as we call it, CPS, as a right of passage to death rather than any hope for survival, and I think what the EXCOR has demonstrated here is that the -- and we've struggled with the comparison groups here, because really what we're talking about is a comparison group, comparison of children who are destined to die. Getting a transplant when the mean wait is 119 days inside of 14 days, which is the practical limitation of the existing devices for these kids, is impossible.

So I think that in many ways that the EXCOR has demonstrated that it does provide these kids the opportunity to be transplanted and the opportunity to do well where the alternative is death.

DR. YANCY: So what I hear you saying, doing the same thing that Jeff allowed me to do, but if I can paraphrase, in your view, this meets a critical unmet need?

DR. NYKANEN: Absolutely.

DR. YANCY: Dr. Connor.

DR. CONNOR: I agree that EXCOR definitely improves the duration of time that we can bridge here.

I do wonder if there's a bit of lead time bias, and maybe if it's not as dramatic as we see, and I still think it's dramatic but, you know, with ECMO, and I'm not a clinician, it seems that you wait as long as you possibly can before you put someone on ECMO because you know the duration is short, whereas because EXCOR is much better, you can start a patient on it sooner. And so in terms of the overall time to wait, there might be sort of a lead time bias in what we see on EXCOR, but I think that's a good thing, and it speaks to the effectiveness of the device, but still may lead to a bias.

DR. YANCY: You know, the alternative, taking the bias in a different direction is given the number of children who required the ECMO prior to the Berlin Heart and how that disadvantages the outcome, this may allow you to obviate that exposure.

DR. CONNOR: That is a good point.

DR. YANCY: Dr. Nykanen again.

DR. NYKANEN: Just also to address that the ability to put patients on early, I think, occurs in the setting of a chronic heart failure management program. I have had anecdotal experience with two patients that I have treated in my center where the focus has not been get them onto to support because they really came into the emergency room crashing, and they had to be crashed onto support or left to die. We made that decision with the family in the space of about 15 or 20 minutes. It's an incredibly difficult time.

At that point, my center had to make the decision, now we've got a patient who's on mechanical support. What do we do? And I think one of the issues that the committee might have is how does this get rolled out, and in my center, again not being a transplant center, the focus was how do we get that patient on support to a center that can offer this type of therapy, and that's exactly what we did with good outcome.

So I don't think it's necessarily being able to institute it earlier in patients who may need it, but there's still going to be a significant subset of patients that are going to show up to the emergency room who are going to be nearly dead where if you don't make the decision very quickly, it's going to have to happen, and I think there still will be a role to transition patients from ECMO or other mechanical support services onto something

that is more chronic and long term.

DR. YANCY: This remains the critical question as it is the first question because it is a basis in part for the requirement to meet the humanitarian use exemption and its probable benefit. So I'd like to be certain that everyone who wants to contribute to this discussion has the opportunity to do such. So, Dr. White, please.

DR. WHITE: Thank you. Dr. White, New Orleans. I think it's important that we recognize both the comments that Dr. Nykanen made and Dr. Connor. I believe we've made a very sincere effort at turning a cow into a horse statistically in order to compare the two groups. It's clear that ECMO doesn't provide the length of time that you can get from this device, the EXCOR device. I think we need to recognize the EXCOR device is not without risk. It is a high-risk device, but despite that high risk, it does provide a clear benefit for the patients that receive it.

DR. YANCY: You know, Dr. Lange is from Texas. He might tell you the cows look pretty good. Dr. Page.

DR. PAGE: I agree with what's been said already. I think it's important to recognize that the ECMO group is a reference group. There is no control here, and as a matter of fact, the trial was conducted without any randomization, without a control group because there's nothing to compare it to.

That being said, I am seeing adequate demonstration of

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probable benefit to help that outweighs risk of injury for this device.

DR. YANCY: Thank you for the input. Dr. Moon, please.

DR. MOON: I think we have to remember that -- I mean these results are outstanding. The ECMO group is obviously not a good control group and probably were sicker patients I would guess in retrospect. However, regardless of whatever the group was that we compared them to, 90 percent survival to transplant or successful wean is remarkable, and in that regard I think it's irrelevant what our control group is.

With that being said, we have to remember that this was a group with very strict criteria for inclusion, and I just want to remind everything that there is a patient that this probably will work in. However, we can see from the compassionate and emergency use side that there's going to be groups of patients that it shouldn't sort of be a knee-jerk response. Like, for example, we're going to talk about single ventricle, but if every hypoplastic case that goes bad, I don't think every single hypoplastic case that goes bad should have one of these devices put in before they die.

DR. YANCY: Are there other members of the Panel that wish to speak to this point? Dr. White, your light is on. Are you still thinking about horses? (Laughter.)

Are there any other Panel members that would like to speak to this?

Dr. Zuckerman, then in response to Question 1a, please

comment on the difference and duration of support and success rates, survival to transplant or successful wean, between patients treated with the EXCOR and ECMO, this Panel believes that the technology being evaluated, the EXCOR, provides considerably more time by a full order of magnitude or greater for children that are in need of transplantation and the bar of probable benefit has been met and likely exceeded by a clear margin. They believe that there is no other device available that does a similar thing, that the reference population, that is children treated with ECMO, are being treated with an unapproved device for this indication with a significant complication rate that accelerates over a short period of time, and believe that the application of this device will improve the opportunity for transplantation for children that are desperately ill, and it's been passionately stated that this device will fulfill an unmet need and will be a significant contribution in pediatric cardiology. Is that acceptable?

DR. ZUCKERMAN: Yes, that's a very helpful summary.

DR. YANCY: Next question, please. The next question is to please comment on your interpretation of the secondary endpoint results.

Remember, this is days of transplant eligible support and the ability to de-intensify concomitant hemodynamic support by looking at a number of subjective and objective metrics. Is the patient awake? Is the patient ambulating? Is the patient sedated, intubated? Is the patient still receiving other mechanical support including ECMO? Is the patient eating?

Dr. Hirshfeld.

DR. HIRSHFELD: Well, since there wasn't a large crowd of people volunteering to comment, I'll comment for the purpose.

I think that these findings are consistent with the findings that we just discussed, that patients who have this device implanted, who are fortunate enough to escape serious complications of the device, clearly derive physiologic benefit from the kind of support that they get, and this is very consistent with the adult bridge-to-transplant concept, and I think it's just replicating the way we see seriously ill adults with heart failure as being optimally managed.

DR. YANCY: Thank you. Dr. Lange.

DR. LANGE: I would agree with the general concept, is that I think that secondary endpoints, I think if we're going to use this in the future though, what I would encourage is the days of transplant eligible support is very subjective, 99.3 percent of the time they were eligible, and that was just because we said as long as they're alive, we're going to do it on a day-by-day basis. Therefore, they're eligible. So I just think we need to define that a little bit. I think all of us agrees that they weren't eligible all of the time if they're fungemic or septic or things of this nature or had a stroke in the last 24 hours. So I would say, if we use this in the future, I would encourage FDA to come out with more specific definitions.

DR. YANCY: Dr. Lange, that's a good point because clearly it

wasn't completely objective, that there was some subjectivity, and a lot of it had to do with physician-centric, patient-centric factors and availability of donors. So a very good point.

Other comments about the secondary endpoint?

Yes, Dr. White.

DR. WHITE: I'd like to echo Dr. Lange's report or comments, and also I'd like to add to that, that we should be looking at other measures of eligibility.

One of the problems we have with children with congenital heart disease and a problem that shows up on LVADs in particular is increased PRAs, that you may be eligible for transplant but may have problems receiving a heart because of the elevated PRAs that might show up, and we didn't have any information on that from your study. If we have a postapproval study, I think that should be included.

DR. YANCY: Well, especially given the incidence of bleeding.

Dr. Weinberger.

DR. WEINBERGER: Yeah, I think that when we're talking about these secondary endpoints, we're operating more from a sense of what things are rather than from data because looking back at the data, I can't tease out how long it took patients to wake up, how long it took them to ambulate. So there's a sense, and the sense is that these patients seem to do better. I think that that's supplied more in the way of testimonials than

in the way of objective data.

DR. YANCY: And I think the closest we had was the metric that Dr. Lange mentioned. I, too, didn't see anything very granular about some of these other outcomes.

Yes, Dr. Nykanen.

DR. NYKANEN: Just as a comment, I do think that the fact that we're talking about these patients being awake, ambulating, whether they're sedated or not or intubated is a big step forward, that no patient on conventional mechanical support, as a child right now, ever achieves really being awake and certainly not ambulating. They're always sedated, often intubated, and never eating.

So I think that again the fact that we're talking about this speaks I think to some of the efficacy of the strategy at least.

DR. YANCY: So you are correct that the context really is important here, and we shouldn't lose sight of that.

Other comments about the secondary endpoint?

Well, if the Panel will allow, let me attempt to phrase our response to Dr. Zuckerman.

Regarding Question 1b, please comment on your interpretation of the secondary endpoint results.

It's the sense of this Panel that the secondary endpoint results are consistent with the primary effectiveness result, specifically that there is

evidence of probably physiologic benefit. We do believe that going forward, particularly if this were to become a PMA application, that more objective metrics would be required for the secondary endpoints specifically with regards to transplant candidacy and evidence of preformed antibody formation.

Is that acceptable?

DR. ZUCKERMAN: Thank you. That's a very good summary.

DR. YANCY: Next question, please.

Question 2a is being highlighted for you. Let me read into the record the Primary Safety Endpoint Results. This is on page 2 of your handout.

The overall serious adverse event rates and the upper bounds of the confidence interval for Cohorts 1 and 2 study patients were below the pre-specified success criterion of 0.25 serious adverse events per patient day of support (as shown in the table that appears at your place). However, 33 percent of patients in both Cohorts 1 and 2 had neurologic complications, which occurred at a higher rate compared to other types of adverse events. This rate was also higher in Cohorts 1 CAP, 3A, and 3B.

I will just highlight two findings from the table. Cohort 1, the success criterion again was less than 0.25 events per patient day. What was observed was 0.068 events per patient day, and for Cohort 2, what was observed was 0.078 events per patient day.

Before we accept deliberation on this question, there was an unanswered question, and if I can get the Sponsor to indulge us, if anyone was able to quantitate the number of events per patient -- several Panel members came to me during the break and wanted that separate metric. My apologies for not bringing it to bear earlier.

