APPENDIX A: DEVICE DESCRIPTION

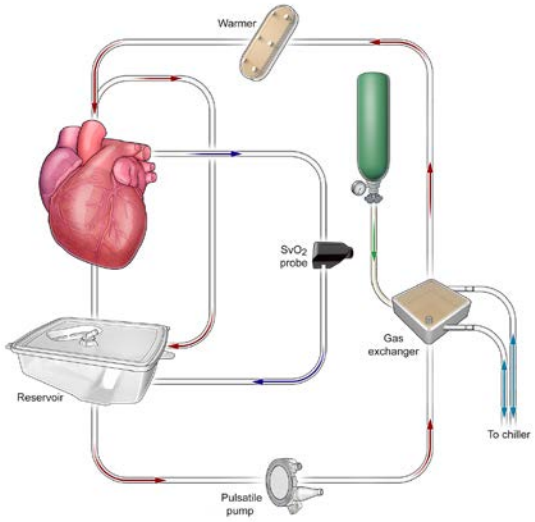
TransMedics® OCS™ Heart System Description

The TransMedics® OCS™ Heart System is a device designed to transport non-standard (i.e., "extended criteria") donor hearts to the transplant recipient site, by using extracorporeal circulation to maintain heart viability via continuous perfusion of the organ with temperature controlled, oxygenated blood (obtained from the donor) supplemented with the TransMedics' Heart Solution Set.

Current preservation methods for donor hearts include flushing the heart with a specially prepared ice-cold solution that contains electrolytes and nutrients, followed by packing the organ in a sterile container and wet ice for transportation to the recipient's transplant center.

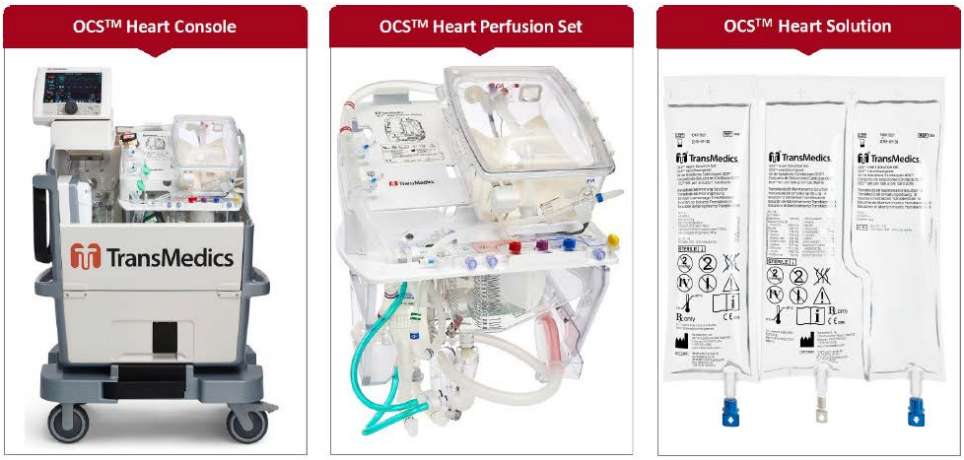
The schematic below illustrates the OCS fluid flow during preservation of a donor heart. Note that pictures, figures and much of the descriptive text that follows are taken or summarized from the TransMedics PMA submission (P180051).

Schematic of OCS Fluid Flow



The TransMedics® OCS™ Heart System is composed of 3 major components:

- OCS Heart Console
- OCS Heart Perfusion Set (consists of the Heart Perfusion Module (HPM) and the Heart Perfusion Accessories)
- OCS Heart Solution



TransMedics® OCS™ Heart Console

The OCS Heart Console is the portable electromechanical base unit for the OCS Heart System that includes the following major components:

- electronics
- software
- fluid pumping systems (e.g., solution delivery subsystem [SDS], pulsatile pump to circulate perfusate)
- monitoring systems
- power supply
- batteries
- gas cylinder
- mobile base
- Wireless Monitor

The Wireless Monitor displays perfusion and pressure parameters and allows the user to evaluate parameters and adjust specific system settings during transport of the donor heart. The Heart Console provides a rigid compartment to house and protect the HPM during transport.

TransMedics® OCS™ Heart Perfusion Set (HPS)

The Heart Perfusion Set (HPS) consists of the Heart Perfusion Module (HPM) and the disposable HPS Accessories.

Heart Perfusion Module (HPM)

The HPM is a sterile, single use disposable set that provides a closed extracorporeal system to perfuse, maintain and support the heart. It interfaces with the Heart Console to oxygenate and provide a temperature controlled perfusate to maintain the heart in a near-physiologic state. It also incorporates a number of sensors and monitors to assess the preservation conditions, such as fluid flow rate, pressure, temperature, oxygen saturation, and hematocrit. In addition, venous and arterial lactate levels from the donor heart can be sampled through ports in the system.

The HPM includes the following components:

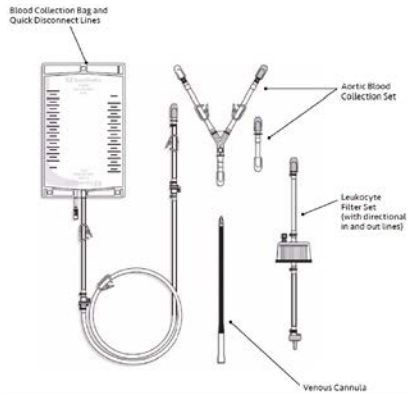
- Clamshell-shaped, heart-specific polycarbonate chamber
- Integrated and easily accessible blood sampling and de-airing manifold
- Integrated pulsatile pump head interface
- Integrated low-shear titanium blood warmer (resistive elements/plates)
- Integrated blood oxygenator (i.e., gas exchanger)
- Integrated sensors (ECG, pressure, and temperature) and circuitry to communicate with the Heart Console

Heart Perfusion Set Accessories (HPS Accessories)

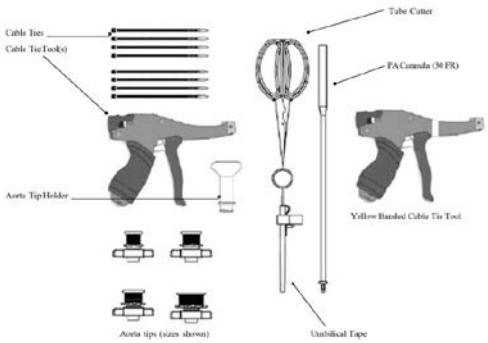
The HPS Accessories are sterile, single use, disposable accessories necessary to instrument the heart and manage the perfusate. The HPS Accessories include:

- **OCS Blood Collection Set** – intended to collect and process the donor blood:
    - Blood Collection Line
    - Leukocyte Filter Line
    - 34FR Venous Cannulae
    - Aortic Blood Collection Set
- **OCS Heart Instrumentation Tool Set** – intended to connect the heart to the HPM circuit:
    - Cable Ties
    - Cable Tie Tool
    - Aorta Connector 4X
    - Aorta Tip Holder
    - Tube Cutter
    - Tourniquet Kit
    - PA Cannulae
- **OCS Cardioplegic Arrest Set** – intended to infuse cardioplegia to terminate the preservation, directly prior to transplantation:
    - Cardioplegia Drain Line
    - Cardioplegia Administration Connector
    - Heart Sterile Drape
- **OCS Heart Solution Line Set** – intended to infuse OCS Priming Solution and then infuse the OCS Maintenance Solution to the HPM:
    - Quick Prime Line
    - Solution Delivery Cassette
- **OCS Monitoring Accessories Set** - intended to facilitate monitoring of the heart function: Tuohy-Borst Valve

