Summary MinutesSUMMARY MINUTES

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

CIRCULATORY DEVICES PANEL

April 6, 2021

Via Videoconference

Attendees:

Chairperson

Richard A. Lange, M.D., MBA
Texas Tech University
El Paso, TX

Voting Members

George W. Vetrovec, M.D., MACC, MSCAI
VCU Health Pauley Heart Center
Richmond, VA

James C. Blankenship, M.D.
University of New Mexico
Albuquerque, NM

Jason T. Connor, Ph.D.
ConfluenceStat, LLC
Orlando, FL

Ralph G. Brindis, M.D., M.P.H., MACC, FSCAI
University of California, San Francisco
San Francisco, CA

Keith B. Allen, M.D.
St. Luke's Hospital of Kansas City
Kansas City, MO

Temporary Voting Members

Murray Kwon, M.D.
David Geffen School of Medicine at UCLA
Los Angeles, CA

Pramod Bonde, M.D.
Yale School of Medicine
Woodbridge, CT

Alfred H. Stammers, MSA, CPBMT, CCP
Specialty Care
Brentwood, TN

David Yuh, M.D.
Stamford Health
Stamford, CT

Robert W. Yeh, M.D., M.Sc., M.B.A.
Harvard Medical School
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Temporary Voting Members (cont.)

Craig Selzman, M.D.
University of Utah
Salt Lake City, UT

Marc R. Katz, M.D.
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Joaquin E. Cigarroa, M.D.
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John Hirshfeld, M.D.
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Allen Burke, M.D.
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Mark Nuszkowski, M.D.
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Christopher O'Connor, M.D., MACC
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Jeffrey Borer, M.D.
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Marc Moon, M.D.
Washington University in St. Louis
St. Louis, MO

Colleen M. Gallagher, Ph.D., MA, LSW, FACHE, HEC-C
The University of Texas MD Anderson Cancer Center
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Patient Representative

Debra Dunn
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Industry Representative

Gary Jarvis
Alfa Medical
Eden Prairie, MN

Food and Drug Administration

Bram Zuckerman, M.D.
Director, Office of Cardiovascular Devices
Office of Product Evaluation and Quality

Aden Asefa, M.P.H.
Designated Federal Officer

CALL TO ORDER

Panel Chairperson Richard A. Lange, M.D., MBA, called the meeting to order at 9:03 a.m. He noted the presence of a quorum and affirmed that the Panel members had received training in FDA device law and regulations. He announced that the Panel would be discussing, making recommendations, and voting on information related to the premarket application for the TransMedics Organ Care System (OCS) Heart.

PANEL INTRODUCTIONS

Chairperson Lange asked the Panel members and the FDA staff to introduce themselves. He announced that Jacqueline Alikahanni, the consumer representative, would not be attending the meeting.

CONFLICT OF INTEREST STATEMENT

Aden Asefa, M.P.H., Designated Federal Officer, read the Conflict of Interest statement and reported that no conflict of interest waivers had been issued.

She announced that Gary Jarvis would be serving as the industry representative.

TEMPORARY VOTING MEMBER STATUS STATEMENT

Ms. Asefa noted that Drs. Marc Moon and Christopher O'Connor had been appointed as temporary voting members.

GENERAL ANNOUNCEMENTS

Ms. Asefa then made general announcements to the public regarding transcripts and speaker identification. She introduced Shirley Simson as the FDA press contact.

SPONSOR PRESENTATION

Introduction

Waleed Hassanein, M.D., introduced the sponsor presentation and provided background information on TransMedics. He noted that only 30% of donor hearts are actually used for transplants, that longer waiting times are associated with higher mortality, and that cold storage restricts the utilization of donor organs. He gave a device description, reviewed the proposed indication for use, and presented results from the Heart EXPAND + CAP clinical trials.

Clinical Need to Expand Donor Heart Utilization

Maryjane Farr, M.D., reviewed key aspects of end-stage heart failure, noting that an estimated 46% increase in prevalence is expected within the next 10 years. She discussed the benefits and complications of ventricular assist devices as compared to cardiac transplant,

the drawbacks of cold storage, and challenges due to supply. She emphasized that the limitations of cold storage typically restrict utilization to the healthiest and youngest standard criteria donor hearts in close proximity to intended recipients, and that there is a significant unmet need for new preservation technologies to address these issues.

Heart EXPAND and EXPAND CAP Trials

Jacob Schroder, M.D., discussed key components of the EXPAND and EXPAND CAP studies. He reviewed the primary safety and effectiveness endpoints, inclusion and exclusion criteria, rationale for performance goals, and secondary endpoints. He noted that combined results from both studies support the safety and effectiveness of the OCS heart system, that 84% of extended criteria donor hearts were successfully transplanted, and that all-cause patient survival at 30 days post-procedure is comparable to routine heart transplant outcomes.

PROCEED II Trial Summary

Dr. Hassanein presented findings from the earlier PROCEED II trial. He informed the Panel that it was the first trial of ex vivo organ perfusion technology in the United States, that it was designed to demonstrate non-inferiority of the OCS to cold storage for preservation of standard criteria donor hearts, and that it had met its primary effectiveness and safety endpoints. He then produced long-term survival data, noting that cardiac graft-related mortality was similar in the OCS and control groups, and that published peer-reviewed data from centers in other countries have shown favorable short and long-term outcomes up to five years post-transplant.