DR. CANTER: Charles Canter, St. Louis. Please put up the slide.

These are the SAE per patient rates for all the cohorts, 1, 2, the CAP, 3A, and 3B. As you can see, that four out of the five that are represented here, they clustered around four adverse events per patient, and the 3B, older one, which was a smaller number, they were higher. Again, interpreting these results outside of the context of how many similar events would occur in patients in severe heart failure in an intensive care unit makes assessment of these numbers as a marker of the EXCOR I think somewhat problematic.

DR. YANCY: I do appreciate your responsiveness to the query. Let's leave this graphic up and take just a minute to see if there are any Panel members who want to either discuss this or have a secondary question? Val.

DR. JEEVANANDAM: I'm ready to discuss it unless somebody has a secondary question.

DR. YANCY: Yes, Dr. Posner.

DR. POSNER: I just have one question. Is the number SAE per

patient just SAEs divided by N? So we don't know if one patient had eight events and one patient had one event.

DR. CANTER: Correct.

DR. YANCY: Any other primary comments about the graphic before us in terms of these data?

Hearing none, then if we can go back, and thank you. If we can go back to Question 2a, please.

The question is as follows: Please comment on the clinical significance of the stroke rate and neurological outcomes that were observed in patients treated with the EXCOR.

This is in the context of evaluating the primary safety endpoint result, and this is again in the setting of the humanitarian use exemption where we have to have some reasonable assurance that it is presumably an acceptable safety profile.

Dr. Jeevanandam.

DR. ZUCKERMAN: If I could just make a minor correction to Dr. Yancy's statement. The HDE provision is safety and probable benefit, not reasonable assurance.

DR. YANCY: Thank you. Dr. Jeevanandam.

DR. JEEVANANDAM: So I think if you look at this data de novo, you know, one would be alarmed by the 33 percent stroke rate. Obviously a lot of these patients have been rescued by transplant as opposed to an adult

patient population. The pediatric patients must be much more plastic and can recover from their strokes.

So if you compare this VAD to an adult VAD, you know, it would compare unfavorably. However, there is nothing in the pediatric population to really compare this to. So there's no alternative.

So, you know, how do you discuss safety? Do you discuss safety as a de novo concept and say 33 percent stroke rate is high, but then you do have a greater than 90 percent success rate getting transplanted, or do you put it in the context of, you know, a 10 or 25 cc pump which, you know, with the low flows that are required in the infants, you know, you almost can't avoid having clot formation there no matter how much you anticoagulate these patients. So I think, you know, the rates are high, but I think they would almost be expected to be high, but the overall results are good.

So, you know, it's a dichotomy because, you know, what do you compare the safety to, and if you compare the safety to ECMO or you compare the safety to nothing and death, then I think it's safe, but if you compare it to an adult VAD, it's not, but you can't compare it to an adult VAD because the flow patterns are very different.

So I think all in all it's safe.

DR. YANCY: That was helpful. Dr. Borer.

DR. BORER: Yeah, I certainly agree with Dr. Jeevanandam, but

I would say this is a difficult question, and I have to answer it in two parts.

Strokes and infection, which we'll talk about, do occur with the Berlin LVAD, but remember that they didn't occur in the great majority of patients, and indeed most patients reached transplant, and that was true in all the populations we looked at. The two cohorts in the study, the non-IDE population, even the single ventricle population, most patients actually did well. The majority did well. Some had strokes. Perhaps the rate is higher than we would like.

But the problem with answering this question as rigorously as it's written, it says comment on the clinical significance, and I can't because I don't know. We don't have the follow-up data. That's what we would need to comment on the clinical importance of these events.

I'm happy with the data we were presented during the discussion. They suggest to people that the kids do reasonably well within the context of having a horrible disease to begin with, and I again point out that the majority of patients in this database did not have a stroke.

So I think that the answer is that the stroke risk is something I'm concerned about, but certainly I believe that in this context it's outweighed by the probable benefit.

DR. YANCY: So, Jeff, let me push back in two ways because earlier when we talked about the stroke risk, you correctly pointed out the neurological plasticity in this patient population. So can you revisit what you

said in the context of how that influences clinical significance?

DR. BORER: Absolutely. A very important point. That's why I say I can't really answer the question properly because to do that, I would need to know the one and two-year follow-up to know what the neurological, or three-year or four-year follow-up or five-year follow-up, to know what the neurological outcome was and really what the outcome of the infections were as well that we're going to talk about next.

So I think that I'm cautiously optimistic by what I heard. I can't tell you what the clinical significance is. I'm hoping that the plasticity of the child's nervous system is such that a lot of the deficit can be remediated or will be remediated by normal healing, but I do know as one of the investigators said, it takes a long time for the nervous system to recover from an incident, from an ischemic incident. It can take a year for maximal recovery, and we haven't heard those data yet. I'm optimistic, but I don't know the answer.

DR. YANCY: So what I have so far is, yes, it's safe, and I have probably safe from Dr. Borer, and if Dr. Zuckerman will permit, let me just repeat what we started with today regarding the HDE application.

To determine that the device does not pose an unreasonable or significant risk of illness or injury and that the probable benefit to health outweighs the risk of injury or illness from its use.

So that is the language. That's the context of safety, and that's

the kind of thought process we're trying to drill down on now.

Dr. Page.

DR. PAGE: Well, let me at the outset say that I think given the definition of safety that we're provided, this meets that acceptable definition.

That being said, I am very troubled by the level of sophistication or lack thereof in terms of surveillance and prophylaxis for clot. A real concern here is stroke, and if it weren't troubling, it would almost be quaint that every four hours we peek at the tube and the pump to see if we can find a clot, and that determines whether we change out the device, and we're using dipyridamole, and there's no experiences yet with more sophisticated antiplatelet therapy.

So I'd call on the transplant and pediatric heart failure experts to look to the future of defining a better way of both surveillance and prophylaxis for thrombotic complications.

DR. YANCY: You know, I can tell you with a 20-year experience in adult transplant medicine, trying to come up with anything other than observational data, particularly regarding drug efficacy, is very, very difficult, but I'm very sensitive to your comments.

Dr. Slotwiner.

DR. SLOTWINER: I think it's remarkable how low the other complications are, particularly infection, and clearly stroke risk will be the

focus of any postmarket approval study if this device does get approved, and I think being an adult patient physician, the term stroke has a different implication to me than clearly the impact is in this population. So as everybody else has said, I think we just need a lot more data, but in balance, I think the benefits clearly outweigh the risks.

DR. YANCY: Well, but do remember some of these strokes were fatal. So I mean it's still a real issue.

Yes, Dr. Moon.

DR. MOON: Yeah, I agree that I think that it's a serious issue, and I don't think we can just sign off on it completely, nor should the Sponsor sign off on it with postapproval studies. I mean if you look at the Kaplan-Meier survival curve, for stroke, actually the incidence was over 40 percent of a stroke, 42, 43 it looked like on the graph. With other devices, if we had a new valve here we were assessing, we wouldn't approve it with a 42 percent stroke rate probably. So, you know, the benefits of the device are there and are proven, but these aren't insignificant strokes. They're not TIAs for the most part. These are true embolic strokes that leave kids not being able to use their right arm, and that was considered a mild result long term. So I don't think we can just sort of say, oh, it's fine and forget about it. I think we need to keep investigating it and try to figure out what's causing it and make it better.

DR. YANCY: So, so far I have two votes for safe, Dr. Slotwiner

and Dr. Jeevanandam, and three in the probably range, Dr. Borer, Dr. Page, and Dr. Moon. Did I get that correct? I don't want to misrepresent anything.

DR. PAGE: As we define safe, I think I would say, yes, in the context of --

DR. BORER: I would, too.

DR. PAGE: -- the study definition.

DR. BORER: I would, too.

DR. YANCY: So that makes it four in favor of it being safe by the study definition and one that remains probable.

Dr. Weinberger.

DR. WEINBERGER: I'm a little bit troubled by the study definition, which I feel bound to by the process. The study definition makes these devices look incredibly better than a different compilation of what really happened. So if you look at rates, the rates look extremely low, .06 compared to a point predictor of .25. This looks like an incredibly safe device, but when you look at the patients, 30 to 40 percent of patients had strokes, and I think that this metric is really unacceptable as a safety metric going forward. This really hides what's going on here.

So I will say that as pre-specified by the FDA, this certainly does meet the metric. My sense is that relative to death, it's better to have a one-third chance of stroke. And so in the context of the effectiveness, the

safety or relative safety is acceptable, but this method and this tabulation in this metric is really not acceptable going forward.

DR. BORER: Can I --

DR. YANCY: So let me push back for just one second. Just a minute, Jeff. In the context of the humanitarian device exemption, fewer than 4,000 applications a year, about 300 transplants per year, each center in the country doing about 5 to 7 cases, some perhaps doing a bit more, some quite a bit fewer, do you still have the same conviction as you expressed it for the safety bar?

DR. WEINBERGER: It's not that the -- I think the safety bar, the way it's been defined and the metric used, covers up many sins. That's my problem with it. I think that when we drill down and looked at the data in a way that uncovers what's going on clinically, we -- at least I get the sense that this would be an acceptable risk in the context of the benefit.

DR. YANCY: Dr. Borer.

DR. BORER: Yeah, may I just ask for a clarification. As I recall the data from the book and from the presentation, 40 percent strokes is not correct. You have to determine what population you're talking about. We had a study done here, and the stroke rate was not 40 percent.

DR. MOON: That was the Kaplan-Meier curve. If they want to show it again, you'll see it. It's 42 percent.

DR. BORER: But the Kaplan-Meier curve was for people with

single ventricle as I recall. Was that not right? I mean maybe we need a clarification about this.

DR. YANCY: The Kaplan-Meier was assigned to first stroke, and there were 60 percent that were free after about 40 days. So there was exposure.

DR. AUGUSTINE: But there were different numbers presented in terms of Cohorts 1 and 2 versus --

DR. BORER: Right.

DR. AUGUSTINE: -- Cohorts 1 through 3.

DR. BORER: Right.

DR. AUGUSTINE: And in Cohorts 1 and 2, which I believe is what you're getting at, people who met the inclusion and exclusion criteria, that number was 29.2 percent in both Cohort 1 and Cohort 2.