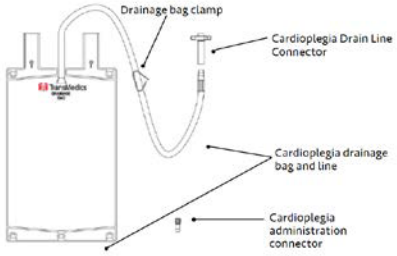
OCS Blood Collection Set



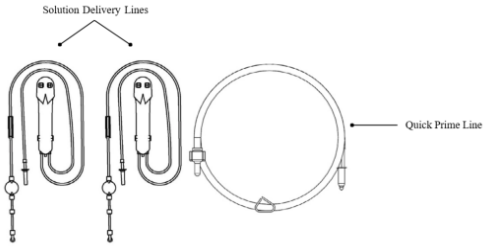
OCS Heart Instrumentation Tool Set



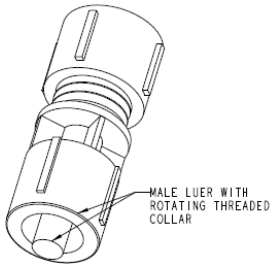
OCS Cardioplegic Arrest Set



OCS Heart Solution Line Set



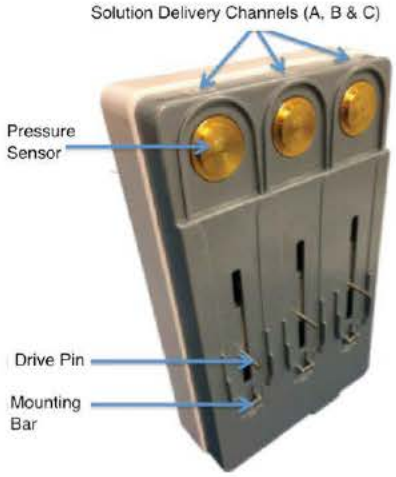
OCS Monitoring Accessories Set



TransMedics® OCS™ Heart Solution Set (OCS Heart Solution Set) and Solution Delivery Subsystem (SDS):

TransMedics Heart Solution Set

Solution Delivery Subsystem



Heart Solution Set

The OCS Heart Solution Set is a 3-chamber bag solution set (500ml per chamber) containing two proprietary heart preservation solutions: (1) OCS Priming Solution and (2) OCS Maintenance Solution. The OCS Maintenance Solution is comprised of two component solutions, an amino acid/electrolyte solution and a glucose solution, which are supplied in two separate chambers. The two chambers are joined by a peelable seal that is breached immediately prior to use to mix the components. The composition of the OCS Priming and Maintenance Solutions are shown in Tables A.1 – A.3.

Table A.1 Composition of the OCS Priming and Maintenance Solutions

Substance	**Purpose**
OCS Priming Solution[1]	
Mannitol	Osmotic pressure
Sodium Chloride	Electrolyte balance
Sodium Glycerophosphate	Phosphate Source for metabolic balance
Potassium Chloride	Electrolyte balance
Magnesium sulfate heptahydrate	Electrolyte balance
Hydrochloric Acid	pH adjustment during manufacturing
Water for Injection	Fluid
OCS Maintenance Solution[2]	
Calcium Chloride (g)	Electrolyte to support metabolism
Magnesium Sulfate (g)	Electrolyte to support metabolism
Potassium Chloride (g)	Electrolyte to support metabolism
Sodium Chloride (g)	Electrolyte to support metabolism
Adenosine (g)	Nutrient to support metabolism

Dextrose (g)	Energy Source
Amino Acids	Nutrients to support metabolism
[1] OCS Priming Solution of 500 mL to prime the OCS circuit. [2] OCS Maintenance Solution is commonly administered at rates of 10-30 mL/hour. This is the composition after the two separate OCS Maintenance Solution chambers are mixed.	

Table A.2 Composition of the Glucose Solution

Component	Purpose
OCS Glucose Solution	
Glucose Monohydrate	Energy source
Water for Injection	Fluid

Additionally, the OCS Heart System requires the user to supply certain additives (as outlined in the instructions for use) as listed below:

Table A.3 Required Heart Perfusion Additives

Substance	Purpose
Sodium Bicarbonate	Buffer
Heparin	Anti-coagulant
Methylprednisolone	Anti-inflammatory
Multivitamins	Nutrient to support metabolism
Ciprofloxacin or Equivalent Gram-Negative Antibiotic	Antibiotic
Cefazolin or Equivalent Gram-Positive Antibiotic	Antibiotic
Human albumin	Oncotic pressure
Regular Insulin	Support metabolism
Epinephrine 0.25mg in 500mL of Dextrose 5% solution, plus Regular Insulin	Replenish depleted catecholamines ex-vivo

The OCS Heart Solution Set is not intended to be administered directly to the heart donor or to the recipient. The donor heart is arrested prior to removal using a cardioplegia solution. After transport and prior to transplantation into the recipient, the donor heart is arrested on the OCS through the use of mechanical cooling and arrest with a cardioplegia solution, at which time the perfusate (including the donor blood, OCS Priming Solution, and OCS Maintenance Solution) are flushed from the donor heart.

Solution Delivery Subsystem (SDS)

The SDS is mounted in the Heart Console and the infusion rate (via integral pump) for each of its three channels can be independently set. The cassettes contain a syringe, which the SDS automatically refills from the solution bag, and the Wireless Monitor provides information on the mode of operation, delivery rate, volume remaining, and volume infused. The SDS can be set to operate in either Aortic Pressure (AOP) control mode or in Manual Delivery mode. In AOP

control mode, the SDS will adjust the delivery rate of OCS Maintenance Solution to maintain a user specified aortic pressure. Manual Delivery mode allows the user to set the delivery rate of the solution at a fixed rate.

OCS – Heart System Batteries

The OCS operates on AC power or from one of three replaceable lithium-ion batteries, which can be replaced one at time while the Heart Console is operating. Each battery is designed to provide about 1 hour 20 minutes of operating time. The Wireless Monitor also has a single non-user replaceable lithium-ion battery that is able to support the monitor for up to 6 hours. The sponsor claims that the OCS System can be used in a variety of settings such as the operating room, ambulance, helicopter, airplane or sports utility vehicle.

SYSTEM SPECIFICATIONS

Tables A.4 – A.8 show OCS – Heart System operating and performance specifications.

Table A.4 Clinical Parameter Alarm Ranges

Function	Alarm Limit Range	Default Lower Limit	Default Upper Limit
Blood Temperature (°C)	33.0 – 38.0	33.5	37.5
Coronary Flow (CF) (mL/min)	100 – 1500	600	900
Aortic Flow (AOF) (mL/min)	100 -1500	800	1200
Aortic Mean Pressure (AOP) (mmHg)	20 – 120	60	100
Pulmonary Artery Mean Pressure (PAP) (mmHg)	0 – 50	N/A	15
SvO2 (%)	55 – 70	60	N/A
HCT (%)	16 – 30	18	N/A
HR (BPM)	20 – 190	40	140

Table A.5 OCS System Physical Specifications

Unit	Specifications
OCS™ Heart System	
Power Consumption	Input voltage 100V to 240V, 50/60 Hz and 375 VA
Batteries	Lithium Ion cells Operating life of 4 hours minimum on 3 battery packs
Dimensions	Length <30 inches Width < 19 inches Height < 30 inches
Weight	Less than 100 lbs with the HPM and without Mobile Base
Wireless Monitor	
Power Supply	Heart Console when docked
Batteries	Lithium Ion cells Operating life of 6 hours minimum on battery power

Dimensions	Length < 10 inches Width < 10 inches Thickness < 4 inches
LCD	Type: VGA Size: 8.4" (Diagonal)
Weight	Less than 5 lbs
Mobile Base	
Weight	Less than 27 lbs

Table A.6 Pumping System Specifications

Perfusion Pump	**Specifications**
Flow Rate Type	Pulsatile
Pump Cycle	Synchronous with ECG R-wave, or Default: 60 beats per minute
Pump Mode	Asynchronous ECG Synchronous
Range of flow rates	300 to 4,500 mL/min

Table A.7 Performance Specifications for OCS – Heart System

	Specifications
Heating Capabilities	
Temperature Settings	34.0 – 37.0 ºC
Temperature Maintenance	Maintain temperature ± 2°C of the set point at an ambient temperature of 25°C after achieving ± 0.5°C at the 37°C set point
Temperature Rise Time	Have a temperature rise time of 30 minutes maximum with 1.5 liters of donor blood and 0.5 liter of prime solution at 30°C to indicated 37°C, when the device is operating on AC power at a blood flow rate of 1 liter per minute indoors with an ambient temperature of no less than 20°
Gas Delivery	
Flow Rate	150-500 mL/min
Accuracy	± 20%
Gas Composition	85% O_2, 1% CO_2, 14% N
Minimum Oxygen Transfer Rate	27.5 ml/min/LPM at a blood flow rate of 500 ml/min
Minimum Carbon-dioxide Transfer Rate	20 ml/min at a blood flow rate of 500 ml/min
Solution Delivery	
Flow rate	1 – 99 mL/min
Flow type	Positive displacement
Solution Delivery Modes	Manual Auto AOP (AO Pressure Control) Off

Auto AOP Set Point	Range: 40 mmHg – 100 mmHg; Default 75 mmHg

Table A.8 System Sensor Specifications

Sensor	Specifications
Temperature	
Measurement Range	0 - 45.0ºC
Accuracy	± 1ºC
Blood Flow Rate (Transducers)	
Measurement Range	0 – 6.5 L/min
Accuracy	± 12% and ± 140 mL/min
Perfusate Pressure	
Measurement Range	-25 mmHg to 225 mmHg
Accuracy	The greater of ± 7% or ± 10 mmHg
Oxygen Saturation	
Measurement Range	50-99%
Accuracy	± 5%
Hematocrit	
Measurement Range	15-50%
Accuracy	± 5%

APPENIX B: REGULATORY

OCS Heart System Design Changes

Table B.1 shows some of the major design changes made to the OCS Heart System during the course of the EXPAND clinical study (G140111).