Statistical Considerations for Long-Term Survival

Chris Mullin, M.S., discussed concerns regarding the underlying assumptions of FDA's model for long-term survival. He pointed out that no clinical justification was provided for the selected cut points, that the model is inaccurate at predicting long-term survival, and that the results show it is not valid or reliable for extrapolation of long-term data.

TransMedics Positions on FDA Questions and Training, and Post-Approval Programs

Dr. Hassanein presented data supporting the sponsor's conclusions on each of the FDA panel discussion questions. He then summarized the proposed training and post-approval plans.

Clinical Perspective and Benefit-Risk Assessment

Ashish Shah, M.D., informed the Panel that the current proposed indication for use is aimed at extended criteria hearts. He reiterated that donor hearts in the EXPAND and CAP trials had significantly more risk factors than standard criteria donor hearts, and were rejected 60 times on average before being accepted by trial centers. He noted that all-cause

survival through the first year in both trials was comparable to the national average for standard criteria donors, and that cardiac related survival was high. He claimed that approval of the OCS could significantly increase the total number of procedures performed in the United States and would offer the possibility of heart transplant to thousands of patients on waiting lists.

Q&A

Keith B. Allen, M.D., asked why overall survival was better in the CAP trial than it was in EXPAND. **Dr. Hassanein** replied that nothing was done differently in CAP and then showed the results of a poolability analysis between the two studies. He also explained that a match run turndown is a combination of the number of centers and patients listed at an institution, that the total cross-clamp time was looked at as a potential factor for the primary effectiveness endpoint, and that the del Nido solution was used to standardize cardioplegia for the trial.

Christopher O'Connor, M.D., asked if the sponsor believes that the device offers no advantage over cold storage in standard criteria hearts. **Dr. Hassanein** replied that the sponsor believes the OCS would significantly benefit any type of heart that is preserved in it. He pointed out that benefit was demonstrated in the EXPAND and CAP population, and that the proposed indication matches those results. He noted that outcomes from patients with cross-clamp times greater than four hours showed 100% cardiac related survival.

Joaquin E. Cigarroa, M.D., asked for clarification on the adjudication process. **Dr. Hassanein** informed him that a single medical monitor adjudicated all of the adverse events in the EXPAND and CAP trials.

Craig Selzman, M.D., asked if there were patients in the PROCEED trial who met the inclusion criteria for EXPAND, and what their outcomes were.

Pramod Bonde, M.D., asked how the sponsor is reconciling trial data with the new allocation policy. **Dr. Hassanein** specified that EXPAND and CAP were conducted according to the new allocation system, and that all PGD events were related to mechanical circulatory support, ECMO, or intra-aortic balloon pumps.

FDA PRESENTATION

Device Description; Clinical/Regulatory History; Summary of Nonclinical Information; Proposed PAS; Panel Discussion Questions

Catherine P. Wentz, M.S., introduced the review team and outlined FDA's presentation. She noted that the PROCEED II and EXPAND trials provide critical insights into the safety and effectivenss of the OCS device. She apprised the Panel of device design changes and protocol adjustments in the EXPAND study, and of the rationale behind an IRB site termination. She further related that animal studies were limited in scope and number, that they did not include myocardial histologic analysis, and that the sponsor chose not to adopt study design considerations recommended by FDA. She then identified key issues for the Panel's deliberation.

Clinical Data Sources and Predicted Survival

Xuan Ye, Ph.D., reviewed clinical data from the PROCEED II, EXPAND, and EXPAND CAP studies, and discussed FDA's predictive analysis based on survival models. He furnished detailed information on primary safety and effectiveness endpoints, long-term survival analysis, and parametric models used to extrapolate longer-tem survival probabilities beyond three years. He noted that the prediction for longer-term survival has many irregularities and is limited by strong model assumptions and data availability.

Clinical Review

John S. Sapirstein, M.D., summarized FDA's assessment of the PROCEED II and EXPAND trials. He began his presentation by providing background on why FDA was focusing on both studies, noting that PROCEED II provided a broad evaluation of all donor hearts, while EXPAND focused primarily on extended criteria donor hearts. He gave an overview of IDE protocols and trial execution, and reviewed the primary effectiveness endpoints, key secondary endpoints, and concurrent and post hoc analyses from both studies. He noted that the OCS Heart System was associated with decreased cold ischemic time for donor organs, shorter waiting list durations, and longer preservation times.

Clinicopathologic Analysis

Andrew Farb, M.D., described the methods used by FDA for analysis of hearts perfused with the OCS system but turned down for transplant in the EXPAND, EXPAND CAP, and PROCEED II studies. He presented the findings for each study and apprised the Panel of insights gained from further analysis of 20 turned-down donor hearts that had normal left ventricular function in the immediate antemortem period. He concluded that the findings show, in most cases, that the OCS system did not provide effective organ preservation or that its use caused severe myocardial damage.

Post-Approval Study

Ms. Wentz apprised the Panel of the sponsor's post-approval study plans and of FDA's concerns with the proposed primary endpoint and performance goal.

Clinical Summary

Fernando Aguel, MSE, recapped FDA's presentation. He reiterated the Agency's belief that there are multiple limitations in the design, execution, and analyses of the PROCEED II, EXPAND, and EXPAND CAP studies that pose challenges to the assessment of benefit-risk. He noted that there are challenges regarding study design and conduct, and that there is uncertainty regarding the safety of the device and whether its use may be associated with myocardial damage. In addition, there is concern regarding the unknown impact that the system could have on the pool of transplantable donor hearts and its influence on long-term survival for transplant recipients.