DR. BORER: Right. That's exactly what I was talking about.

DR. MOON: Right. That's the overall incidence. That's not the Kaplan-Meier incidence.

DR. YANCY: Dr. Lange.

DR. LANGE: I just want to highlight Dr. Weinberger's point. His point is this, and that is if a patient does fine and dies on day 5, their SAE per day is .2. We would consider that acceptable by this definition, and his point is that we need to refine that definition. I think that's his point.

DR. YANCY: Yeah, point well made. If the Sponsor could very

briefly give us clarification on the stroke occurrence.

DR. CANTER: Charles Canter, St. Louis. The rate of strokes in the IDE cohort was 29 percent, okay. There were 24 patients in each Cohort 1 and 2, and 7 patients in each cohort got strokes.

We indeed showed the Kaplan-Meier curve that Dr. Moon is referring to, which is the freedom from first stroke for people who are transplanted or censored. It also showed that if you looked at a hazard function curve, from that Kaplan-Meier, there's an ongoing risk of stroke with continued days on the device. So what happens is the risk of stroke in the device is not just related to the device. It's also related some degree to the luck of the draw of donor availability for individual patients. There's a lot of factors, not just the device, that are associated at the risk of stroke, you know, in a child when you're waiting on a VAD.

DR. YANCY: Point made. I appreciate that. Dr. Posner.

DR. POSNER: I'd just like to point out a number of people have said that these youngsters have very good neuroplasticity, and I think that's an overstatement. Clearly their plasticity is better than a 60 or 70 year old, but some of these children we've seen today are 7 years old, 11 years old. They're going through a heart transplant. They could be immunosuppressed. They may come from an environment where they're not going to get all the wonderful care of the Mayo Clinic to develop that plasticity, and so I think we have to say that we really don't know what the

significance is until long-term studies are done on the population of patients that survive the stroke, get the transplant, and go out two to three years.

So, you know, I would give you a no answer on the significance of the long-term effect of the stroke, and I think we've all said that at one time or another during today's discussions.

DR. YANCY: I appreciate that. I'm trying to keep up.

Dr. Lange, I'm assuming your vote is the same as Dr. Weinberger, within the definition safe?

DR. LANGE: Safe, yes. Within this question, the comment on the clinical significance, I'm with Dr. Barrett [sic], I can't do that.

DR. YANCY: Okay. Dr. Hirshfeld.

DR. HIRSHFELD: I'd just like to follow up on a comment that I made earlier in that I think that the definitions of quality of life outcome and neurological outcome that have been used to provide data to us are really inadequate to describe exactly what's going on with this patient population, and we're told that the patients who were stroke free had a PSOM, if I'm remembering correctly, of about 1.5.

And what we don't know is what fraction of patients had a PSOM of 0, in other words, if they got through the whole experience and got transplanted and were neurologically normal, and what fraction of patients had some neurological impairment left over from this procedure.

And I think the importance of this is that we still don't have a

good feel for what we're accomplishing by this entire enterprise in terms of how many children who present at imminent risk of death and receive this device actually exit from the experience successfully transplanted and with a really good quality of life. We don't have that fraction that we haven't seen.

DR. YANCY: Let me do this. Is there anyone -- just a minute. Is there anyone on the Panel who abjectly disagrees that this is a safe device even by the provided definitions?

UNIDENTIFIED SPEAKER: Disagrees?

DR. YANCY: Disagrees, yes.

Okay. Thank you. Dr. Augustine.

DR. AUGUSTINE: You know, it seems that there are several issues with the difficulty in answering this question and potentially have impact on how to think about this issue moving forward. There is the initial limited information in terms of baseline neurologic status in these patients before transplant.

Looking at some of the data in FDA's summary, baseline function by PSOM in those who could actually be assessed was already in the moderate range and some of them then had improvement.

So I think the assumption that we are comparing to zero in a number of ways is flawed. So there's going to be some inherent stroke rate in children with complex congenital heart disease and children in fulminant heart failure who don't become implanted. So the baseline is not zero.

We're not thinking about 30 percent compared to 0. It's 30 percent compared to some unknown that certainly is greater than 0.

The next issue similarly is that it's not just the stroke rate that we need to consider, but again those long-term outcomes, and in the same vein, again what is the comparison for those who are not intervened upon, and speaks to the need for improved data collection in terms of registries, in terms of other kinds of data collection so that we can answer these questions in the future. Even if we do follow patients for five years in a postapproval study again, what is the comparison? How do we know what the impact of this device has been? Have we prolonged the period of support to transplant only at the expense of neurologic dysfunction? Or are we going to be able to answer that in some more meaningful way?

But as others have said, I think the take home here is that 70 percent of children survive without discrete acute neurologic events. It doesn't mean that they weren't impacted neurologically. We haven't talked about oxygenation or microthrombotic events. We haven't talked about toxic metabolic effects and the other myriad ways in which they are impacted neurologically. But in terms of discrete events, 70 percent of children are moving out of this without sequelae.

DR. YANCY: Thank you. Your points were excellent and very well put.

If the Panel will allow, let me try to paraphrase what I've heard

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in response to Question 2a. Please comment on the clinical significance of the stroke rate and neurological outcomes that were observed in patients treated with the EXCOR, and this is being responsive to the question of safety.

What the Panel is willing to comment to you, Dr. Zuckerman, is that overall there are some residual concerns that remain that are interpreted in the context of the severity of illness of the patients that were studied here, specifically the children, and with regards to their ability to recover and overcome the initial impact of having had a stroke. We also acknowledge that this is a complex environment where other factors may contribute to a stroke rate independent of the device.

With that having been said and in the context of the definitions of safety for the HDE application, more Panel members than not believe that these data reach that bar, but hopefully there will be soon longer-term outcomes that will help us have a better perspective on this, and should this be revisited with a PMA, we would insist on seeing quality of life.

Is that responsive?

DR. ZUCKERMAN: That's a very helpful summary. Thank you.

DR. YANCY: As we go to the next question, I need to enter into the record the next comment.

Although pump change was not considered an adverse event

for this study, 52.3 percent of patients implanted at IDE sites and 45.6 percent of all patients implanted at any site required one or more pump changes due to visible thrombus in the pump circuit. There was also a higher incidence of ischemic neurologic events in patients requiring a pump change (31.6%) compared to patients who did not receive a pump change (13.5%). A detailed examination of the available data did not reveal any specific events, anticoagulation deficiencies, or co-morbidities as contributing to the incidence of pump thrombus.

Question 2b is before us now. Please comment on the clinical significance of pump changes including the high stroke rate that was observed in patients treated with the EXCOR who required pump change for visible thrombus.

We had quite a bit of deliberation about this when the Sponsor spoke. We'd love for one or two members to kind of crystallize what we heard. Dr. Somberg.

DR. SOMBERG: The question is that fact, the last statement, because I thought -- it says a detailed examination did not, you know, reveal any specific events in anticoagulation. I thought it was said that we couldn't determine it given the way. So we really don't know that. I mean is this fact or is this really sidestepping or covering over an issue that we really don't have data on because I thought the hematologist who was from the Sponsor said that we couldn't really make a determination on that. Can you clarify

that for me?

DR. YANCY: My understanding from the hematologist, Dr. Massicotte, was that there was no gross evidence that coagulation deficiencies were related to events. I'm assuming that did not misrepresent what you said. There's no need to get up. But I'm assuming I did not misrepresent you.

So with that in mind and considering that this is the question per se that the FDA would like to address, I think the comments remain as they are, with the understanding that we may not all agree in principle with what's positioned here.

Dr. Connor.

DR. CONNOR: I think in some ways that the rate of pump change is a bit irrelevant in the grand scheme of stroke. I mean stroke rate is very important but, you know, for instance we know you have to change bandages frequently after a surgery. Maybe that doesn't mean the fact that you have to change them a lot means having bandages on there is a bad thing.

I think there probably does exist data, and I mentioned the idea of doing the Kaplan-Meier curve for time to pump change can be illustrative, maybe even going to sites that had low stroke rates and seeing if they had higher pump change rates to see how that factored in. I think there's a lot of data there, and even maybe, you know, querying sites that

had low stroke rates and figuring out what they did differently, and I understand there's very limited data.

Ideally perhaps even, you know, given the transparency of the device, a parent who is probably with these children very, very often could be educated, you know, what to look for and then bring it to the attention of nurses who don't have the ability to look as often.

So I think in answer to the question, maybe that pump change isn't really the most important metric.

DR. YANCY: So that's very helpful and, Dr. Somberg, I'm assuming that what you're really getting at is that you do believe that there is a question here, that it is significant if we're having pump changes, and that may be related to other factors. Is that correct?

DR. SOMBERG: That's what I thought, but if saying this statement is correct, that it's really related to the thrombus formation in the pump, I think that's very important and maybe the Sponsor could look towards automating the system of observation. If it's a transparent system, you could put a light transmittance. That's the simplest way you look for platelet aggregates, right? And you could have a feedback system such as, you know, if your respirator stops, an alarm goes off. If there's a change in transmittance, there will be an alarm. So you could automate this if that's the case.

I suspect, as what you were saying, Dr. Yancy, I think is

present, that it has to do with anticoagulation and that in a postmarketing study, which we will get to, that might be two different schemes because I think we're working on a very -- and some of my colleagues have commented, the pediatric pharmacology is always deficient. So maybe we could work in this sphere to make it much less so and there could be the standing group which we've already seen, and then some more maybe aggressive, modern, or whatever adjectives you want to use.

DR. YANCY: Dr. Lange.

DR. LANGE: I think one of the things that was remarkable, and not terribly surprising, is that people on Coumadin, only 20 percent of the time are they therapeutic, and people on unfractionated heparin or low molecular heparin, only 40 percent of the time are they therapeutic, and we're unable to tie that to either thrombus or to ischemic events. And so I'd like, in the future, to be able to tie those things together or untie them, one of the two.

DR. YANCY: Either dismiss them or say they're important.

DR. LANGE: Yes, sir.

DR. YANCY: All right. Dr. Moon.

DR. MOON: Yeah, just one relevant story about Coumadin.