Table B.1 Major Design Changes made to the OCS – Heart System during the EXPAND clinical study (G140111)

File Received (Date)	Date Acknowledged or Approved	Changes from previous version
Original/A001 (b)(4)	(b)(4) APPROVED	- Use of Maquet Quadrox-i Small Adult Oxygenator (to accommodate new heart cooling procedure immediately prior to re-implantation) replacing Novalung Oxygenator used for PROCEED II - Addition of a second compliance chamber (and associated one-way valve and tubing) was added to make the tubing more compliant and facilitate perfusate flow to the donor heart. Animal studies suggested a more physiological waveform with these design changes and acceptable lactate uptake even with lower coronary flows, which appeared to also reduce the heart weight gain - Addition of "Y" prime line with pressure relief valve in perfusion module.
S002 (b)(4)	(b)(4) CONDITIONAL APPROVAL – *full approval* (b)(4)	- Replacement of Cardinal Health MedSystem III pump with TransMedics Solution Delivery Subsystem (SDS) - Addition of Automatic AOP mode
First Subject Transplanted 9/16/2015		
S007 (b)(4)	(b)(4) Acknowledged	Users were instructed not to use AOP in automatic mode (use only manual mode) due to a software bug that created AOP instability.
3 Subjects Transplanted 9/16/15, 9/24/15 and 10/21/2015		
S009 (b)(4)	(b)(4) APPROVAL	Automatic AOP mode software bugs fixed. AOP mode allowed to be used again.
S013 (b)(4)	(b)(4) APPROVAL	Removal of second compliance chamber and one-way valve design verified in G140111/Original – citing design harmonization between US and OUS designs.
S014 (b)(4)	(b)(4) Acknowledged	Increase upper limit of AOP to from 80 mmHg to 100 mmHg.
S015 (b)(4)	(b)(4) Acknowledged	Protocol updated (Version 1.3) to include increases in upper limits for AOP and CF: AOP 40-100 (from 80 mmHg) and CF 400-900 ml/min (from 800 ml/min)

Clinical Protocol Changes

Table B.2 outlines some of the major clinical protocol changes made over the course of the EXPAND clinical study (G140111).

Table B.2 Major Protocol Changes made during the EXPAND clinical study (G140111)

G140111 (Date)	Overview of submission	FDA Action
Original (b)(4)	**Original IDE for EXPAND** Single-arm clinical study evaluating the use of the OCS – Heart System to perfuse and maintain donor hearts during transport. 55 subjects/20 sites. **Protocol Version 1.0**	**7/23/2014** **Conditional Approval Letter** – all conditions of approval are related to informed consent.
A001 (b)(4)	**Response to approval conditions** – changes made to the informed consent form as requested. **Protocol Version 1.1**	**9/3/2014** **Approval Letter**
S001 (b)(4)	**Changes made to the Case Report Forms (CRFs)** – as recommended by FDA in minor study design considerations **Protocol Version 1.2**	(b)(4) **Approval Letter**
First Subject Enrolled 9/16/2015		
S007 (b)(4)	**Users instructed not to use AOP in automatic mode** (use only manual mode) due to a software bug that created AOP instability.	(b)(4) **Acknowledgement e-mail**
S009 (b)(4)	**Software update from 3.3.1-C to 3.3.2-C** – restriction on automatic AOP lifted.	(b)(4) **Approval Letter**
S015 (b)(4)	**Protocol Changes (Protocol Version 1.3) to align with S014 design change** - AOP upper range limit increased to 100 mmHg - CF upper range limit increased to 900 ml/min - New ranges are AOP 40-100 mmHg; CF 400-900 ml/min	(b)(4) **Acknowledgement e-mail**
48/55 subjects enrolled. 44/48 subjects with 30-day data. At least 3/44 deaths and at least 7/44 cases of PGD.		
S018 (b)(4)	- **Requested enrollment increase by 20 subjects (55 to 75)** - New **Protocol Version 1.4** including statistical plan and definition changes[a]	(b)(4) **Approval Letter**
S026 (b)(4)	**Termination of IRB approval at Spectrum Health** – IRB/PIs note differences in study content between training materials, protocol and instructions for use. Following 11 months of discussion between Spectrum Medical and TransMedics, "…the IRB determined, based on the study document discrepancies (i.e., discrepancies that impacted study merit and therefore criteria for approval), and based on the lack of resolution of these issues by the Sponsor, that this meets the definition of serious and continuing non-compliance by the Sponsor; and "…that IRB approval is terminated for this study at Spectrum Health." 8 subjects were transplanted at this site under EXPAND.	(b)(4) **Conditional Approval Letter**
S026/A001 (b)(4)	**Response to the 4 conditions of approval in 3/2/18 FDA CA letter**	(b)(4) **Submission OK e-mail** All outstanding SDCs and FC remain unaddressed.

Last subject Transplanted 3/25/2018		
S029 (b)(4)	**Request for a Continued Access Protocol (CAP)**	(b)(4) **Conditional Approval** Requested 48 subjects; FDA approved 18 subjects, sufficient for approximately 6 months enrollment at expected enrollment rates.
S029/A002 (b)(4)	**Response to conditional approval letter 11/21/18**	(b)(4) **Approval**
S031 (b)(4)	**Request for expansion of CAP to 39 subjects** (21 additional subjects)	(b)(4) **Conditional Approval Letter** 5 SDCs and 2 FC (1 new FC) remain and are repeated
S031/A002 (b)(4)	**Response to conditional approval letter 9/12/19**	(b)(4) **Approval Letter** 5 SDCs and 2 FC remain and are repeated

[a]The redlined protocol changes were as follows:

- 55 subjects changed to 75 subjects
- On page 26, the following sentences added:
  - In the case of missing outcome data, a multiple imputation model will be used to present a complete outcome analysis.
  - For this study, major protocol violations include:
    - Donor and recipient's Inclusion/Exclusion Criteria Violation
    - Failure to follow IFU
    - Failure to follow protocol
- On page 28, the following added: 9.5. Site Poolability: A site effect analysis will be conducted to assess the poolability of data. Sites with fewer than five subjects will be grouped into a larger Analysis Site. A chi-square test will be performed to evaluate site impact with a p-value of 0.15 defined as the threshold. If the p-value < 0.15 then analysis adjusting for site will be considered.
- Table 2: Definition of Severity scale for Heart PDG deleted.

FC = Future considerations

SDC= Study design considerations

(b)(4)

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APPENDIX D: In Vitro Bench Testing

I. Battery Testing

The OCS – Heart System console can be powered using 3 lithium ion batteries which have demonstrated the ability to power the system for 4 hours (i.e., 1 hour 20 minutes for each of the lithium ion batteries, which can be replaced individually by the user). Other specifications for the Heart Console batteries include:

Table D.1 Heart Console Batteries

Heart Console Lithium Ion Batteries	
Shelf-Life	5 Years
Discharge Cycle limit	100
Single Battery Run Time	1 hour 20 minutes
3-Battery Run time	4 hours
Time to Recharge	4-12 hours

The OCS Wireless Monitor also contains a lithium ion battery (not replaceable by the user) with a 6 hour single charge life. Other specification for the Wireless Monitor Battery include:

Table D.2 Wireless Monitor Battery

Wireless Monitor Lithium Ion Battery	
Shelf-Life	5 Years
Discharge Cycle limit	100
Single Battery Run Time	6 hours
Time to Recharge	4 hours

The battery testing appears appropriate and supports the labeled shelf-life, power requirements, and cycle limits to assure that the device, when operated on battery power, can support the donor organ as intended.

II. Electrical Safety (ES) and Electromagnetic Compatibility (EMC)

The following electrical safety (ES) and electromagnetic compatibility (EMC) testing was performed on the OCS – Heart System and is considered appropriate and acceptable for the intended use and intended environments of use.