Q&A

Dr. O'Connor asked if the late deaths in PROCEED II could be attributed to ischemia, injury, or the device. **Dr. Sapirstein** recognized that a considerable amount of confounding can happen after the index procedure. He explained that this is the reason why FDA prefers all-cause mortality as the metric and why it did not focus on cardiac related deaths.

Dr. Allen asked if the small amount of animal testing data submitted by the sponsor was acceptable. **Dr. Farb** replied that many of the unanswered questions could begin to be addressed from insights gained from additional animal studies.

Jason T. Connor, Ph.D., asked if the sponsor had an ongoing understanding of the outcomes and how that may have influenced changes in the studies.

Marc Moon, M.D., asked if there were any hearts that were turned down without high lactate elevations. **Dr. Farb** presented data showing the mean and ranges of lactate levels in the 27 turned down hearts in all three studies, noting that 15 had levels less than 0.5.

John Hirshfeld, M.D., stated that he has concerns about the high coronary flow rates in the OCS preserved hearts. He also pointed out that normal hearts metabolize lactate, and that he had not seen any data on the weights of transplanted OCS hearts before and after implantation.

OPEN PUBLIC HEARING

Nina Zeldes, Ph.D., spoke on behalf of the National Center for Health Research. She stated that the EXPAND study alone did not sufficiently demonstrate a reasonable assurance of safety and effectiveness, and that the non-inferiority of the OCS Heart System compared to standard of care does not provide clinical value. She concluded that the evidence does not support approvability of the device.

David Klassen, M.D., discussed the drawbacks of end-stage heart disease therapies, including transplantation. He pointed out that cold storage imposes significant limitations and that the major impediment is lack of donors. He asserted that perfusion technology allows new sources of donors, longer storage times, and addresses the issue of geographic inequity.

Sean Pinney, M.D., stated that he has seen many of his patients die while waiting for heart transplants, that there are not enough donor hearts, and that it is unreasonable to assume that there will be a downturn in demand. He pointed out that the ability to resuscitate, perfuse, and observe hearts while they are in the Organ Care System is a great advancement and that it will allow for expansion of the donor pool.

Gregory Couper, M.D., observed that preclinical studies and subsequent clinical experiences have led to a better understanding of the OCS technology. He emphasized the need for better preservation techniques in the extended criteria donor pool. He affirmed that the OCS platform has proven itself capable of ameliorating the prolongation of ischemic time, that it safely enables long-distance recovery with good outcomes, and that it has the potential to raise the performance level of all heart transplant programs across the country.

Jason Smith, M.D., endorsed the use of the OCS device based on his experience as a participating surgeon in the EXPAND trial. He reported that he observed an improvement in organ function, increased access to donors, and better performance of organs from great distances. He further indicated that patients experienced satisfactory long-term survival and rapid access to transplant.

Mani Daneshmand, M.D., informed the Panel that he has used the OCS heart and lung technologies clinically and in research trials. He acknowledged that there is a significant shortage of donor hearts and that the most eligible donors are not utilized due to logistical issues, inexperience, or other complications. He stressed that the device can overcome many of these issues, that it works, and that it should be made widely available.

Patrick Sullivan, a transplant survivor and co-founder of the Heart Brothers Foundation, described his experience of being on a left ventricular assist device while waiting for a heart transplant. He asserted that technologies such as the OCS will be critical in changing the availability of donor hearts in the United States.

Ron Mallory told the Panel that bleeding and infection complications from LVAD treatment led him to enroll in the OCS Heart System trial. He further related that his new heart came from a location 1200 miles away, that he has had it for four years, and that he is very active and in good condition.

Mark Chibulski stated that he was on an LVAD for 15 months and was transplanted a week after enrolling in the OCS trial. He reported that after the surgery, he felt great and that eight weeks later he was once again playing baseball, going fishing, and exercising at the gym.

Jordan Keshler told the Panel that he received a new heart four days after being accepted into the Donors After Circulatory Death Heart Trial and that he has had no complications. He reported that he has been able to return to doing the things that he loves to do and that he is now involved in helping to promote heart awareness through social media.

Glenn Rockwood, a participant in the OCS trial, told the Panel that the day after his transplant he was up and walking, and that the following week he was released from the hospital. He reported that since then, he has been able to exercise, walk 15 to 20 miles a week, and is living a healthier lifestyle. He proclaimed that the OCS Heart provided him the best possible outcome and that it could do the same for thousands of other patients who are currently waiting for a new heart.

SPONSOR RESPONSE

Dr. Hassanein addressed questions regarding data collection of heart refusals, stringency of matches, cross-clamp time and outcomes, and travel distances. He specified that refusals are collected by number in the SRTR and that matches are regulated by UNOS.

Dr. Allen asked if there were any differences in data or outcomes after the allocation change. He also asked how many patients were in the EXPAND trial pre-allocation versus

post.

Anthony J. Demetris, M.D., addressed pathology issues. He noted that ischemia reperfusion injury is unavoidable regardless of the preservation method, that there were no unusual findings indicating that the device was actually damaging hearts, and that all the observations were consistent with those that would be present under any other circumstances. **Allen Burke, M.D.,** related that the primary feature he saw on the slides was contraction bands, that he saw no inflammatory reaction, and that a heart in cold storage would look exactly the same. He affirmed that contraction bands would be seen on a transplanted heart within the first hour after surgery, and that ischemic damage is often observed in first and second biopsies. He concluded that the slides in the pathology presentation looked good and that he did not see anything that appeared to be irreversible. **Dr. Farb** pointed out that something happened to these hearts that caused them to be refused at the time of transplant and that there could be a potential issue with the device not preserving the myocardium as it is intended to do.