When we first approved bioprosthetic valves, we knew the incidence of stroke was highest in the first three months. So we put all the patients on Coumadin thinking that was going to improve the situation, but when we did

studies comparing the patients on Coumadin with patients off Coumadin, the ones who didn't take Coumadin had a lower stroke rate.

So it could all be temporarily related to sort of the right after surgery, and we saw that after six months or whatever, nobody needed a -- or nobody had a stroke. So --

DR. YANCY: So Dr. Hopkins.

DR. MOON: -- there should definitely be a study on it.

DR. HOPKINS: I was going to touch on -- this can be in terms of clots and having to change out the pump, it could be true-true and related and true-true and unrelated. It's taken us 50 years to figure out how to Coumadinize most appropriately the various kinds of prosthetic valves that we have and hundreds and hundreds of thousands of patients to figure out the mitral position versus the aortic position versus this or that. And it's even more complex in children, where the adult ranges mean nothing in children. The real logic situation and the clotting situation is so different and even almost from month to month.

So it seems to me that it is a design feature of any pump that there will be some clotting, and it has been built into the design that that can be dealt with, with a relatively efficient change-out. You can make it more sophisticated with electronic monitoring. You can look at better adherence to anticoagulation protocols, but this is an inherent design feature of any such pump. So to me, it's acceptable that it is as low as it is

and that the change-out is as easy as it is.

DR. YANCY: Yes, Dr. Augustine.

DR. AUGUSTINE: The fact that clot is expected and that there are systematic ways for monitoring for this raises the question of is it too late by the time you can see it with the naked eye? But at that point, when clot is large enough to visualize with the naked eye, should we be using other technologies to aim for earlier detection so that we can implement that easy pump change-out prior to potentially distant thromboembolic events?

DR. YANCY: So let me try this for the Panel before I capture Dr. Zuckerman's attention.

What I hear everyone saying is that we believe that it is an important observation when there's visible thrombus in this pump, and if that appears to be associated with strokes and a higher stroke rate, whether or not the pump change per se is operative in the stroke event is uncertain, but we do believe that the appearance of thrombus is a concern.

Is that something with which the group concurs?

Is there any amendment or any change to that before we offer that up to Dr. Zuckerman?

So, Dr. Zuckerman, in response to, please comment on the clinical significance of pump changes, including the high stroke rate that was observed in patients treated with the EXCOR who required pump change for

visible thrombus, this Panel believes that it is, in fact, visible thrombus that generates concern and potentially is clinically significant as it appears to be related to a high stroke rate.

We recognize that pump changes occur coincident with this but don't yet have the integrity of data to recognize whether or not that per se contributes to the stroke rate, but our greater concern is visible thrombus.

DR. ZUCKERMAN: Thank you. That's very helpful.

DR. YANCY: Let's proceed and go to the next question. We're now on the subject of labeling.

So I want to remind the Panel that we've just gone through the two most important standards that were required for HDE, that is the definition of safety as provided by the statute and probable benefit, and so we are now moving forward with labeling language.

Again, I'll read this into the record.

The Sponsor has provided the following mortality information regarding patients who received pre-implant ECMO and those with single ventricle circulation.

The table is before you. I won't repeat what's there.

These data show that the incidence of mortality increased in patients receiving pre-implant ECMO and in patients with single ventricle circulation.

Question 3a. Please discuss whether additional language should be included in the labeling regarding patients with single ventricle circulation and those who have had use of pre-implant ECMO. Such language may include data regarding increased mortality in these patients.

So short version, how should this observation regarding mortality for either single ventricle or pre-implant ECMO be represented in the label?

Dr. Jeevanandam.

DR. JEEVANANDAM: I have a problem with this table. It took me a while to figure it out. I think it would be much easier to just say two ventricle ventilation and what the mortality was and single ventricle circulation and what the mortality is or -- yeah. So two ventricle circulation, single ventricle circulation, patients pre-implant ECMO, and then patients without ECMO pre-implant. I think they only have two extra rows, eliminate the column, and just put the numbers out there. This is like double negative, weird --

DR. ZUCKERMAN: Okay. It's good you could figure it out. I couldn't, but do you agree with the general concept that those data are important enough, expressed simply as you have just done, to be put in the label?

DR. JEEVANANDAM: Yes.

DR. YANCY: And I would argue that that is the flavor of the

Panel. Dr. Page, I saw your hand.

DR. PAGE: I'm troubled by what message we're trying to convey, and I think there are two separate situations.

Let's take the ECMO first. You might have the option of starting ECMO versus waiting or proceeding quickly with the VAD. There you have an opportunity, and I think the data are important to know in the first place, but there you have an option, and if you can possibly get to the VAD in time, you wouldn't start the ECMO.

The issue of the single ventricle, I don't think it's appropriate to imply that it's inappropriate to provide this VAD for a single ventricle. I think the survival might be assumed to be lower with that patient, but given the fact that what we've seen is that the likelihood of survival without this is negligible in those patients, then one needs to accept that the potential benefit might not be as great, but you have no other option.

DR. YANCY: That's an important issue. There may be some different opinions from the Panel. Let's go to this side. I think Dr. Borer.

DR. BORER: Actually it's not a different opinion; it's an absolutely supportive opinion. What Dr. Page said was exactly the conclusion I had come to, that is, that these data do need to be presented. They need to be presented in a clear way. There are very few data here, but they need to be presented clearly.

One message is if you have single ventricle, it doesn't mean

that you can't survive if you're on this machine until a donor is found.

The other message is maybe we shouldn't be using the ECMO. Maybe we should be going to this first. Maybe. There's few data, but I think it's very important without necessarily drawing those conclusions in the label to clearly present the data so that the treating physician can draw whatever inferences he or she wants to from them.

DR. YANCY: So to be clear, are you suggesting that we just represent the data as they are quantitatively without any attempt to make a specific comment about the interpretation?

DR. PAGE: Well, I would go so far as to say that based on these data, if one has the option of proceeding with VAD before ECMO, that the data would suggest that that would be advantageous.

DR. YANCY: I totally understand that, but what about single ventricle?

DR. PAGE: For the single ventricle, I would quote the data that we have, and I think it was 7 out of 21 survived to transplant, 1 out of 21 survived to wean. So that's 8 out of 21 survived out of a population that survival was estimated at 5 or 10 percent if they went to ECMO. So I would say that the likelihood of survival with single ventricle is likely lower than non-single ventricle physiology. However, I would represent this as an option for those patients.

DR. YANCY: And, Jeff, you agree with that?

DR. BORER: Yes.

DR. YANCY: Okay. Dr. Zuckerman.

DR. ZUCKERMAN: Yeah. Perhaps this will be helpful for the Panel. It may be possible, Dr. Yancy, just combine Questions 3a and b together because --

DR. YANCY: I thought so.

DR. ZUCKERMAN: -- Dr. Page has got into the heart of the matter.

Right now the label is not acceptable because there isn't a clinical trial section in the label. There are just instructions for how you connect the pump and turn it on and off and all the other key parameters.

So per our standard practice, we would have a clinical trial section that summarizes the Cohort 1 and 2 patients, but we also want to include other relevant data for the practitioner to be able to read and reference, and I think that Drs. Page and Borer have given some comments as to the right context to perhaps put those additional FDA subgroup analyses in with respect to the other 100 patients. In other words, state the data and let the practitioner decide given the mortality rates and other data.

Is that a consensus of the people around the table, or do they have different context that they would put some of these subgroup analyses into?

DR. YANCY: So the statement becomes do we combine

Questions 3a and 3b and take single ventricle pre-implant ECMO as well as compassionate use and emergency use data and just represent all of that quantitatively with very little narrative and allow the user to interpret the data as they would be so inclined?

Are there those that disagree with that approach, or is further discussion needed? I see several hands.

Dr. White and then Dr. Weinberger.

DR. WHITE: Michael White, New Orleans. I think that in my recollection going through all this data, we looked at survival data on the single ventricles, and those being used off label, as it were, were outside the recommendations, but I don't think we carefully considered what the SAEs might have been in all those populations or specifically within those populations, nor did we break it down. And I think if you're just going to use survival data, without any of the -- go ahead. You had a comment about the SAEs?

DR. YANCY: No, at this point, this is Panel deliberation.

DR. WHITE: Okay. I think it would be perfectly reasonable to state that we have determined that the device meets the safety recommendation for those cohorts of patients according to the recommendations, but the safety and the effectiveness off label or outside those recommendations remains quite uncertain and deserves further study.

DR. YANCY: Well, the question is almost tantamount to

whether or not by virtue of not mentioning or specifically excluding single ventricle and pre-implant ECMO, does that become an off-label use of the device?

DR. WHITE: I think it should be for now until we have better information.

DR. YANCY: Dr. Zuckerman.

DR. ZUCKERMAN: Okay. I would have the Panel members look at the proposed package insert, page 29.

The present indication for use that the Sponsor is going for and is acceptable to FDA does not specifically indicate that those indications that were outside of the so-called IDE protocol trial are off label. They're looking for a bridge-to-transplant indication.

DR. YANCY: Could you tell us that page again?

DR. ZUCKERMAN: It's page 29 on the proposed package insert section.

DR. HOPKINS: I think the problem is there's two page numbers. So look at the 29 on the bottom right, not in the bottom middle.

DR. ZUCKERMAN: You're right.

DR. YANCY: Yes.

DR. ZUCKERMAN: So the bottom middle 31 out of 188.

DR. YANCY: All right. So is everybody on that page? Let's get to that page and, Bram, if you could just restate your comment so you can

have our attention.

DR. ZUCKERMAN: Okay. I want to clarify for Dr. White and others, the Sponsor has proposed indications for use in Section 2.2, to use this device as a bridge to cardiac transplantation for children, and it's important to recognize that while they did do a protocolized IDE trial consisting of originally 48 patients, the FDA did look at the other 150 patients or a cohort of 204 patients total and has accepted a more broad indication as a bridge-to-transplant device.

The implication of this statement is that the FDA would label it as a bridge-to-cardiac transplant device, but in the clinical trial section, we would note all the device data, and we would indicate those subsets where there presently seems to be higher mortality than in the focused 48 patient cohort.

DR. YANCY: Thank you. Dr. Hopkins, Dr. Kato, Dr. Hirshfeld, Dr. Somberg.