Electrical Safety

Testing was performed on the OCS Heart System to the following acceptable standards:
ANSI/AAMI ES60601-1:2005/(R)2012 + A1:2012 + C1:2009/(R)2012 + A2:2010/(R)2012

Table D.3 Electrical Safety Testing

	Clause	Result
4	General requirements	Pass
5	General requirements for testing ME EQUIPMENT	Pass
6	Classification of ME EQUIPMENT and ME SYSTEMS	Pass
7	ME EQUIPMENT identification, marking and documents	Pass
8	Protection against electrical HAZARDS from ME EQUIPMENT	Pass
9	Protection against MECHANICAL HAZARDS of ME EQUIPMENT and ME SYSTEMS	Pass
10	Protection against unwanted and excessive radiation HAZARDS	N/A
11	Protection against excessive temperatures and other HAZARDS	Pass
12	Accuracy of controls and instruments and protection against hazardous outputs	Pass
13	HAZARDS SITUATIONS and fault conditions for ME EQUIPMENT	Pass
14	PROGRAMMABLE ELECTRICAL MEDICAL SYSTEMS (PEMS)	Pass
15	Construction of ME EQUIPMENT	Pass
16	ME SYSTEMS	N/A
17	Electromagnetic compatibility of ME EQUIPMENT and ME SYSTEMS	Pass

Electromagnetic Compatibility

Testing was performed on the OCS Heart System to the following acceptable standards: IEC 60601-1-2:2014 (4th Edition)

Essential Performance:

- Pump warm, oxygenated blood
- Display blood flow, pressure and temperature
- Allow user to control functions
- Supplement the circulating perfusate with solutions

Table D.4 Electromagnetic Compatibility Testing

Test	**Standard**	**Test Level**	**Results**
Radiated Emissions	EN55011/FCC Part 15 (CISPR 11)	Group 1, Class A	Pass
AC Mains Conducted Emissions	EN55011/FCC Part 15 (CISPR 11)	Group 1, Class A	Pass
Harmonics Emissions	IEC 61000-3-2	Class A	Pass

Voltage Fluctuation/ Flicker	IEC 61000-3-3	Highest dmax = 4%	Pass
Electrostatic Discharge Immunity	IEC 61000-4-2	±8 kV Contact ±2 kV, ±4 kV, ±8 kV and ±15 kV Air	Pass
Immunity to proximity fields from RF wireless communications equipment	IEC 60601-1-2 Clause 8.10	9 V/m at 710 MHz, 745 MHz, 780 MHz, 5240 MHz, 5500 MHz and 5785 MHz 27 V/m at 385 MHz 28 V/m at 450 MHz 810 MHz, 870 MHz, 930 MHz, 1720 MHz, 1845 MHz, 1970 MHz, 2450 MHz	Pass
Radiated RF Immunity	IEC 61000-4-3	3 V/m 80 MHz – 2.7 GHz 80 % AM at 1 kHz	Pass
Electrical Fast Transients Immunity	IEC 61000-4-4	±0.5 kV, ±1 kV and ±2 kV	Pass
Surge Immunity	IEC 61000-4-5	±0.5 kV, ±1 kV Line-to-line ±0.5 kV, ±1 kV and ±2 kV Line-to-PE	Pass
Conducted RF Immunity	IEC 61000-4-6	3 Vrms AC Mains 6 Vrms AC Mains (ISM Bands)	Pass
Magnetic Field Immunity	IEC 61000-4-8	30A/m	Pass
Voltage Dips/Interrupts	IEC 61000-4-11	0% UT 0.5 cycles at 0°, 45°, 90°, 135°, 180°, 225°, 270° and 315° 0% UT 1 cycle 70% UT 25 cycles, 50 Hz single phase at 0° 0% UT 250 cycles, 50 Hz single phase at 0°	Pass
Radiated Emissions for Transport Environments	ISO 7137 and RTCA DO 160G	Category M	Pass
Radiated Immunity for Transport Environments	RTCA DO 160G	Category R	Pass
Radiated Emissions	CISPR 25	Class 1	Pass

Spurious Emissions	FCC 47CFR Part 15C	Class B	Pass

III. Software

The OCS Heart System is controlled/monitored by software, which is responsible for the functionality, user interface, safety checks and performance accuracy. FDA's review found the following aspects of the software acceptable:

- **Level of Concern** - The firm provided the correct determination of the Level Of Concern and included their supporting rationale: MAJOR.
- **Software Description** - The firm provided an acceptable overview of the device features that are controlled by software, and a description of the intended operational environment, which included information on the programming language and the hardware platform.
- **Device (including software) Hazard Analysis** - The firm provided an acceptable description of the hazards (including clinical hazards) presented by this device, the causes and severity of the hazards, the method of control of the hazards and the testing done to verify the correct implementation of that method of control, and any residual hazards.
- **Software Requirements Specifications (SRS)** - The firm provided acceptable Software Requirements Specification document, which documented the functional, performance, interface, design and development requirements.
- **Architecture Design Chart** - The firm provided an acceptable detailed depiction of functional units and software modules, which included state diagrams as well as flow charts.
- **Software Design Specification (SDS)** - The firm provided acceptable Software Design Specifications, which describes how the requirements in the Software Requirements Specifications (SRS) are implemented.
- **Traceability** - The firm included acceptable traceability among identified clinical hazards and mitigations, requirements, specifications, and verification and validation testing.
- **Software Development Environment Description** - The firm provided an acceptable description of the software development environment, which included a summary of the software life cycle development plan, an annotated list of the control/baseline documents generated during the development process, and a summary of the configuration management and maintenance activities.
- **Verification and Validation Documentation** - The firm provided acceptable unit, integration and system level test protocols, including pass/fail criteria, test reports, summaries and tests results.
- **Revision Level History** - Revision Level History has been reviewed up to Version 3.3.6-C (version 3.3.7-C (b)(4)] was submitted on February 3, 2021 related to cybersecurity and remains under review). *It should be noted that Version 3.3.5-C was the original version proposed for approval under* (b)(4) *; however, the sponsor upgraded the software to Version 3.3.6-C in* (b)(4) .

- **Unresolved Anomalies (bugs)** - The firm provided an acceptable list of the remaining software anomalies, annotated with an explanation of the impact of the anomaly on safety or effectiveness, including operator usage and human factors.
- **Run-Time Error Detection** – Acceptable coding practices appear to have been implemented to prevent common coding errors.

The following aspect of the software review continues to be unacceptable. FDA continues to work with TransMedics to address these issues:

- **Cyber and Information Security: Not Acceptable**
  Three issues remain related to vulnerabilities to Bluetooth DoS, Weak encryption (E0 algorithm or no encryption at all), and man-in-the-middles attacks. Software upgrade 3.3.7-C was submitted to FDA under (b)(4) on February 3, 2021 and FDA continues to work with the sponsor to address all remaining cybersecurity issues.

IV. Sterilization/Packaging/Simulated Shipping Distribution/Shelf-life/Packaging Integrity

Sterilization (via ethylene oxide [EO] gas), packaging, simulated shipping distribution and shelf life (42 months for Heart Perfusion Set [HPS], 24 months for Heart Solution Set [HSS]) followed each by packaging integrity testing were all found to be acceptable for the HPS and the HSS.

One item remains with respect to the disposable HPS: Bacterial endotoxin testing on the HPS and the HSS resulted in acceptable bacterial endotoxin levels, and while TransMedics has opted to label the Heart Solution Set as non-pyrogenic, the labeling for the Heart Perfusion Set does not have a non-pyrogenic label. Although not required, FDA continues to recommend that the HPS set be labeled as non-pyrogenic.

OCS Heart Perfusion Set (HPS consisting of the HPM and HPS accessories)

Packaging

Table D.5 OCS Perfusion Set

Sub-Assembly	Packaging
Heart Perfusion Module	Vented Bag
Blood Collection Set	Tyvek Pouch
Heart Solution Line Set	Tyvek Pouch
Heart Instrumentation Tool Set	Tyvek Pouch
OCS Cardioplegic Arrest Set	Tyvek Pouch
Monitoring Accessory	Tyvek Pouch
Shipping Cartons	Foam Inserts/ Corrugated Cartons

The HPM is first sealed in a Vented Bag (**Figure A** – *taken from* (b)(4)). The Vented Bag ("breather bag") is a poly-to-poly pouch with four Tyvek patches. The Vented Bag is then placed inside a foam insert inside a corrugated carton (**Figure B** – *taken from Transmedics' PMA submission,* (b)(4)).

The HPS Accessories Set (Blood Collection Set, Heart Solution Line Set, Heart Instrumentation Tool Set, OCS Cardioplegic Arrest Set, and Monitoring Accessory) are sealed in individual Tyvek pouches. All components of the HPS are then placed inside the foam insert inside the corrugated carton (**Figure B**) and then EO-sterilized. This corrugated inner carton is then surrounded by foam inserts within an outer corrugated carton for shipping.