Dr. Hassanein provided additional information on lactate levels. He pointed out that if the device is causing injury, it would be seen in the PGD rates of transplanted hearts. He further noted that the PGD was 8%, and that donor hearts with ejection fraction in the sixties often result in non-functional severe primary failure, even with cold storage.

He then clarified that the OCS had extensive animal testing and that additional reports were submitted to FDA. He also explained that the upper limit was increased to maximize perfusion and to minimize the turndown of donor hearts.

Ms. Wentz confirmed that several smaller animal studies were done for the previous PMA or for the EXPAND IDE, but that no comprehensive study was done on the system.

Dr. Hassanein provided information on PROCEED patients who met EXPAND criteria and on device malfunctions related to cannula failure. He also commented on data related to the use of mechanical circulatory support in the PROCEED trial, and on the poolability analysis.

Miriam Provost, Ph.D., provided additional details on the extension of the EXPAND trial. She verified that the sample size was increased by 20 subjects and that a poolability analysis had been conducted. She explained that the sponsor was aware of some of the results of the trial because of annual report requirements, and emphasized that the increase in sample size did not have anything to do with the outcomes.

Dr. Hassanein explained that the protocol changes in the PROCEED trial were for logistical reasons, that they had nothing to do with outcomes, and that they were implemented in both arms.

Dr. Schroder discussed post-transplant MCS in EXPAND patients, noting that the rate of PGD and mechanical circulatory support in the trial was low, and **Dr. Sapirstein** clarified the timing of the endpoint for MCS use, which extended throughout 30 days or initial hospitalization, versus the timing of the primary graft dysfunction assessment, which was restricted to 24 hours.

Dr. Schroder then addressed concerns regarding extended criteria and whether they influenced cardiac acceptance rates, and on the unethical nature of randomization and why doing a single-arm trial was felt to be more principled.

FDA QUESTIONS

Ms. Wentz read Question 1: EXPAND Study Design and Conduct

The following important trial design and study conduct issues may affect the interpretability and validity of the study dataset and analyses:

Study Design

a. Design: EXPAND was carried out as a single-arm investigation and there were limited data for subjects not included in a Per Protocol (PP) population (equivalent to Transplant Recipient [TR] population).
b. Safety: There was no pre-specified primary safety endpoint hypothesis test.
c. Effectiveness: The primary effectiveness endpoint was defined as allograft survival at POD 30 following transplantation in the absence of severe Primary Graft Dysfunction (PGD) involving the left or right ventricle in the first 24 hours post-transplantation. This endpoint was tested against a performance goal of 65%, and moderate PGD was not included.
d. Donor heart inclusion criteria: EXPAND's donor heart eligibility criteria do not identify organs that are uniformly deemed unacceptable for transplantation if preserved using cold static preservation techniques, raising the possibility that there was overlap between hearts accepted for OCS Heart perfusion in the EXPAND (including EXPAND CAP) and PROCEED II studies.

Study Conduct

e. Revisions to Donor Heart Inclusion Criteria: The sponsor's dataset reflects EXPAND donor heart inclusion criteria that were revised after data lock and after the PMA had undergone FDA review. The donor heart inclusion criteria modifications affected 20 donor hearts. Additional criteria were assigned in all instances where donor heart inclusion criteria were revised, of which 17 modifications changed the assignment of single-criterion hearts to multiple-criteria hearts. There were no donor hearts for which criteria were removed.
f. PGD Classification Changes: Despite objective definitions of PGD intended to standardize classifications using data collected within 24 hours after completion of transplant surgery, multiple site-identified PGD classifications in EXPAND were changed during the adjudication process, which took place months or years after the transplant. These changes raise the possibility that individual endpoint determinations in EXPAND were subjective to some degree.

Please discuss the impact of these study design and study conduct issues on assessing the safety and effectiveness and benefit-risk profile of the OCS Heart System.

Dr. Connor remarked that the study design provided no insight into a number of unanswered questions that need to be compared to a control, and that two or three outside adjudicators would have been preferable.

Dr. Hirshfeld commented that he is concerned by the lack of a valid comparison to the findings and if the device really does make a difference in expanding the population of donor organs.

Dr. Cigarroa stated that he is also concerned that there was only one adjudicator.

Ralph G. Brindis, M.D., stressed the importance of randomized clinical trials. He expressed concern about the possibility of indication creep while there are still so many unanswered questions regarding safety and effectiveness.

Dr. Selzman conjectured that even if all the issues were addressed and there had been more adjudicators, the 65% performance goal would probably still have been met.

Bram Zuckerman, M.D., explained that the intent of the question is how to make an observational study as objective as possible. He asked Dr. Selzman what recommendations he would have for transplant, for choosing the right donor, and for adjudicating events in a more unbiased manner. **Dr. Selzman** replied that there should have been a true clinical events committee and that the indications should be more specific. He suggested looking at travel distance rather than expected time, and also observed that trying to answer many of these questions in humans is not possible.

Chairperson Lange summarized the Panel's response:

- There is frustration over the lack of valid comparison.
- The Panel believes that there is an ethical way to find a comparator group.
- The indications should be more specific.