DR. HOPKINS: Thank you, Dr. Yancy. I think the approach that Dr. Zuckerman is proposing is the right approach. I don't think you want to tie the clinician's hands with contraindications based upon these end numbers of data. One would expect that the single ventricle population would be a higher risk population anyway, so again what you're comparing to in that population.

So I think you could put language, and also I remind my adult

cardiac colleagues that sometimes the diagnosis of single ventricle is a little bit in the eyes of the beholder. It could be one and a half ventricles. It could be a ventricle that might grow. So, you know, excluding single ventricles is more difficult than you actually might think at first blush.

So something like careful consideration before use in patients with a diagnosis of single ventricle or an in-place ECMO circuit because and then we show the data would be very appropriate so that they would be given pause, but I don't think you really want to tie the hands of the clinicians with their use.

DR. YANCY: Dr. Kato.

DR. KATO: You know, I would agree with that. I think it's premature given the small numbers of patients and given the fact that this is a humanitarian device exemption. This is not a PMA, to start restricting use and, in fact, you know, okay. So you have a single ventricle. Well, then you still have a 54 percent chance of survival. I mean, you know, so it's not, you know, we have not identified any situations here where it's clearly futile and clearly contraindicated. I think this is a first start. I believe that as much outcome data that is reliable should be published here in this section.

We might be able to put a couple of caveats, narrative caveats, but even then, I would be reluctant to tie the hands of the practitioner because maybe there's a situation where he absolutely must do ECMO for whatever reason and, you know, and I think you're swaying him, excuse me,

not him, but the practitioner, you're swaying the practitioner and biasing that person into a decision which may or may not be true.

DR. YANCY: Dr. Somberg.

DR. SOMBERG: What I wanted to say is this is a highly sophisticated group. So we have to know who we're targeting with this product insert, and many of these people know everything that -- the problem better than many of us here today because they deal with this in the transplant or heart failure units.

With that said, I would hope, and I think, just underscore what Dr. Zuckerman is saying is, that I would hope that there would be a summary of the different situations and the data, the overall data, the data about single ventricle, the data about anticoagulation, and all that presented, so someone could find a succinct summary when they wanted to go to this because a lot of what was said today is not general knowledge, and even if you read the pre-briefing booklet, you wouldn't know a good deal of this. I've learned twice as much as when I read this prior to the meeting. So I think that is critical.

And, finally, I don't think given the small numbers here, that some of these questions will ever be answered in a controlled trial to the best that we can. So I think we should just state the data. People will glean in this field where studies and experiential data is needed, and we'll go ahead and work in that direction, but for us to try to limit the scope of this

potentially helpful device is I think poor judgment.

DR. YANCY: Dr. Hirshfeld.

DR. HIRSHFELD: All the points I was going to make about single ventricle have been eloquently made. So I don't feel I need to add to them.

Were you planning also to discuss the issues of the difference between the Cohort 3 and Cohort 1 and Cohort 2?

DR. YANCY: That is in this section.

DR. HIRSHFELD: Yeah.

DR. YANCY: The proposal right now is to combine Questions 3a and 3b into one response.

DR. HIRSHFELD: Right.

DR. YANCY: So if you'd like to make specific comment there, that would be very welcome.

DR. HIRSHFELD: I'd just like to make a comment which echoes what I made before, which is that I think that this is a device, the use of which is complex enough that if it's not used in an institution that has an experienced and active team employing it, that it's not going to be used to its full advantage.

DR. YANCY: Other comments? Dr. Jeevanandam.

DR. JEEVANANDAM: Just one second but, you know, it's a very quick comment. I mean in terms of ECMO, if you had ECMO, you still have a

75 percent chance of being transplanted and surviving, which in the current -- with adult VADs is the bar that was set for the one approved VAD. So even, you know, using that, at 75 percent, yes. Not 90 percent, but 75 percent is the bar with adults. So I don't have any problem putting that as data and not having a commentary about it.

DR. YANCY: Yeah, it does look like VAD has a better outcome than single ventricle without question.

We need to make some specific comment about the table that you see on page 4 of 4 for the handout at your place. Dr. Hirshfeld began the commentary by discussing his views on the patients that fell in Cohorts 3A, 3B. Remember, these were non-IDE sites.

Additional comments here?

Let me just say that as you're looking at this, the straw man on the table is to accept the FDA's suggestion to combine Questions 3a and 3b into one response, that response being to accept a broad indication as suggested for the device and then include a data table which identifies what seemingly are the higher risk cohorts with the quantitative experience realized in the investigators' efforts, and that would include the non-IDE sites that were proceeding with compassionate use and emergency use.

Dr. White.

DR. WHITE: Part of this question is regarding the scope of any training program, and I don't see anything that's going to help us with that.

DR. YANCY: We did receive a response from the Sponsor on the training program. So if you'd like to comment on that now, you may.

DR. WHITE: Well, for labeling, is that --

DR. YANCY: We're in the labeling section now.

DR. WHITE: Yeah, is it in the labeling section, in the labeling section anywhere? The training program?

I don't recall seeing a plan for a training program in the labeling section, and if somebody could find it, that would be great.

UNIDENTIFIED SPEAKER: (Off microphone.)

DR. WHITE: Well, that's part of the question is please comment on how these data should be incorporated into the labeling, your recommendations regarding the scope of any training program with regard to implant techniques, patient selection, recognition, treatment, and minimization of adverse events, and I don't see that anywhere in the labeling.

DR. SOMBERG: But I think everyone is in agreement that there should be a training program, and the Sponsor outlined the training program, and I don't think the Agency would permit the device to be marketed without a training program. But I concur with those statements that we should have a training program, and it was defined, and there was a slide presented.

DR. WHITE: Okay.

DR. SOMBERG: It may be an omission. I thought I saw it, but I'm not going to go try to find it now.

DR. YANCY: Other comments here?

So, Dr. Zuckerman -- sorry. Dr. Slotwiner.

DR. SLOTWINER: Just, you know, in terms of putting non-IDE sites and emergent implant data into the label, I think putting that data in the clinical trial information section makes sense, but just like patients are not going to choose for the most part if they have a single ventricle or choose if they got ECMO first, it's just the way they happen to come in.

DR. YANCY: Point well made. Yes, Dr. Nykanen.

DR. NYKANEN: I just might ask that the data as it's presented here, it's difficult for me to sort out on this why they didn't meet eligibility criteria, what made the person a Cohort 3A, 3B patient, and in the labeling it may be useful to the practitioner to have a list. I saw it in the background information as to the reasons why these patients did not meet eligibility, and I think in the spirit of giving as much information about the study that has been done so far and the patients that have been implanted so far, would be helpful in the labeling to include the reason for failing to meet the criteria as per the label, whether they be a non-IDE site or whether they have multiorgan failure, sepsis, et cetera, et cetera, et cetera.

DR. HOPKINS: Dr. Yancy.

DR. YANCY: Yes, Dr. Hopkins.

DR. HOPKINS: I think we have to remember this is a HUD, so that the local institutions IRB will be involved with the deployment of the device, and therefore the language for this part of the combined two is really aimed at the institutional IRB as much as anybody else. You're kind of advising them that this device would be optimally deployed within the context of a program in which the prescribing physician has undergone the training program. I don't see anything wrong with that. You're really influencing the local IRB to do what they're supposed to do. You're not restricting anything.

DR. YANCY: But to Dr. Nykanen's point, if you look in what's proposed in the label, indications and contraindications, and then compare that to the inclusion criteria and the exclusion criteria, which is what was used to meet the definition did not meet criteria, the several lists are very different.

DR. HOPKINS: But I thought what was being recommended would be that there would be a suggestion that the prescribing clinician should know these data. Those data can be presented just as we talked about in Question 1b or 2b, and that they should be cognizant of these factors, one of which would be that training and understanding of the data would be a part of it. Why wouldn't that? But again the target here is the IRB, not necessarily the prescribing physician.

DR. YANCY: And that's an excellent point.

So in the interest of time, Dr. Zuckerman, in response to Questions 3a and 3b, it's the feeling of this Panel to accept, first of all, putting the questions together; secondly, to agree with a broad indication for the device as offered, but with the specific inclusion of the experience and event rates for those groups that seemingly had a higher risk or didn't fare as well, allowing a practitioner to reach the definitions that apply to their patients on their own.

Moreover, it's the feeling of this Panel that there should be specific articulation of the training program and specific incorporation of what exactly represents inclusion criteria and exclusion criteria as studied in this HDE.

DR. ZUCKERMAN: Thank you. That's very helpful.

DR. YANCY: Let's go to Section 4. This is the postapproval study. Throughout the day, we've made reference to this several times. Remember that this discussion is an independent discussion and does not necessarily mean that the application has been approved.

DR. SOMBERG: (Off microphone.)

DR. YANCY: I haven't said anything yet. Dr. Somberg is really eager to comment here.

The current postapproval study proposes following participants (n = 24) until transplant or recovery. The longer-term (i.e., 5 year) clinical outcomes of the participants following explant of the device

are not captured. According to the clinical study, the median time on device for Cohorts 1 and 2 was 27.5 and 42.5 days, respectively.

Question 4a, and then we'll just go through Question 4e, represents specific questions that FDA wants us to address regarding the postapproval study.

Question 4a. Please comment on an appropriate comparator for this study, postapproval study, given the limitations of the ELSO registry. For example, please discuss whether the current IDE EXCOR cohort would be appropriate.

Question 4b. Given the high rate of neurologic dysfunction in patients treated with the EXCOR device, please comment on the need for data regarding longer-term neurologic and health related quality of life, (HRQOL) outcomes.

Question 4c. Please discuss the need for longer-term evaluation of the causes and incidence of pump thrombus and its effects on central nervous system morbidity.

Question 4d. Please discuss whether an overall adverse event rate of less than 0.25 significant adverse events per patient day on support remains appropriate given that the new proposed comparator may be SAE rates derived from patients in the EXCOR IDE study where the numbers were significantly less.

Question 4e. Please discuss any other additional topics you

believe are pertinent to the continued evaluation of risk and benefit for this device.

Again, in the interest of time, let me just do a straw man and say for Questions 4b and 4c, I think in general, the Panel is all of one mind, that we certainly need data on longer-term neurological and health-related quality of life outcomes, and we certainly believe the need is real for longer-term evaluation of the causes and incidence of pump thrombus and its effect on central nervous system morbidity.