In addition, some of the HPS accessory sets are provided sterile and individually packaged in a corrugated carton for shipping as separate accessories when needed (*Table taken from* (b)(4)):

Table D.6 HPS Accessory Sets Individually Packaged

Sub-Assembly	Packaging
Blood Collection Set	Tyvek Pouch/Corrugated Carton
Heart Solution Line Set	Tyvek Pouch/Corrugated Carton
Heart Instrumentation Tool Set	Tyvek Pouch/Corrugated Carton
OCS Cardioplegic Arrest Set	Tyvek Pouch/Corrugated Carton
Small Diameter Cable Tie Tool	Tyvek Pouch/Corrugated Carton

Sterilization

According to the sponsor, EO sterilization validation was conducted in conformance with either ISO 11135-1:2007 or ISO 11135:2014, Sterilization of health care products - Ethylene oxide - Requirements for development, validation and routine control of a sterilization process for medical devices. The reference to the two different versions of the standards is in accordance with the time span of the testing conducted for different premarket applications submitted to FDA over time, including (b)(4) OCS [Standard] Heart System, and P160013 OCS – Lung System. While these different premarket applications may have contained different versions of the device, appropriate justification was provided in instances where FDA accepted testing and results performed on an earlier versions of the device.

The sponsor indicates that the EO sterilization cycle validation was conducted using the overkill approach in conformance with ISO 11135, Annex B; Conservative determination of lethal rate of the sterilization Process-Overkill approach.

- EO Sterilization - EO sterilization validation and results are acceptable, demonstrating a sterility assurance level of 10^{-6}.
- Ethylene Oxide (EO) Residues - The levels of EO and ethylene chlorohydrin (ECH) reported after 1X and 2X full cycles of EO sterilization met the recommended levels of

EO and ECH for devices used for periods up to 24 hours (ISO 10993-7:2012, page 35). This is acceptable for the OCS – Heart System, where device use did not exceed 9 hours.

- Endotoxins - The three test samples showed endotoxin levels of 0.00806, 0.00908 and 0.00940 EU/ml (0.00500 is the Limit of Detection of the test) or 16.1, 18.2 and 18.8 EU/device. These are all below the Current USP Requirement of ≤ 20 EU/device for Medical Devices and the current FDA Requirement of ≤ 0.5 EU/mL or ≤ 20 EU/device for Medical Devices. The bacterial endotoxin testing (BET) and results are acceptable.

Simulated Shipping Distribution and Packaging Integrity Testing

To demonstrate the HPS packaging materials can withstand the rigors of shipping and distribution maintaining the integrity of the sterile barrier, the sponsor subjected twelve 2X EO-sterilized HPS test articles to simulated shipping distribution (ISTA Procedure 1A) followed by packaging integrity testing consisting of visual inspection, dye penetration (ASTM F1929-15), seal strength (ASTM F88/F88M-15). In addition, the sponsor conducted performance testing.

Shelf Life and Packaging Integrity Testing

To demonstrate the packaging materials can maintain the integrity of the sterile barrier during the indicated shelf life, the sponsor subjected five HPS sets that were 2X EO-sterilized to **real-time aging at nominal room temperatures (60-80°F) for 42 months** followed by packaging integrity testing consisting of visual inspection, dye penetration testing (ASTM F1929-15), seal strength testing (ASTM F88/F88M-15), and performance testing. Results support a labeled shelf-life of 42-months.

For the SDS Cassette/Infusion Pump, twelve EO-sterilized test articles were subjected to accelerated aging (ASTM F1980-16) at 50°C to mimic a **real-time age equivalent of 42 months**, followed by a visual inspection for loose components, production leak testing and functional flow testing. Results support a labeled shelf-life of 42 months.

According to the results of the simulated shipping distribution and shelf life followed each by appropriate packaging integrity and performance testing, the overall packaging system appears to effectively withstand the rigors of shipping and distribution, maintain the integrity of the sterile barrier and performance of the Heart Perfusion Set during shipping and distribution and through the indicated shelf life.

OCS Heart Solution Set

Packaging

The OCS Heart Solution is provided in a three-chamber bag manufactured using Biofine film, a multi-layer film composed of polypropylene and synthetic rubber with a total thickness of 195 µm.

Sterilization

The OCS Heart Solution is provided sterile by moist heat sterilization, in accordance with FDA-recognized standard USP <71> Sterility Tests. Post-sterilization, devices were subjected to

simulated shipping distribution using climactic conditions to which the OCS – Heart Solution will be exposed. All inner and outer pouches maintained their sterile barrier by demonstrating that they met the pre-determined acceptance criteria for visual inspection, dye penetration, and seal strength.

The sponsor performed bacterial endotoxin testing on the OCS Heart Solution in accordance with the FDA-recognized USP <85> Bacterial Endotoxin Test. Acceptable levels of bacterial endotoxins were submitted - reported levels of bacterial endotoxin (< 0.1 EU/mL) are below the FDA recommended level of ≤ 0.25 EU/mL.

Simulated Shipping Distribution and Packaging Integrity Testing

To demonstrate OCS Heart Solution packaging materials can withstand the rigors of shipping and distribution maintaining the integrity of the sterile barrier, the sponsor subjected 32 final, finished, and terminally sterilized OCS Heart Solution Sets to simulated shipping distribution (ASTM D4169-16) followed by packaging integrity testing consisting of visual inspection test, dye penetration test (ASTM F3039-15), seal strength test (ASTM F88/F88M-15). In addition, the sponsor conducted performance testing.

Shelf Life

The sponsor indicated a shelf life of 24 months for the OCS Heart Solution. After real-time aging, four batches of solution were produced and tested, including evaluations for pH, color, clarity, osmolality, particulate matter, endotoxins, and sterility as well as chemical analysis of glucose, 5-HMF, adenosine, electrolytes (sodium, potassium, magnesium and calcium), and all amino acids. The stability of the of the OCS Heart Solution consists of chemical analysis and functionality testing to demonstrate the integrity of the sterile barrier since the bag itself is the sterile barrier. The sponsor concludes that after 24 months of aging, the priming solution, the B-Glucose solution and the B-Amino acid solution have good physical and chemical quality. Package integrity testing consisted of visual inspection test, seal strength test (ASTM F88/F88M-15) and dye penetration test (ASTM F3039-15).

According to the results of the simulated shipping distribution and shelf life followed each by appropriate packaging integrity and performance testing, the overall packaging system appears to effectively withstand the rigors of shipping and distribution, maintain the integrity of the sterile barrier and performance of the OCS Heart Solution Set during shipping and distribution and through the indicated shelf life.

OCS Heart Console (Reusable Component)

The sponsor's reprocessing instructions in Chapter 5, Cleaning and Maintaining the OCS, of the TransMedics Organ Care System – Heart Application User Manual include sufficiently clear reprocessing instructions to ensure that the device can be adequately reprocessed by the end-user for safe use in between patient treatments.

V. Biocompatibility

The patient (blood and tissue/heart) contacting components of the subject device include:

- Heart Perfusion Set (HPS)
- OCS Heart Solution Set

The Heart Perfusion Set (HPS) consists of the Heart Perfusion Module (HPM) and the disposable HPS Accessories. The HPM provides the sterile blood circuit and protected environment for a heart within the OCS Heart System. The OCS Heart Solution Set consists of two proprietary heart preservation solutions to replenish the nutrients and hormones (adenosine) that the metabolically active donor heart requires – i.e., the OCS Priming Solution and the OCS Maintenance Solution.

The subject device, when used as intended, is considered an external communicating device, contacting tissue/blood for a limited duration (< 24 hours). Therefore, per the FDA Guidance ISO 10993-1, the following endpoints are recommended for biocompatibility evaluation of the patient-contacting components (in their final, finished, sterilized form) of the subject device:

- cytotoxicity
- intracutaneous irritation
- sensitization
- acute systemic toxicity
- genotoxicity
- material-mediated pyrogenicity testing

Per the Sponsor, all materials used to comprise the HPS and OCS Heart Solution Set bags were included for biocompatibility testing (a list of all materials was provided). All test units underwent Ethylene Oxide (ETO) sterilization before biocompatibility testing.