Ms. Wentz read Question 2: EXPAND Inclusion Criteria - The EXPAND Study intended to utilize hearts that otherwise would not have been accepted for transplant. However, EXPAND's donor heart eligibility criteria do not identify organs that are uniformly deemed unacceptable for transplantation if preserved using cold static preservation techniques. For example, 40 of 75 (53%) [64/116 (55%) in the pooled EXPAND+CAP] of the transplanted donor hearts met a single inclusion criterion, and 18 of those 40 (45%) [33/64 (52%) in EXPAND +CAP] met the single inclusion criterion of expected cross-clamp (ECCT) $\geq$ 4 hours. Additionally, at least one donor heart met EXPAND Study criteria but due to a logistical error was transported via cold static storage and successfully transplanted.

Please discuss whether there was overlap between the standard hearts studied in the PROCEED II randomized trial and hearts studied in EXPAND and EXPAND CAP. If you believe there was overlap between "extended" and standard donor hearts, please discuss the effect that commercial availability of the OCS Heart device may have on the availability of acceptable donor hearts for transplantation, and overall long-term survival.

Dr. Allen stated that he has concerns about indication creep, noting that if the device is approved it will not be used for extended criteria patients only. He questioned whether proper controls can be put on the device post-approval to negate these concerns and pointed out that he has not seen any provision for them in the company's plans.

Murray Kwon, M.D., opined that the inclusion criteria in the initial study design were too liberal.

Dr. Moon suggested that animal studies would provide information as to whether the device is causing damage to hearts or not.

Chairperson Lange summarized the Panel's response:

- There is concern about indication creep, that the current indications may be too liberal, and that there will not be proper controls.
- There are also questions regarding which group of patients would benefit from the device, if there is one, and who that group would be.
- The Panel does feel that there is overlap and is concerned that if the device is approved with the current information, there will be indication creep.

Ms. Wentz read Question 3: Transplantability - OCS Heart arterial lactate level was the principal criterion given for not continuing to transplantation after preservation of the donor organ on the OCS Heart System for 5 PROCEED II donor hearts, 18 EXPAND donor hearts, and 4 EXPAND CAP donor hearts. FDA is unclear as to the utility of this metric as the principle criterion for determining transplantability, noting that 2 EXPAND CAP hearts were transplanted with arterial lactate levels of 6.3 and 7.8mmol/L at the end of OCS perfusion (one of which had an initial arterial lactate > 5mmol/L), as well as the many (>50%) turned down hearts that had final arterial lactate levels <5mmol/L.

Please discuss the accuracy and reliability of lactate levels as the principle determinant for not transplanting accepted donor hearts. In your discussion, please consider the impact on patients who undergo sternotomy in preparation for transplant in whom the transplant was not performed due to lactate levels greater than the target range.

Dr. Moon asserted that patients should never be given sternotomies until lactate levels are deemed to be acceptable. He insisted that animal studies should be done to make these determinations.

Dr. Allen pointed out that a sternotomy would not be done until a heart is believed to be transplantable. He acknowledged that determining transplantability is always subjective and that there are other factors besides lactate levels.

Chairperson Lange summarized the Panel's response:

- Sternotomies should not be done unless there is certainty that a heart will definitely be used.
- Lactate should not be the sole determinant.

Ms. Wentz read Question 4a: PROCEED II and EXPAND Study Analysis - Long term survival: In PROCEED II, the observed all-cause mortality rate following transplantation was higher after donor heart preservation using the OCS Heart device than after cold static preservation (SOC); the magnitude of the survival benefit for patients transplanted with SOC hearts was clinically meaningful and persisted over the long term. The Kaplan-Meier survival analysis for EXPAND demonstrates survival rates of 83.8% at 1-year, 82.2% at 2 years, and 77.7% at 3-years, and the Kaplan-Meier survival analyses for EXPAND+CAP demonstrates survival rates of 87.2% at 1-year, 85.5% at 2 years and 80.8% at 3-years. The Table below includes contemporary survival rates for 1 and 3 years from the 2019 Scientific Registry of Transplant Recipients Annual Report, just published a few weeks ago.

Please discuss the clinical implications of these results with respect to whether there is a long-term benefit of preserving donor hearts using the OCS Heart System.

Dr. Connor stated that there is not enough data to make long-term projections and that he is more concerned about what is happening in the first six months.

Robert W. Yeh, M.D., M.Sc., observed that there is no way of knowing if there is long-term benefit without having a comparator.

Dr. Moon remarked that associating the excess deaths to infection or malignancy is troubling.

Ms. Wentz read Question 4b: Wait Times: According to the Scientific Registry of Transplant Recipients (SRTR), nearly 40% of patients newly listed in 2018 underwent heart transplantation within 3 months, and approximately 57% had undergone transplantation within one year of listing. In 2019, 3% of subjects died while waiting for a donor organ while 12% were removed from the list for reasons other than death or transplantation; 6-month mortality for patients removed from the list was approximately 20%. Although EXPAND was not prospectively designed to use the SRTR as a comparator, the EXPAND OCS Heart group had shorter wait times than patients in the SRTR.

Please discuss the strengths and limitations of this comparison, and whether the results of EXPAND indicate a probable benefit of shorter wait times. In addition, please discuss the wait time analysis in the context of post-transplantation long-term survival.

Dr. Allen insisted that a good control group is needed.