If we all agree with that, we can go ahead and present that to Dr. Zuckerman and focus our conversation on a, d, and e.

Dr. Posner.

DR. POSNER: Just a quick comment. I think Dr. Augustine hit the nail on the head, that the long term is important but you have to have a baseline, and I think what you said is absolutely correct, but I would start that out by saying a baseline neurological function has to be taken before you do the long-term studies.

DR. YANCY: Thank you. Yes, Mr. Barrett.

MR. BARRETT: I just have a general comment, or maybe it's more of a request as it relates to postmarket surveillance.

You know, we've heard a lot already, discussion about the important unanswered clinical questions, and we've heard the term registry used and the term study used and the term postmarket study used, and in

particular as it related to Question 4e, but really to all the questions, I just ask the Panel to carefully consider which of the important, unanswered questions could reasonably be answered in a registry as opposed to requiring a well-controlled clinical study.

DR. YANCY: Thank you. Are there other -- yes. Mr. Dubbs.

MR. DUBBS: I think just saying longer term is not sufficient. I think we should define what that period is. Otherwise, the next time it's evaluated, someone may say, well, maybe it should have been five and a half years instead of three and a half years or seven years, et cetera. So I don't think using longer term without some definition is appropriate.

DR. YANCY: Point well made. Other comments on just bringing forward what would be 4b and 4c as pretty much completed thoughts, and in focusing our discussion on the others?

Dr. Borer.

DR. BORER: Yeah, of course, I agree about 4b and 4c.

4a, I'm not entirely sure what we're looking for here, and I am sympathetic to the comment that was just made about what needs to be a controlled study. What we really want to know here or what we'd like is a little more precision in the outcome -- I think what we would like is a little more precision in the data we have about use of the new device. I'm not sure what comparator we could use other than the data that have been collected in this current application. The ELSO registry is really very

inadequate as a comparator. It's not going to get any better. If this device is approved and is available, my guess is less ECMO, more new device is going to be used. So the ELSO registry will be even less adequate.

I think what we have here is an initial set of data that have been collected, and we can compare new results to this set of data if we want to, but I'm not sure really why we have to do that. I think again we need more precision about the outcomes with this device, and that's observational. It doesn't have to be controlled.

I would say with regard to 4d, if a standard is to be created, a new standard for a comparison, then I think the standard has to be what the data shows happens in this population. The .25 standard was created from no particularly rigorous methodology.

We now have some data. We could define, sort of, an expected event rate and see whether in the long-term study with the training program and whatever developments are going to be made with regard to anticoagulation, et cetera, et cetera, whether the number of adverse events or the rate of adverse events can at least stay within the envelope that's been created that we think is probably effective and safe for an IDE.

I don't think we can ask for more than that. I mean this is, you know, this is something that's really meant for compassionate use. We're being asked to approve an IDE. We're not being asked to approve a PMA as

was said. I don't think we should ask for more than what is reasonable.

DR. YANCY: Okay. So, Jeff --

DR. ZUCKERMAN: Can I respond to that first --

DR. YANCY: Dr. Zuckerman.

DR. ZUCKERMAN: -- or do you want to go first, Dr. Yancy?

DR. YANCY: No, Dr. Zuckerman, please.

DR. ZUCKERMAN: Okay. So I think that's a very helpful start given to us by Dr. Borer. So let me try to simplify the issues.

Right now we have an IDE study. Should these patients be followed long term and will we get the relevant neurological information and health-related quality of life information given that we have limited data in this initial HDE study? That's question A on the table.

Question B is, is there a need, given some of the comments that were made today regarding lack of information in the neuro health-related longer-term quality of life sphere as well as the fact that the use and results from this device may drift over time with an HDE approval, to do a new postapproval study number 2? What is a reasonable approach, Dr. Borer, and others?

DR. YANCY: So in response to that, I think, Jeff, you've helped us out because you suggested that in response to 4d, and in response to Dr. Zuckerman, that we should use the prevailing, if you will, updated adverse event rate for a postapproval study.

DR. BORER: I think specifically in answer to Bram's question, which I now understand a lot better, I think the answer is both. I think the population involved in this study should be followed long term, and I think the FDA suggestion of five years is absolutely appropriate.

I think we do need the long-term information about quality of life, neurological status, et cetera, et cetera, using this strategy. As I said before, we can't attribute any badness to the VAD that's being used, but we do have to know what this strategy means.

However, I'm very concerned about the issue of lack of baseline. If we have lack of baseline, then we really don't know what our strategy is doing.

So I think in addition to following these patients long term, we should have a second study in which we define some things that weren't defined here, so that we can compare what we're doing now going forward with what we have. I think both kinds of studies are appropriate.

DR. YANCY: Dr. Somberg.

DR. SOMBERG: I agree with Dr. Borer and what Dr. Zuckerman said about taking the current IDE study and following it out.

I think we also need to establish a registry of those people who are going to receive this device for the next, since it's a small number, for the next year or two, everybody who receives the device, and follow them out for the future to see what is happening to be able to give some

feedback on this.

The third thing that I'm concerned about, and I don't think it's burdensome, and it may benefit the device and the Sponsor, is the pharmacologic therapy to try to prevent anti -- or neurologic events. Maybe it will worsen the situation, maybe it will have no effect, or maybe it will markedly benefit it, but I think it would behoove the Sponsor who is really having an important addition to the care of these type of patients to get together with a group of anticoagulation specialists and pharmacologists who have emphasis in the pediatric area, trying to come up with -- they have a current protocol, and I think they should try to improve that a bit to a more updated protocol, and then within the universe of people who were getting it, to have a comparative group in that, and that will possibly obviate this major deficiency of the system, which is a neurologic event if it is treatable.

DR. YANCY: Dr. Hirshfeld and then Dr. Slotwiner and then Dr. White.

DR. HIRSHFELD: So I'd like to propose a comparator group which is scientifically invalid, which I think would be illuminating, and that is that a comparison should be made to the outcomes of patients who are successfully bridged to transplant to patients who were transplanted without requiring mechanical circulatory support prior to transplant. It's obviously scientifically invalid because of the different degree of

preoperative severity of illness.

However, in the context that these patients are competing for a limited resource, namely the available pool of donor hearts, you could armchair one of two possibilities. One would be that these patients might do better because they were in better shape because of the benefit from the pre-transplant circulatory support, or that they did more poorly because of the injuries that they experienced as a result of the pre-procedural circulatory support.

And I think this would not be a valid comparison except in the context that we're dealing with a limited donor pool and society at some point needs to decide what the best allocation of that donor pool is.

DR. YANCY: My sense though is that we're already collecting pediatric heart transplant data in already established registries. So we do have that kind of reference.

DR. HIRSHFELD: I'm just suggesting that in going forward, that if this device is approved, that the transplant community will need to examine that question.

DR. YANCY: And I think that's evident, but thank you. Dr. -- I'm sorry. We need to keep going. Dr. Slotwiner, and I'll come back.

DR. SLOTWINER: Thanks. I just wanted to address the question that Mr. Barrett brought up, the discussion of registries versus controlled trials, and I think to answer the question of thromboembolic

events, a registry would not be sufficient, and I think that is really going to be the key issue going forward if approval is granted, and I think a carefully designed trial would be necessary.

DR. YANCY: And then Dr. White.

DR. WHITE: I had a couple of comments. One was in relationship to the donor pool. If these patients are going to go to the top of the list, we want to make sure that their chances of having good outcomes are at least equivalent to those that are not going to be going this route. So I think that's a very pertinent comment and one we should be careful about.

The second is with relation to Dr. Barrett, Mr. Barrett, I'm very much in favor of there being a long-term registry, particularly if we're not going to make anything outside the Cohort 1, Cohort 2 recommendations off-label use, because as soon as this device is available, if we have single ventricles, ECMO, everybody's a candidate for this device, we're going to have no way of tracking that, no way of knowing what's going on, no way of knowing what those outcomes are.

If you make the label more exclusive, then it has to be reported to the IRB and it has to be reported to the Sponsor, but if you open up the label so that there's no reporting of off-label use of this device, then we have no way of tracking that, and I think that's very, very critical information.

So, you know, it may be necessary that we have this 24 patient

postapproval study to answer your question specifically, but I do think we need a long-term registry, at least five years of enrollment, to find out what's going to happen with these less attractive candidates for the device. Otherwise, it's just going to be going, going, going, and we're never going to know what's happening.

DR. YANCY: Well, realize, we have more than just the 24 patients. We have the right to make that decision, but the denominator is actually 200 patients or thereabouts. So if we included IDE and non-IDE, it would be a little bit better, a bigger denominator.

I think Dr. Hopkins, Dr. Connor, and then Dr. Nykanen, and then we'll try to put this in some phraseology for the FDA.

DR. HOPKINS: Thanks, Dr. Yancy. I'm very concerned about the cost that we're talking about strapping onto the back of this device with all these studies. A study as opposed to a registry is enormously expensive. There's the potential that the company would have to pay for every MRI, every neurological exam, you know. It's all a good idea, but I would also suggest we don't have a control group. You face the same problems that the company and the FDA faced some years ago, and we don't have a putative mechanism for any of these side effects, and good controlled studies are done when you have a hypothesis on a putative mechanism. We don't have a putative mechanism. We don't even know if the Coumadin and heparin protocols have anything to do with this.

So I looked up, while we were talking, there are about as said 50 transplant centers. At least 40 of those belong to the Pediatric Heart Transplant Study Database. Almost all of them belong to the Pediatric Cardiac Surgical Clinical Research Network of the NHLBI.

So I like the idea of a good five-year registry that includes the markers that we're talking about and the fact that these are virtually all major academic centers. We're talking about 50 centers maximum, maybe adding three or four a year over the course of five years. A good registry that looks at the markers that we're all concerned about that is succinct as it will have to be in a transplant center, with the transplant, there's no group of patients that is more carefully followed and the outcomes analyzed than cardiac transplant patients.

So I don't know that we need to force this company to duplicative studies and expense for that kind of follow-up research, but a registry that would sync in with all of these others and give us those missing pieces of data would then allow a mechanistic, hypothesis-driven controlled research project at some point in the future. Thank you.