Summary of the biocompatibility testing, and results are shown in the Table D.5 (*summary of table from* (b)(4))

Table D.7 Biocompatibility Testing OCS – Heart System

Biocompatibility Test	**ISO Test Standard**	**Results**
Cytotoxicity Test (MEM Elution)	10993-5	Non-cytotoxic
Intracutaneous Reactivity (2 extracts)	10993-10	No irritation
Sensitization (Guinea Pig Maximization, 2 extracts)	10993-10	No delayed dermal contact sensitization
Acute Systemic Toxicity (2 extracts)	10993-11	No systemic toxicity observed
Genotoxicity (3 methods, 2 extracts each) • *in vitro* Bacterial Reverse Mutation • *in vitro* Mouse Lymphoma Assay • *in vivo* Mouse Peripheral Blood Micronucleus Assay	10993-3	Non-mutagenic
Pyrogenicity (USP <151> Rabbit Pyrogen)	10993-11	Non-pyrogenic

Hemocompatibility (2 methods, direct and indirect contact)	10993-4	Non-hemolytic
USP Physicochemical Tests: • Non-volatile residue • Residue on Ignition • Heavy Metals • Buffering Capacity	USP<661> Containers, Plastics	Meets USP limits; no significant extractables

In addition to cytotoxicity and hemolysis testing, the Sponsor provided information reporting on the chemical properties of the Heart Solution Set three-chamber bag used as the primary packaging material for the TransMedics solutions for organ preservation. The aim of this chemical analysis is to show that the three-chamber bag is chemically suitable for storage of the solutions. The Sponsor states that chemical testing (USP<661> testing) was performed and results are shown to have passed all the tests.

Information on the colorants included in the blood/tissue contacting materials was also provided and acceptable.

VI. Performance/Bench Testing

The in vitro/bench testing performed on the OCS – Heart System (*Heart Console 1.6, HPM 1.4, Software Version 3.3.6-C*) is a combination of base verification/validation testing provided on earlier/different versions of the OCS Systems (e.g., OCS – Lung System, OCS – Liver System, OCS – [Standard] Heart System), followed by additional verification/validation testing performed to support the device design changes made to the OCS – [Extended Criteria] Heart System that was ultimately used in the EXPAND Study, as well as testing to support the changes made to the OCS – Heart System over the course of the EXPAND clinical study (G140111).
NOTE: *Software Version 3.3.7-C (*(b)(4)*) was submitted to FDA on February 3, 2021 to address remaining cybersecurity issues and is currently under review.*

A general list of the tests performed in support of the OCS Heart System seeking marketing approval is shown in Table D.6.

Table D.8 OCS Heart System In Vitro/Bench Testing

Test Performed	**OCS Device & Version Tested**
Bench Studies on the OCS System	
Shock and Vibration Testing	OCS – Heart Console 1.6
Operational Temperature and Humidity Testing	OCS – Heart Console 1.6
Operational Altitude Testing	OCS – Heart Console 1.6
Bench Studies on the OCS Heart Console	
Operational OCS Driven Rain Test (exposure to elements)	OCS Heart Console 1.5
ECG Synchronization Mode Verification	OCS Heart Console 1.5, HPM 1.4 and 1.5

Mechanical Design and Verification – Mobile base and wireless monitor	OCS Heart Console 1.5
OCS Heart System PCBAs Electrical Test	OCS Heart Console 1.5
OCS Battery Pack Life-Cycle Test	OCS Lung Console 1.0
Wireless Monitor Battery Life Cycle Test	OCS Lung Console 1.0
High Speed SvO_2/HCT Probe Accuracy Test	SvO2/HCT Probes, Rev H
Zoll X-Series Defibrillator Verification	OCS Heart Console 1.6
Verification of u-blox OBS21-24 Bluetooth Serial Adapter	OCS Liver Console 1.6
Gas cylinder Regulator Reliability Verification	Premier Industries Gas Regulator
Gas Cylinder Regulator Performance Verification	OCS Heart Console 1.6
Transonic Flowmeter Board Verification	OCS Heart Console 1.6
Gas Cylinder Retention Strap Verification	OCS Heart Console 1.5
Bench Studies on the Heart Perfusion Set (HPM plus HPS Accessories)	
RoHS Front End Board	HPM 1.4
Heater Plate and Blood Temperature Sensor Accuracy	RTD Assembly
Reservoir Blood Defoaming Test	HPM 1.5
Reservoir Filter Effectiveness	HPM 1.5
Process Validation Cable Tie Tool Tensioning	Cable Tie Tool
HPS Aorta Connection Pull and Leak Testing with Panduit Cable Tie Tool	Cable Tie Tool
Pressure Transducer Accuracy Verification	HPM 1.5
Maquet Oxygenator Performance Testing	Maquet Oxygenator
Stress Testing of Maquet Oxygenator with Reinforced Connectors	Maquet Oxygenator with TransMedics Oxy Connector Covers
Tensile Strength of HPM Tubing Connections	HPM 1.4
SDS Cassette Life Testing	SDS Cassettes

The main differences between the device versions identified in the testing in Table D.6 and the device versions that are subject of this PMA include:

- Heart Console 1.5 utilized the Cardinal Health MedSystem III pump, whereas the **Heart Console 1.6** (subject of this PMA) utilizes the Solution Delivery Subsystem (SDS) developed by TransMedics.

- Heart Perfusion Module 1.5 utilized the Novalung Oxygenator and had a flow switch in the perfusion circuit to direct flow either to the aorta or to the left ventricle. **HPM 1.4** uses the Maquet Quadrox-i Small Adult Oxygenator and removes the flow switch and tubing path to the left ventricle.

- **The OCS Heart System**, OCS Lung System, and OCS Liver System are similar in their fundamental design concepts and share some identical components or assemblies

between the systems. As such, when a different system's testing was used in support of the OCS – Heart System, the sponsor provided appropriate justification for the applicability of this testing.

A list of a majority of the design changes made to the OCS – Heart System over the course of the EXPAND clinical study that required additional validation/verification testing include:

Table D.9 Device/Design Changes made to OCS Heart System during G140111

G140111 Supplement	Design Changes	FDA Action and Date
S002 – 30-day supplement	• Replacement of Carefusion Pump with TransMedics Solution Delivery Set • Software upgrade to 3.3.0-C	Approval (b)(4)
S004 – 5-day notice	• Addition of new RoHS-compliant Printed Circuit Board (PCB) • Replacement of Connectors in the Heart Perfusion Module • Addition of New Pressure Transducer and Cable Assembly • Replacement of One-Way Valve Prior to Aortic Compliance Chamber • Re-routing of Vent Line of Oxygenator • Replacement of Stopcock at Aortic Access Port • Replacement of Bag Spike in Solution Delivery Cassette	Acknowledge (b)(4)
S005	Software upgrade from Version 3.3.0-C to Version 3.3.1-C	Acknowledge (b)(4)
S009	Software upgrade from Version 3.3.1-C to Version 3.3.2-C – fix bugs associated with AOP control.	Approval (b)(4)
S012	• Replacement of Bluetooth Module • Addition of a panel to wireless monitor to allow for battery replacement • Replacement of Flow Meter Board	Acknowledge (b)(4)
S013	• Removal of Aortic Compliance Chamber • Removal of One-way valve and associated tubing, couplers, fasteners	Approval (b)(4)
S014	Software upgrade from Version 3.3.2-C to Version 3.3.3-C – increases upper limit of AOP from 80mmHg to 100mmHg.	Acknowledge (b)(4)
S017	• Replacement of gas regulator • Replacement of IV spike and cap • Addition of ferrite bead in wireless monitor to reduce radiated emissions • Replacement speaker for wireless monitor	Acknowledge (b)(4)
S019	New version of the cable tie tool	Acknowledge (b)(4)

S021	Change in main control spring of the gas cylinder regulator	Acknowledge (b)(4)
S022	Replace PCB capacitor	Acknowledge (b)(4)
S025	• New One-Way Valve in SDS Cassette to replace old obsolete valve • New Supplier of LCD Backlight Inverter Cable • New Supplier of 2 GB SD Cards • Extended Aeration Time of ETO Sterilization	Acknowledge (b)(4)
S030	• Software upgrade from Version 3.3.3-C to Version 3.3.5-C • Update to OCS Battery PCB	Acknowledge (b)(4)
S032*	• Software upgrade from Version 3.3.5-C to Version 3.3.6-C – *including aircraft immunity mitigations, and revisions to the pump head mechanical stop.* • Material change for Large Ball Valve • Addition of a trace to the PCB	Approval (b)(4)

** NOTE: S032 was also provided within (b)(4), and therefore is part of the OCS – Heart System under consideration for approval under (b)(4)*

Overall, the testing performed and results of the testing on the OCS – Heart System was determined to sufficiently represent the OCS – Heart System used in the EXPAND Clinical Trial and the version intended for marketing, i.e., **OCS – Heart Console Version 1.6, OCS - Heart Perfusion Module Version 1.4.** As mentioned in the Software Section above, the remaining cybersecurity issues are presently being addressed (b)(4)).