Dr. Connor remarked that the correct questions would be, "Is it better to wait for a different organ?" or "Would it have been better to get standard of care equally as fast?"

Chairperson Lange summarized the Panel's response:

- There is general consensus that the waiting time would be shortened.
- There is some enthusiasm for doing it if it keeps patients off mechanical circulatory support, provided they are not given suboptimal hearts.

Ms. Wentz Question 4c: FDA believes that collectively the PROCEED II, EXPAND, and EXPAND CAP analyses suggest sub-optimal survival when the device is used to preserve structurally and/or functionally “standard” donor organs whose only criterion for device use is preservation time anticipated to be prolonged (≥ 4 hours).

Please discuss whether the device, if approved, has demonstrated a reasonable assurance of safety and effectiveness for donor hearts considered non-standard on the basis of anticipated prolonged preservation time only.

Dr. Allen stated that the data has not suggested this and that firmer guidelines are needed.

James C. Blankenship, M.D., opined that if the alternative is wasting the heart, it could be assumed that the device is sufficiently safe.

Dr. Bonde pointed out that organs have been safely transported over long distances in the OCS and that the majority of them were utilized. He suggested that a more firmly defined preservation time is needed.

Chairperson Lange summarized the Panel's response:

- Some of the Panel members believe that the device has not been shown to be safe and effective;
- some are willing to accept that the heart might not otherwise be used; and
- some feel that there is a safety signal in the fact that these hearts have been implanted.

Ms. Wentz read Question 5: Pathophysiology and Pathology

In PROCEED II, compared to patients transplanted with SOC donor hearts, the group of patients transplanted with OCS Heart System-perfused donor hearts had a numerically greater need for mechanical circulatory support post-transplant, more frequent acute rejection episodes, lower average cardiac index, longer average ICU stay, and longer average initial hospital duration. In EXPAND and EXPAND CAP, pathology results from hearts perfused on the OCS Heart System but turned down for transplant suggested that the OCS Heart System may have contributed to myocardial damage in some donor hearts.

Please discuss the implications of these pathophysiologic and pathologic observations on the effectiveness of heart preservation and/or potential myocardial damage associated with donor heart perfusion using the OCS Heart System. In addition, please discuss the possibility that hearts were turned down for transplantation due to preservation with the OCS Heart System. If you believe they were, please discuss the impact of hearts turned down for transplantation following OCS Heart perfusion on the pool of available donor hearts.

Jeffrey Borer, M.D., pointed out that the numbers are too small to define performance descriptors and positive/negative predictive value. He further stated that additional studies will have to have the necessary amount of subjects so that useful and precise outcomes can be defined.

Dr. Selzman remarked that the device provides an element of safety for the population that is being studied. He noted that it saved 6% of subjects from getting potentially bad hearts.

Chairperson Lange noted that some Panel members feel that the system prevented suboptimal hearts from being implanted and that others are concerned that it may be responsible for prolonged cross-clamp time associated with temperature management.

Ms. Wentz read Question 6a: Indications for Use

Proposed Indications for Use Statement:

The TransMedics Organ Care System (OCS) Heart System is a portable extracorporeal heart perfusion and monitoring system indicated for the resuscitation, preservation, and assessment of donor hearts in a near-physiologic, normothermic and beating state intended for a potential transplant recipient. OCS Heart is indicated for donor hearts with one or more of the following characteristics:

- Expected cross-clamp or ischemic time ≥ 4 hours due to donor or recipient

characteristics (e.g., donor-recipient geographical distance, expected recipient surgical time); or

- Expected total cross-clamp time of ≥ 2 hours PLUS one of the following risk factors:

    - Donor Age ≥ 55 years; or
    - Donors with history of cardiac arrest and downtime ≥ 20 minutes; or
    - Donor history of alcoholism; or
    - Donor history of diabetes; or
    - Donor Left Ventricular Ejection Fraction (LVEF) ≤ 50% but ≥ 40%; or
    - Donor history of Left Ventricular Hypertrophy (LVH) (septal or posterior wall thickness of > 12 ≤ 16 mm); or
    - Donor angiogram with luminal irregularities but no significant coronary artery disease (CAD)

Please discuss whether the EXPAND Study donor heart inclusion criteria (or an inclusion criteria subset) identifies a reasonable set of objective "extended" or "expanded" heart criteria that define hearts not routinely used for transplantation after cold static storage. If so, please provide additional discussion as follows:

a. Based on the available data, please discuss whether the objective set of inclusion criteria used to define "extended" donor hearts intended for preservation on the OCS Heart System will result in an increase in donor heart utilization and acceptable survival results for recipients.

Dr. O'Connor surmised that the four hours cross-clamp time defined as geographic distance may provide optimal protection against the likelihood of creep into the normal heart criteria.

Dr. Bonde disagreed that distance on its own should be a criterion, and that donor quality and risk factors should also be considered.

Marc R. Katz, M.D., stated that the recipient population should be better defined.

Dr. Hirshfeld cautioned that the Panel members are not even convinced that the device has an impact on organ viability.

Chairperson Lange summarized the Panel's response:

- There is some sense that this will result in an increase in donor heart utilization.
- It is necessary to ensure that the device will only be used for organs that would not otherwise be acceptable.
- There is concern about patient survival.

Dr. Zuckerman asked the other cardiac surgeons if they agree that the recipient population should be better defined.

Dr. Allen stated that he generally agrees, but emphasized that high-risk recipients often need the best hearts available.