DR. YANCY: So the reason we're here today is, in fact, because the randomized control trial couldn't be done, and so a registry becomes a reasonable opportunity, and with contemporary research methodologies, we ought to be able to answer questions with reasonable precision with an appropriately designed registry that's sufficiently data dense, information

collected correctly and enacted on appropriately.

Dr. Connor.

DR. CONNOR: So I think I agree strongly with what Dr. Hopkins said. So I think what Dr. Hirshfeld said is a great idea, and especially if this works really well, presumably the transplant list is going to explode, and then there's the huge public health question of who should get these hearts and how should the list be made, but that seems like a public health question, not a question that regulatory-wise should be put upon the Sponsor, even though I agree it's a completely important question.

So I think I'm agreeing strongly with that, that we should focus our questions, make sure that the strokes which we're concerned about aren't long term, debilitating, and not worth, you know, saving the patients to that extent but, you know, small focused questions and make sure that the Sponsor can come back in a number of years with quality data and save these bigger questions for NHLBI.

DR. YANCY: Dr. Nykanen, briefly please.

DR. NYKANEN: Very briefly because I would parrot the comments that were already made. This is a group of patients that is intensely studied, and I think we'd miss an opportunity with a postmarket study. I think we'd missed the opportunity to follow every single one of these patients, which is what I think we should be doing. We don't know enough about it. We need the surveillance. So that would give us the

opportunity of getting every single one.

I would suggest that the current cohort of the, what was it, Cohorts 1 and 2, there be some requirement to follow them out formally with respect to their neurologic outcome because these are kids who are ultimately palliated, and I think that we need to see how good that palliation is, and this is a population that's been reasonably well defined, entered into in a good way, and I think that we can take the opportunity to formally look at them over the next five years.

I think a registry should not be limited to five years. I think it should be indefinite.

DR. YANCY: So, Dr. Zuckerman, we have deliberated the group of questions under the postapproval study.

For Question 4a, regarding comment on an appropriate comparator, the Panel has had some difficulty identifying an appropriate comparator, but at the least, it should be the current IDE group with longitudinal follow-up, and there should be some consideration for expanding it to include the non-IDE group. The Panel believes strongly that again at the least a registry should be constructed that is designed to address many of the questions that have been raised today.

With regard to Question 4b, the Panel believes strongly that this should be longer-term follow-up, in this case, define it at least one year, for neurological and health-related quality of life outcomes after exposure

to the EXCOR device.

For Question 4c, the Panel believes strongly that there is a need for longer-term, up to five-year evaluation of the causes and incidence of pump thrombus and its effect on central nervous system morbidity.

For Question 4d, the Panel believes that it's appropriate to target an overall adverse event rate of less than 0.1 significant adverse events, which is the prevailing rate that currently exists in the data that we were allowed to review, and that that would represent the new comparator for serious adverse events going forward in a postapproval EXCOR study.

Then with regard to other additional topics that are pertinent, there have been a number of statements made about the adequacy of anticoagulation and attempting to understand how that relates to particularly the incidence of pump thrombus and neurologic events.

Are those responses sufficiently appropriate for your need?

DR. ZUCKERMAN: Yes, with two clarifying comments. So when you answered Question 4b, you were speaking about a new registry study of new patients.

DR. YANCY: What I'm hearing is that we are suggesting two things, that we're looking at a longitudinal follow-up of the IDE EXCOR patients as a minimum and asking you to consider the non-IDE, and then in addition to that, establishing a new registry a priori or prospectively for new implants. Did I misrepresent the committee?

No, so that's it.

DR. AUGUSTINE: I have a question about that. Is it new implants? Or it sounded to me like people were talking about all transplants, to be able to answer questions that relate to device-related concerns.

DR. YANCY: So specifically regarding all transplants. I think the point that I tried to make and that Dr. Hopkins really amplified is that that is an ongoing effort that is germane to the pediatric transplant community.

Your second question, Dr. Zuckerman.

DR. ZUCKERMAN: I'm sorry. Now, I'm confused with the first question. For the second study, that would be a registry of all new implants --

DR. YANCY: Yes.

DR. ZUCKERMAN: -- of the Berlin Heart --

DR. YANCY: Yes.

DR. ZUCKERMAN: -- device.

Okay. The second point is that while Dr. Hopkins made a very good point that there are certain mechanisms potentially available where the Sponsor may be able to do this in a reasonable and least burdensome fashion, such as working with the NIH, and I would mention I believe that there's an INTERMACS Pedi meeting here tomorrow, the Sponsor does not

have to assume that they need to work under any particular organizational structure. The key thing is that they just have to get the data to FDA in an appropriately designed study.

However, I do think that the INTERMACS structure potentially could be one way to facilitate this data collection in a least burdensome fashion, so would certainly suggest that as one option to the Sponsor.

DR. YANCY: So our responses are acceptable then otherwise?

DR. ZUCKERMAN: Yes.

DR. YANCY: Thank you. What remains now is Question 5, and Question 5 revisits the Questions 1 and 2 that has to do with, based upon the study results, please discuss whether you believe the overall data demonstrate a reasonable assurance of safety and probable benefit for the EXCOR in the intended patient population. Please discuss all of the key factors that influence your assessment.

So I think that at this point, we have had quite a bit of discussion about reasonable assurances of safety and probable benefit. Are there any individuals on the Panel who wish to make a comment separate from what we've already entered into the record?

Dr. Zuckerman, it's the feeling of the Panel that our responses to Questions 1 and 2 capture the sentiment that we would have for Question 5. Is that acceptable?

DR. ZUCKERMAN: Yes, it is.

DR. YANCY: Let me suggest now as we go into the final phase, what will happen next is a very brief, hopefully three to five minute or less summary from FDA and a similar brief summary from the Sponsor, followed by posing of the critical question that will require a vote from your seat with devices that should be present at your seat.

So that everyone can kind of regroup for this last section, we're going to take a five-minute break, and we will resume at 5:20.

(Off the record.)

(On the record.)

DR. YANCY: If the Panel members can have a seat at the table. FDA and Sponsor, if you can be prepared for brief comments.

At this time, the Panel will hear summations, comments, or clarifications from FDA followed by the same from the Sponsor.

Particularly for the comments that the Sponsor will make, this is not the time to present any new data. This really is for purposes of clarification.

I think the Panel members would be especially grateful if both the FDA and the Sponsor are relatively brief in their comments.

So we will ask the FDA first to bring forward any additional summations, comments, or clarifications.

DR. ZUCKERMAN: Thank you. FDA has no additional comments.

DR. YANCY: That was really brief. (Laughter.) Dr. Fraser.

DR. FRASER: This is Charles Fraser. I won't be quite that brief.

I'd like to thank the Panel for your very thoughtful deliberations today and great questions, the representatives of the Food and Drug Administration, particularly my fellow investigators who we've affectionately named the Dream Team, our Berlin Heart colleagues, and all in attendance for the privilege of presenting these data and our conclusions about the Berlin Heart EXCOR Pediatric VAD.

As we have said many times before, this is the first ever prospective pediatric circulatory support trial, and we should be grateful to the children and their families. Their terrible diseases necessitated desperate and aggressive therapy, and their courage in this process is humbling.

The community of pediatric heart failure medical specialists looks forward to the day where this device is readily available for all in need who could potentially benefit.

Our conclusions based on the extensive and thoroughly reviewed study data is that the EXCOR Pediatric VAD is indicated to provide mechanical circulatory support as a bridge to cardiac transplantation in children.

The primary study effectiveness objective has been met. The EXCOR device provides survival opportunities superior to ECMO as a bridge

to cardiac transplantation.

Furthermore, the primary safety objective has been met. The rate of serious adverse events associated with the EXCOR support is significantly lower than the rate of events of patients supported with ECMO.

While we acknowledge and in no way want to minimize the incidence of stroke in the study population, we are convinced this rate is lower than that associated with ECMO in all study groups. While ECMO support prior to Berlin Heart implantation is associated with increased risk, outcomes for this subpopulation are acceptable and superior not only to ECMO controls, but to the only other obvious comparison which is death.

We reaffirm our position that extensive training as per the training guidelines set forth in the study design are necessary for successful device application. We offer the additional opinion that the study data support the contention that optimum outcomes are achieved in centers with broad commitment to the field of heart failure therapy in children, including focused expertise and medical pediatric cardiology, transplantation, critical care, circulatory support, hematology, anticoagulation, pediatric neurology, and infectious disease.

While transplant-eligible patients with two ventricle circulations and normal cardiac morphology represent the most ideal patient population, we believe that this therapy should also be considered in carefully selected patients with single ventricle variance and other complex

congenital cardiac malformations who are otherwise suitable for transplant.

The data demonstrate the device satisfies the criteria for HDE approval.

Finally, we would like to reiterate our point that the entire field of heart failure treatment in children is, and no pun intended, in its infancy. Thusly, it is appropriate that a robust registry process and ongoing analyses be instituted to allow data drive refinement of these therapies. We believe this will be much more effectively achieved than through a small postapproval study. Thank you very much.

DR. YANCY: Dr. Fraser, thank you very much for the entirety of your commentary today. Thank you very much.

Before we proceed to the vote, it is appropriate now for us to request that Robert Dubbs, our Consumer Representative, Mr. Barrett, our Industry Representative, and Dr. Posner, our Patient Representative, express any additional comments. We'll start with Mr. Dubbs.

MR. DUBBS: My only comment is I feel that it's been shown to be appropriate and safe.

DR. YANCY: Thank you, sir.

Mr. Barrett, do you have any comments?

MR. BARRETT: Thanks, Dr. Yancy. This will be my last chance to talk at this Panel meeting. So I want to say first of all, that as a father of three boys, how moved I was by the patient stories that we heard today;

second of all, how much I truly appreciate the important work that this company and these clinical teams are doing; and lastly, that it really has been a privilege to serve on this Panel. Thank you.

DR. YANCY: Thank you for those comments.

Dr. Posner.

DR. POSNER: Yes, I'd like to take an opportunity to say how impressed I am by the Panel and the presentation by the applicant, and I think this is a very good device that serves a purpose, and based on the discussion here, the information that's going to be necessary to be given to the physicians that use it and the patients that have to make that decision for their children as to whether they use it is all going to be available to them with the registry, the packet insert, and all the things that were brought up by the Panel, and it's just been really great to be a part of this Panel. Thank you.