VII. In Vivo

FDA reviewed several other small non-GLP animal studies for the OCS Heart System under (b)(4) and G140111. FDA does not believe that these previous animal studies are applicable to the current OCS Heart System design/function, and they were not designed to address fundamental safety/effectiveness questions

Table D.10 Previous Non-GLP Animal Studies

Study Title	***Animal Study VV0310, Appendix 12.2***	***Animal Study VV0431, Appendix 12.3***	***Animal Study VV0445, Appendix 12.4***	***OCS Heart with SDS and HPM with Integrated Cooling VV0691***
Submission	(b)(4)	(b)(4)	(b)(4)	*G140111/S013*
Date	*April 2010*	*June 2012*	*June 2012*	*February 2016*
Device Version	*OCSHC v.1.5* *Sync* *HPS Rev 1.4* *HSS Rev 1.5* *SW 2.0.1*	*OCSHC v.1.0* *No Sync* *HPS Rev 1.5* *HSS Rev 1.5* *SW 2.0.1-C*	*OCSHC v.1.0* *No Sync* *HPS Rev 1.5* *HSS Rev 1.5* *SW 112.2.8*	*OCSHC v.P1.6* *Sync OFF* *HPS Rev 1.4* *HSS Rev 1.5* *SW 3.3.2-C*

Objectives	*V/V OCS meets intended use operating from SW 2.0.1 with ECG sync.*	*V/V OCS preservation conditions and aortic cannulation method integrity during transport*	*V/V OCS preservation conditions and aortic cannulation method integrity during transport*	*To generate a metabolic and hemolysis profile and software trend session files*
Sample Size	*N=3 pig hearts*	*N=2 pig hearts*	*N=2 pig hearts*	*N=2 pig hearts*
Duration	*≥6 hours*	*About 8 hours*	*About 6-7 hours*	*≥6 hours*
Procedures	*Hearts connected to system, beating, perfused, Synchronized for "most" of session. ≥30 minutes car travel.*	*Hearts connected to the largest aortic cannula (1.25 inches) via cable tie (worst case pressure). Hearts beating, perfused. Subjected to IEC 60068-2-64, IEC 60068-2-27, and MIL-STD-810G shock/vibration testing.*	*Hearts remained securely attached to the aortic cannula without visible tissue damage or leaks during use and transport conditions. New metal cable tie evaluated.*	*Resting mode entire study. Hearts supported on subject device without sync function.*
Evaluations	*Pressures Flows Blood gases electrolytes*	*Attachments secure at aortic cannula without visible tissue injury or leaks.*	*Attachments secure at aortic cannula without visible tissue injury or leaks.*	*Pressures Flows Blood gases electrolytes*
Overall Results	*Perfusion maintained within specs**	*All acceptance criteria met.*	*All acceptance criteria met*	*Plasma free hb ≤ 81 mg/dl. Metabolic trend was stable. SvO2/HCT probe compatible with OCS. Subject device meets intended use.*
Ph Trend (V+A)	*7.39-7.57. no trend*	*N/A*	*N/A*	*N/A*
Lactate ranges (V+A) mmol/L	*0.2-2.7, generally decreasing*	*N/A*	*N/A*	*0.3-1.4*
Hematocrit (V+A)	*22-27*	*N/A*	*N/A*	*21-27*
Mean AOP	*23-66*	*5-89*	*10-84*	*min-max 44-67*
Heart Weight	*N/A*	*N/A*	*N/A*	*H1.02.17.16 / Pre 401 g / Post 485.48 g / +84.48 g* *H1.02.18 16 / Pre 326g / Post 388.12g / +61.52 g*
Conclusions	*OCS ability to maintain parameters during preservation. SW 2.0.1 met intended use.*	*The attachment method to secure the cannula to the aorta was acceptable in transit.*	*The attachment method to secure the cannula to the aorta was acceptable in transit.*	*Acceptance criteria were met, and subject device performs as intended.*
FDA Consultant Comments	***Possibly obsolete device version including SW.***	*Possibly obsolete device version. Small sample size precludes predictable clinical data.*	*Possibly obsolete device version. Small sample size precludes predictable clinical data.*	*Possibly obsolete device version; device version unclear. Sync not evaluated.*

	Small sample size precludes predictable clinical data.	***AOP range is large and does not fall within specifications.***	***AOP range is large and does not fall within specifications.***	*Small sample size and study design of limited relevance to clinical use.* ***Cardiac weight increases of 21% and 19% raise concerns for potentially clinically significant cardiac edema.***

Appendix 15.7

Pathology Reports for Turned Down Hearts

Pathology Report – Turned Down Heart

Subject (b) (6) **:**

- Heart 1
- Heart 2

(b) (6) [redacted]

July 14, 2009

Re: Pathology reports from recent turned-down hearts

Donor Heart
Date: 3/30/2009
Path No: (b) (6) [redacted]

Gross evaluation: The heart is received in 10% formalin along with a pathology report and twelve (12) microscopic slides, already dissected by (b) (6) [redacted] By report, the fresh heart weight was 260gm. The heart shows evidence of instrumentation on the OCS. There is a small (3mm) patent foramen ovale. The heart is otherwise grossly unremarkable, with minimal hypertrophy, chamber dilation or atherosclerotic coronary artery disease. Additional microscopic sections were taken from the ventricles, atria, pulmonary artery, aorta and coronary arteries.

Microscopic evaluation: The sections show significant ischemic changes in the left ventricle, right ventricle and interventricular septum. There are several areas of microinfarction (Figures 1-3) in the sampled tissue, consisting of myocytes with coagulation necrosis including the presence of contraction bands. The myocyte nuclei have been lost and there is an early neutrophilic infiltrate in these areas. In addition, there is necrosis of individual myocytes (Figure 4) diffusely throughout the myocardium, also with an early neutrophilic infiltrate. There is no evidence of granulation tissue, fibrosis, myocarditis, iron deposition, amyloidosis, or storage disease.

Comment: The presence of coagulation necrosis with loss of nuclei and early neutrophilic infiltrates demonstrates that the ischemic injury occurred at least 12-24 hours prior to harvesting the heart. The diffuse nature and pattern of the ischemic injury seen here is often reported in association with several clinical conditions including closed head injuries or intracranial hemorrhage, extensive use of inotropes and pressor agents to maintain blood pressure, cocaine use and pheochromocytoma. The physiology that is common to these conditions involves increased sympathetic tone that can lead to vasospasm in the setting of increased myocardial demand, resulting in microinfarcts and single myocyte necrosis. In summary, the damage seen here pre-dates the reported time on the OCS system. Clinical correlation is needed.

(b) (6) [redacted]

Donor Heart
Date: 4/3/2009
Path No: (b) (6) [redacted]

Gross evaluation: The heart is received in 10% formalin along with a pathology report and eleven (11) microscopic slides, already dissected by (b) (6) [redacted] By report, the fresh heart weight was 559gm (normal range 270-360gm). The heart shows evidence of instrumentation on the OCS. There is a probe patent foramen ovale. The right atrium, tricuspid valve, right ventricle, pulmonic valve and pulmonary artery are unremarkable. The left atrium is mildly dilated and the mitral valve shows mild fibrosis and focal calcification around the annulus. The left ventricle demonstrates moderate hypertrophy and mild dilation. The thickness of the interventricular septum at the midpoint between base and apex is 1.8cm. The thickness of the left ventricular posterior free wall (exclusive of papillary muscle thickness) is 1.6cm. The thickness of the right ventricle is 0.7cm. The hypertrophy appears symmetric. Within the left ventricular myocardium and interventricular septum, there are several small (6-7mm) areas of hemorrhagic myocardium. These areas are in the territory of the left main coronary artery; none are seen in the right coronary distribution. The aortic valve is tricuspid and unremarkable. The left main coronary ostium originates from the aorta quite posteriorly, very close to the commissure between the left and noncoronary cusps (Figures 1-3). As a result, there is an acute angle take-off of this coronary artery from the aorta. There is minimal gross coronary artery disease and no evidence of thrombosis or fixed obstruction. Additional microscopic sections were taken from the ventricles, atria, pulmonary artery, aorta and coronary arteries.

Microscopic evaluation: The sections show ischemic changes in the left ventricle, right ventricle and interventricular septum. The sections of the grossly identified areas of hemorrhage show evidence of ischemia-reperfusion injury, with contraction band necrosis and interstitial hemorrhage (Figure 4). There are occasional areas of microinfarction in the remainder of the sampled tissue, consisting of myocytes with hypereosinophilia, wavy fibers, and occasional contraction bands without cellular infiltrate or loss of myocyte nuclei (Figure 5). The background myocardium shows moderate myocyte hypertrophy, mild interstitial fibrosis and mild edema. The coronary arteries show 15-20% stenosis by intimal proliferative lesions representing early atherosclerosis. There is no evidence of inflammation, granulation tissue, replacement fibrosis, myocarditis, iron deposition, amyloidosis, or storage disease. There is no myocyte disarray.