Dr. Moon stressed the importance of doing animal studies.

Dr. Allen pointed out that under the old allocation, organs from distant locations would have been amassed under the standard of care and distributed locally.

Ms. Wentz read Question 6b: Please discuss whether the available study data provide a reasonable assurance of safety and effectiveness for donor hearts defined by each of the individual donor heart criteria. If not, please explain your concerns.

Dr. Allen remarked that the totality of the criteria needs to be considered along with other factors such as donor times and recipient status.

Dr. Kwon pointed out that most of the two-hour criteria seem to be arbitrary, that there is no indication in the data that any of them would be benefitted, and that this is a patient group that would be easy to study.

Alfred H. Stammers, M.S.A., asked if there should be an upper boundary on the donor age.

Ms. Wentz read Question 7: Benefit/Risk - The EXPAND single-arm study was designed to leverage the results of the PROCEED II randomized, controlled trial for standard criteria donor hearts, to allow for expanded indications for use in non-standard criteria donor hearts. However, reasonable assurance of safety and effectiveness was not determined for the OCS Heart System for the preservation and transplantation of standard criteria donor hearts. In FDA's opinion, the OCS Heart System studied under the EXPAND clinical study was not designed as a stand-alone clinical study, and it is for this reason that FDA is considering the results from both the PROCEED II and EXPAND studies in its assessment of the OCS Heart System benefit-risk assessment.

The OCS Heart EXPAND study met its 30-day primary endpoint of transplant recipient and allograft survival in the absence of severe primary heart graft dysfunction (PGD) in the first 24 hours post-transplantation (tested against a performance goal of 65%). However, lower survival with OCS preserved standard hearts (sustained over the long-term), high turn-down rate for hearts preserved on the OCS Heart System (13% overall), potential injury to some donor hearts being preserved on the OCS System, and the subjectivity of the "extended" donor heart inclusion criteria creating potential overlap with standard hearts, raise concerns related to how the OCS System may affect the pool of viable donor hearts available to recipients, as well as overall longer-term survival for heart transplant patients.

Given the totality of the evidence regarding the effectiveness and safety profile of the OCS Heart System (i.e., the results of the pivotal randomized PROCEED II study, the single-arm EXPAND study and the supplementary EXPAND CAP data), please discuss whether the benefits of the OCS Heart System outweigh the risks.

Dr. Moon opined that using the device would be better than having discarded organs. He suggested a standard-of-care versus OCS study for the "two-hour plus" patients to determine where the device stands in terms of safety and organ damage.

Dr. O'Connor agreed. He stated that FDA should use the results from PROCEED II.

Dr. Cigarroa remarked that it would be challenging to not use PROCEED II data in determining safety and effectiveness for patients who would otherwise be transplanted with an ischemic time burden of less than four hours.

Dr. Allen stated that he does not think the device is better than standard of care in

short ischemic time and may even be a lot worse. He further stated that the benefit-risk is predicated on how well FDA can establish appropriate controls for use of the device in a properly defined population.

Chairperson Lange summarized the Panel's response:

- there is concern about using the device for patients who have an ischemic time of less than two hours;
- there is more enthusiasm for using it in those whose ischemic time would be more than four hours plus additional risk factors; and
- there is some apprehension as to whether all sites would see the same benefits as those that were seen at Duke University.

Ms. Wentz read Question 8: Proposed Post-Approval Study (PAS) - Post-approval studies are often required at the time of approval of a PMA to address remaining questions or provide information on the continued safety and effectiveness of the approved device. These studies are not intended to provide initial support for reasonable assurance of safety and effectiveness, as that determination must be established prior to device approval. If a PAS is requested, the sponsor has proposed two post-approval studies to continue to evaluate the performance of the OCS Heart System:

- A 175 patient, single-arm, prospective, multicenter, observational post-approval registry with follow-up out to 12 months, and outcomes out to 5 years; and
- A single-arm, observational post-approval follow-up data analysis in which outcomes obtained from the existing national Scientific Registry of Transplant Recipients (SRTR)/OPTN database for the 75 subjects transplanted in EXPAND will be obtained and analyzed out to 5 years.

Please comment on whether additional objectives, design features, or surveillance are recommended for the Post-Approval Studies. Specifically, please discuss the appropriateness of the proposed primary endpoint (e.g., 12-month survival from cardiac graft related death), the 86% performance goal (considering a post-hoc, un-adjudicated analysis of cardiac graft-related survival at 12-months in EXPAND was 95%), as well as other follow-up assessments necessary to evaluate the long-term safety and effectiveness of the device.

Dr. Connor recommended tracking all patients who use the device and to identify whether they are on label or not, as a way of measuring creep. He also said that an observational trial can still be done and suggested matching OCS patients with patients who would prefer to wait as comparators.

Dr. Brindis discussed the possibility of utilizing the UNOS database for propensity matching or other comparison techniques.

Dr. Hirshfeld specified that the unit of analysis should be the donor heart and not the recipient.

Chairperson Lange summarized the Panel's response:

- A comparator is needed, which could either be individuals on a waiting list or the UNOS database.
- A larger patient population is required.
- There is a need to ascertain whether there really is creep and if the device is being used for the right indication.
- Data collection should be more comprehensive.
- The unit of analysis should be the donor heart.

Dr. Bonde also recommended identification of factors that affect donor heart performance within the first year.

SUMMATIONS

Mr. Aguel thanked all of the participants for sharing their insights and observations.