DR. YANCY: Thank you, sir. We are on time, and it is time for the Panel vote. The Industry, Consumer, and Patient Representatives do not have a vote at this point.

As Chair, I will only vote if there's a tie.

The voting instructions are as follows: We will proceed with the vote on the Panel's recommendation to FDA for this HDE. The voting procedure has changed to an automated system. The Panel is expected to respond to three questions relating to safety, effectiveness, and risk versus

benefit.

Mr. Swink will now read three definitions to assist in this humanitarian device exemption voting process. Mr. Swink.

MR. SWINK: The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990 and the Food and Drug Administration Amendment Act of 2007, allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device humanitarian device exemption applications that are filed with the Agency.

The purpose of the HDE provisions is, to the extent consistent with the protection of the public health and safety and with ethical standards, to encourage the discovery and use of devices intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect or are manifested in fewer than 4,000 individuals in the United States per year. The HDE must stand on its own merits, and your recommendation must be supported by safety and probable benefit data in the application or by applicable publicly available information,

FDA may approve an application if, upon the basis of the information submitted in the HDE or any other information before the agency, FDA determines that:

(1) There is a showing of reasonable assurance that the device is safe under the conditions of use prescribed, recommended, or suggested

in the labeling thereof.

(2) The device is not ineffective under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

(3) The applicant has demonstrated that there is a reasonable basis from which to conclude that the probable benefit to health from the use of the device outweighs the risk of injury or illness, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

I'll now read the definitions of safety and valid scientific evidence are as follows:

Safety as defined in 21 C.F.R. Sections 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.

Valid Scientific Evidence as defined in 21 C.F.R. 860.7(c)(2) is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the

safety and effectiveness of the device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

The Sponsor has proposed the following Indications for Use.

The EXCOR Pediatric is intended to provide mechanical circulatory support as a bridge to cardiac transplantation for pediatric patients. Pediatric candidates with severe isolated left ventricular or biventricular dysfunction who are candidates for cardiac transplant and require circulatory support may be treated using the EXCOR Pediatric.

The following questions relate to the approvability of the Berlin Heart EXCOR Pediatric VAD. Please answer them based on your expertise, the information you reviewed in preparation for this meeting, and the information presented today.

So I'm going to try this again. We have your electronic voting devices in front of you, and so we're going to start with a test question. Please press 1 to vote yes, 2 to vote no, and 3 to abstain.

So we'll start with a test question, and once you put your vote in, you cannot change it. And after we start this vote, your name should disappear from the screen.

All right. The poll is now closed.

We're going to vote on all three questions first, and then I'm

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going to read into the record how everybody voted, and then we'll tally the votes, and then we'll go around the table explaining how you voted.

Voting Question 1: Is there reasonable assurance that the Berlin Heart EXCOR Pediatric Device is safe for use in patients as a bridge to cardiac transplantation for pediatric patients who meet the criteria specified in the proposed indication?

Please vote now. Press 1 to vote yes, 2 to vote no, and 3 to abstain.

The poll is now closed.

We'll now proceed to Question 2.

Voting Question 2: Is there reasonable assurance that the Berlin Heart EXCOR Pediatric Device provides probable benefit as a bridge to cardiac transplantation for pediatric patients who meet the criteria specified in the proposed indication?

The poll is now closed.

We'll now move onto Question 3.

Voting Question 3: Do the benefits of the Berlin Heart EXCOR Pediatric Device for use in patients as a bridge to cardiac transplantation for pediatric patients who meet the criteria specified in the proposed indication outweigh the risks of the Berlin Heart EXCOR Pediatric Device for use in patients as a bridge to cardiac transplantation for pediatric patients who meet the criteria specified in the proposed indication?

The poll is now closed.

So now we'll read the votes into the record.

All right. Question 1 is unanimously yes for everyone. So that passes, 16 to 0.

I want to note for the record that Dr. Jeevanandam has left early, and he did not vote today.

Question 2 is unanimously yes.

Question 3 is unanimously yes.

I will now read the official scores for the record.

On Question 1, the Panel voted 16 to 0 that the data shows that the data shows that there is reasonable assurance that the Berlin Heart EXCOR Pediatric Device is safe for use in patients as a bridge to cardiac transplantation for pediatric patients who meet the criteria specified in the proposed indication.

On Question 2, the panel voted 16 to 0 that there is reasonable assurance that the Berlin Heart EXCOR Pediatric Device provides probable benefit as a bridge to cardiac transplantation for pediatric patients who meet the criteria specified in the proposed indication.

On Question 3, the panel voted 16 to 0 that the benefits of the Berlin Heart EXCOR Pediatric Device for use in patients as a bridge to cardiac transplantation for pediatric patients who meet the criteria specified in the proposed indication do outweigh the risks of the Berlin Heart EXCOR

Pediatric Device for use in patients as a bridge to cardiac transplantation for pediatric patients who meet the criteria specified in the proposed indication.

The three voting questions are now complete. We will now collect the voting devices. Please pass them to the center of the table.

DR. YANCY: Let me congratulate the Panel on our deliberations and our activities today.

As a matter of record, Dr. Jeevanandam voted affirmatively on all three questions, and so the unanimity of our responses is consistent, and the vote that I would have cast would have been the same as the Panel.

So I think that we've done very good work, and we've responded to a patient population in need, and we have accepted the application from the Sponsor enthusiastically.

What I'd like to do now is to go around the table, and as you so incline, request that the Panel members speak to the vote that you cast. As there were no votes that were negative, we don't need to have anyone justify a negative or discuss an amendment that would have caused them to vote positively.

So beginning with Dr. Augustine, if there is a comment that you'd like to enter into the record, we would love to accept that now.

DR. AUGUSTINE: I'm pleased with the unanimous vote in this population of critically ill children, potentially at the end of life without appropriate intervention or alternatives for palliation to transplant. In this

setting, I feel that the risks that we've discussed at length today are warranted in light of the significant benefit that was demonstrated when compared to ECMO.

DR. YANCY: That was so well said, I think everyone can simply say I concur. Dr. Moon.

DR. MOON: I concur. However, I do want to remind the Sponsor that the stroke rate is high and don't stop working to make it lower.

DR. YANCY: Dr. Austin.

DR. AUSTIN: I concur and recognize that this, first off, this isn't the final. I think that this is our recommendation, but I would hope that the FDA would go with our recommendation, but I also think it's important to recognize that this is the first generation of devices and there will be more to come.

DR. YANCY: Thank you. Dr. Ferguson.

DR. FERGUSON: I'd simply concur.

DR. YANCY: Dr. White.

DR. WHITE: Thank you all for your work.

DR. YANCY: Dr. Page.

DR. PAGE: I concur. I agree with the comment that we should not be complacent with this stroke risk. We can do better than this.

DR. YANCY: Dr. Weinberger.

DR. WEINBERGER: I concur and thank the Sponsor for opening

a new chapter in the treatment of heart failure in children.

DR. YANCY: Dr. Lange.

DR. LANGE: Congratulations to Dr. Fraser, Dr. Canter, and the Sponsor. What I would urge the Sponsor is if you have any respect and regard for the investigators and you're truly concerned about the individuals that you roll this out to, and you enjoy your reputation as a company, tomorrow, before you meet to decide how to roll it out to the other 12 sites, you'll meet about how to solve the problems that afflicted 91 percent of patients in Cohort 1 and 79 percent in Cohort 2.

DR. YANCY: Dr. Slotwiner.

DR. SLOTWINER: Well, I concur with all that's been said, and I just want to compliment the Sponsor and the investigators on opening this new chapter for these desperately ill children and offering them hope and their families, as we heard today from two outstanding examples. Thank you.

DR. YANCY: Dr. Hirshfeld.

DR. HIRSHFELD: I concur.

DR. YANCY: Dr. Somberg.

DR. SOMBERG: I too want to congratulate the Sponsor for efforts in this regard. It's a small area. It has a great need, and I do hope they undertake besides a registry, a prospective study, a small one albeit, but one to look at possible pharmacologic therapy adjuncts to their helpful

device.

DR. YANCY: Dr. Borer.

DR. BORER: I agree with all the previous comments, and I would echo John Somberg's comment that we shouldn't forget about the need for the postmarketing data collection.

DR. YANCY: Dr. Kato.

DR. KATO: I would also concur and echo the thoughts of my colleagues here. I would like to suggest to the Sponsor to ensure that all the information they gather on patients is disseminated to all of their sites because, you know, with maybe 300, 400 devices out there, you know, everybody can learn from everybody else, and that's going to be very important in order to move this field forward.

DR. YANCY: Dr. Nykanen.

DR. NYKANEN: I would concur as well, and I don't have to say that with great power comes great responsibility. Given the tenacity that I think has been demonstrated by both the company who was willing to invest in a desperately ill pediatric population, a very small market I would say, and the tenacity of the investigators in seeing this through in a very difficult study design, I think that my concerns about the future for investigation in this area are probably unwarranted because I think that the people involved are motivated by the right thing.

DR. YANCY: Dr. Hopkins.

DR. HOPKINS: I concur as well, and would also like to again say what a terrific job the principal investigators did along with FDA staff and the Sponsor to make a single arm study which most people say can't be done scientifically to make it really work in this case, and that's really excellent, excellent science.

DR. YANCY: Dr. Connor.

DR. CONNOR: Yeah, I agree strongly, particularly with Dr. Hopkins there, and I think, you know, this device will heal a lot of kids' broken hearts, but I think a lot of parents' broken hearts, too, and I think that's very important.

DR. YANCY: That's an excellent last word. I want to thank the Panel. You did good work today, and it's been a joy to work with you. I'd like to thank the FDA for the clarity and directness of your presentations, Dr. Zuckerman for your leadership and nudging, and to the Sponsor for your professionalism, your resourcefulness, for your clarity. I think we did a good thing today.

Dr. Zuckerman, you can close things out.

DR. ZUCKERMAN: I just want to thank Dr. Yancy and the rest of the Advisory Panel for a hard day's work but an extremely productive day's work.

DR. YANCY: We're adjourned. Thank you.

(Whereupon, at 6:00 p.m., the meeting was adjourned.)

CERTIFICATE

This is to certify that the attached proceedings in the matter of:

CIRCULATORY SYSTEM DEVICES PANEL

July 21, 2011

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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