Carmelo A. Milano, M.D., stated that cold static storage is a primitive and limiting strategy, and that the sponsor provided clear answers to each of FDA's concerns. He presented a slide showing one-year survival for the EXPAND and CAP cohort, noting that the rate is similar to SRTR data for general heart transplantation. He pointed out that this represents more than 80 hearts that would not have been utilized. He reminded the Panel of what the OCS would mean for the field of heart transplantation and that it has the potential to significantly expand the number of transplants in the United States.

FINAL COMMENTS

Debra Dunn, Patient Representative, stated that she agrees with Dr. Milano's comments, that she understands the risk factors, and that the device is an advancement in cardiology.

PANEL VOTE

Ms. Asefa read the safety and effectiveness definitions as defined in 21 C.F.R. Section 860.7, and the proposed indications for use. She then explained the voting procedure and read the voting questions.

Question 1: Based on data in the briefing materials and presentations at today's meeting, do you believe that there is reasonable assurance that the OCS Heart System is safe for use in patients who meet the criteria specified in the proposed indication?

The Panel voted 9 yes, 7 no, with 2 abstentions.

Question 2: Is there reasonable assurance that the OCS Heart System is effective for use in patients who meet the criteria specified in the proposed indication?

The Panel voted 10 yes, 6 no, with 2 abstentions.

Question 3: Do the benefits of the OCS Heart System outweigh the risks for use in patients who meet the criteria specified in the proposed indication?

The Panel voted 12 yes, 5 no, with 1 abstention.

Chairperson Lange asked the Panel members to discuss their votes.

George W. Vetrovec, M.D., indicated that he voted yes on all three questions. He stated that the device seems to be safe and effective, and that he is hopeful that appropriate final decisions will be made with respect to distance and timing.

Dr. Blankenship indicated that he voted yes on all three questions. He stated that he would have felt more comfortable if there had been a comparator, that the benefits outweigh the risks, and that if the device is approved, it should not compete with standard of care.

Dr. Connor indicated that he voted no on all three questions. He stated that he believes there is a place for the device, specifically with four-hour and longer hearts, and that the optimism expressed by the transplant surgeons causes him to worry about indication creep.

Dr. Brindis indicated that he voted no, no, and yes. He stated that the device will help alleviate disparities in care due to transport barriers and that he believes an ethical randomized clinical trial can be devised.

Dr. Allen indicated that he voted no, yes, and yes. He stated that many of the issues could have been addressed with some key animal studies and that he hopes FDA can provide controls for preventing indication creep.

Dr. Kwon indicated that he voted no on all three questions. He stated that he was troubled by the number of patients who ended up on MCS in the first 30 days and that there were no proper controls.

Dr. Bonde indicated that he voted yes on all three questions. He stated that the issue of donor limitation could be addressed by an improved MCS system and utilization of the device.

Colleen M. Gallagher, Ph.D., indicated that she voted no, yes, and yes. She stated that the data did not prove the safety of the device and that the labeling should be explicit about its use.

Mr. Stammers indicated that he voted no on all three questions. He stated that the possibility of benefit without additional risk is questionable given the lack of safety and efficacy data.

Dr. Yeh indicated that he abstained on all three questions. He stated that he would have voted differently if there had been more stringent criteria.

Dr. Selzman indicated that he abstained on Question 1 and voted yes on Questions 2 and 3. He stated that he has concerns about the warming and cooling aspects and would like to better understand it. He encouraged additional preclinical work and agreed that greater than four hours would be an important addition to the indications.

Dr. Katz indicated that he voted yes on all three questions. He stated that this is a big step forward towards expanding the number of transplants, that constraints should be put on the use of the device, and that an animal study would help clarify some of the questions.

Dr. Cigarroa indicated that he voted no on all three questions. He stated that the ongoing production of lactate as well as longer overall out-of-body and ischemic time is

concerning. He added that he would change his vote on risk-benefit if there were animal studies and a large, carefully designed registry with the PMA.

Mark Nuszkowski, M.D., indicated that he voted yes on all three questions. He stated that the sponsor will have to keep improving the technology in order to keep selling it and that he believes good things will come from it.

Dr. O'Connor indicated that he voted yes on Question 1, abstained on Question 2, and voted yes on Question 3. He stated that there is a large unmet need, that doing a randomized trial in the expanded population would be unethical, and that there should be a restricted indication of greater than four hours including risk factors.

Dr. Borer indicated that he voted yes on all three questions. He stated that this technology seems to provide a reasonable approach to improving the supply of donor hearts.

Dr. Moon indicated that he voted yes on all three questions. He stated that the device is not intended to replace standard of care but to offer a treatment for organs that would otherwise not be used.

Dr. Hirshfeld indicated that he voted yes, no, and no. He stated that the PROCEED data suggests a possible harm and that with no interpretable comparator for the EXPAND trial, it is not possible to decide whether or not there is efficacy.

Chairperson Lange stated that if he had voted, he would have voted no on all three questions.

CLOSING REMARKS

Dr. Zuckerman thanked the Panel and Chairperson Lange.

ADJOURNMENT

Chairperson Lange then adjourned the meeting at 7:07 p.m.

I certify that I attended this meeting on April 6, 2021 and that these minutes accurately reflect what transpired.

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Aden Asefa, M.P.H.
Designated Federal Officer

I approve the minutes of this meeting as recorded in this summary.

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Richard A. Lange, M.D., MBA
Chairperson

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