Comment: The ischemic injury seen in this heart likely occurred on the OCS device run. The etiology of the injury most likely relates to the chronic ventricular hypertrophy resulting in increased muscle mass, in combination with the acute angle take-off of the left main coronary artery. The hypertrophy and fibrosis are chronic pathologies that occurred in the donor prior to implementation on OCS. The etiology of the hypertrophy is unknown; there is no evidence of aortic stenosis, and the absence of myocyte disarray and asymmetric hypertrophy make hypertrophic cardiomyopathy less likely, although not formally ruling out this diagnosis. Regardless of the etiology, the degree of hypertrophy (independent of the coronary anatomy)

may have been a concern had this heart been transplanted. The ischemia-reperfusion injury is in the distribution of the left main coronary artery and may be related to the acute angle take-off. Clinical correlation is needed.

Respectfully submitted,

(b) (6)

Pathology Report – Turned Down Heart

Subject (b) (6)

(b) (6)

November 4, 2013

(b) (6)

Summary:
Fusion of the left and right coronary cusps of the aortic valve, subendocardial acute ischemia

Gross evaluation:
The specimen was received in formalin, labeled with the UCLA surgical pathology number (b) (6) and the UNOS identification number (b) (6). The specimen consisted of a heart that had been partially dissected, a portion of aorta attached to a plastic cannula, a separate portion of aorta and two plastic cannulae.

The fixed heart weight, absent the cannulae and separate portions of aorta, was 375gm. By report, the weight of the entire fresh specimen, inclusive of cannulae, was 433gm. The inferior vena cava and superior vena cava were ligated and there was a retention suture in the right atrial appendage. A ligature was present in the pulmonary artery. There was epicardial hemorrhage in the posterior left atrium, posterior right ventricle and the anterior right ventricular outflow tract; in no case did this involve the myocardium.

Right atrium: The inferior vena cava, superior vena cava and coronary sinus entered the right atrium in the standard fashion. The fossa ovalis was closed. There was no clot in the right atrial appendage. The right atrial myocardium was grossly unremarkable.

Tricuspid valve: The tricuspid valve was structurally normal. There was a focus of endocardial hemorrhage (5mm) at the annulus of the posterior leaflet of the tricuspid valve; this may be secondary to prior placement of a central catheter. The valve was otherwise unremarkable.

Right ventricle: The right ventricular wall had the usual configuration. The wall thickness was 0.4cm. There was no evidence of dilation or hypertrophy. The myocardium was grossly unremarkable.

Pulmonic valve: The pulmonic valve was structurally normal and grossly unremarkable.

Pulmonary artery: The attached segment of pulmonary artery was unremarkable save for the procedural ligation.

Left atrium: The left atrium had been previously opened. The pulmonary veins entered the left atrium in the usual configuration. There was a 4mm mural thrombus at the fossa ovalis. There was no thrombus in the left atrial appendage. The left atrium was otherwise unremarkable.

Mitral valve: The mitral valve had been previously opened. The mitral valve was structurally normal. There were two cuspal hematomas (0.2 cm and 0.3 cm) on the posterior leaflet of the mitral valve. The valve was otherwise unremarkable.

Left ventricle: The left ventricle had been previously opened. The posterior wall thickness was 1.1 cm at the mid-ventricle. The lateral wall thickness was 1.3 cm at the mid-ventricle. The anterior wall thickness was 1.3 cm at the mid-ventricle. There was mild left ventricular hypertrophy with no significant dilation. There was a focal area of hemorrhage (0.9 x 0.9 x 0.8 cm) in the lateral left ventricular wall, deep within the myocardium. The myocardium of the anterior, posterior and lateral walls of the left ventricle was otherwise grossly unremarkable.

Interventricular septum: The interventricular septum thickness as 1.5 cm at the mid-ventricle. There was subendocardial discoloration and mottling of the myocardium from the apex to the mid-ventricle measuring a maximum of 2.0 cm (circumferentially) x 0.5 cm (thickness from left ventricular endocardium) suspicious for edema vs. ischemia.

Aortic valve: The aortic valve had been previously opened. There was fusion of the left and right coronary cusps at the commissure over a distance of 0.8 cm. There was fusion of the right and non-coronary cusp over a distance of 0.1 cm. While not perfectly "textbook", the fusion appears to be congenital rather than acquired. There is no evidence of healed endocarditis, calcification or thrombosis. The left and right coronary cusps are mildly thickened near the free edges. The right coronary cusp contains small (less than 0.1 cm) fenestrations near the free edge. The noncoronary cusp is unremarkable save for a small (0.2 cm) cuspal hematoma. The cusps can fully coapt, and there is no evidence of functional regurgitation in the form of endocardial fibrosis or a "jet lesion" in the left ventricular chamber; the left ventricular chamber also does not show signs of dilation.

Aorta: The segments of aorta are grossly unremarkable. There is no evidence of aneurysm, dissection or atherosclerosis.

Coronary arteries: The coronary ostia are widely patent. The epicardial coronary arteries follow the usual course in a right dominant fashion. There is no evidence of atherosclerosis or thrombosis. There is no myocardial bridging or other anomalies.

Microscopic evaluation:

Microscopic slide key:

1: Posterior left ventricle
2: Lateral left ventricle
3: Anterior left ventricle
4: Interventricular septum
5: Right ventricle and interventricular septum

6: Left ventricle
7: Interventricular septum
8: Right ventricle and interventricular septum
9: Left coronary arteries
10: Right coronary arteries
11: Aorta
12: Left atrium, right atrium, pulmonary artery
13: Interventricular septum
14: Interventricular septum
15: Left ventricle
16: Aortic valve, right coronary cusp
17: Aortic valve, left-right commissure and left-noncoronary commissure

Microscopic description:
Myocardium: The sections of the left ventricular, right ventricular, interventricular septal and right atrial myocardium show occasional foci of subendocardial myocyte ischemia manifest as hypereosinophilia and contraction band necrosis. Additionally, there is focal epicardial hypereosinophilia and contraction band necrosis. There is no evidence of inflammation or host tissue reaction in any of these areas. There is focal hemorrhage in the areas identified grossly. The background myocardium shows chronic changes of mild myocyte hypertrophy, subendocardial myocyte vacuolization and occasional thick-walled intramyocardial arterioles. There is no significant interstitial fibrosis.

Coronary arteries: The sections of the coronary arteries show minimal intimal thickening and no stenosis, thrombosis or other pathologies.

Aortic valve: The sections of aortic valve at the left-right commissure show a single valve cusp joining the aortic wall, most consistent with a congenitally bicuspid valve. There is focal fibrous thickening of the fibrosa near the free edge of the right coronary cusp without destruction of the underlying architecture, inflammation or neovascularization. There is no evidence of healed endocarditis.

Aorta: The sections of the aorta show mild medial degeneration with focal increased accumulation of amorphous basophilic material between smooth muscle cell layers.

Discussion:
The predominant pathology involves the fusion of the left and right coronary cusps of the aortic valve. This has the appearance of a congenital anomaly rather than an acquired lesion. In addition, there is mild medial degeneration of the ascending aorta; while non-specific, this is often seen in patients with congenitally bicuspid aortic valves and can progress to aneurysmal dilation, although it did not appear to do so in this case. Physical exam findings during life and evaluation of any available pre-mortem echocardiograms would be the most helpful in evaluating the effect of this pathology on aortic valve function. In any event, it is likely that the aortic regurgitation on OCS was the result of an inability of this structurally abnormal valve to

adequately close over the aortic cannula. The resultant low coronary artery pressure and flow likely resulted in the early subendocardial ischemia observed microscopically.

Annotated gross and microscopic images are attached in a PowerPoint file.

Respectfully submitted,

(b) (6)

Pathology Report – Turned Down Heart

Subject (b) (6)

(b) (6) [redacted]

May 14, 2013

PROCEED II STUDY, SITE #009, (b) (6) [redacted]

Summary: Findings consistent with likely congenital connective tissue disease

Gross examination:
The specimen is received in one part, in formalin, and labeled (b) (6) [redacted] Proceed-II, Site #009, Date (b) (6) [redacted]. The specimen consists of a 360gm heart with has been incised with a single transverse section. There is scant epicardial hemorrhage. The superior and inferior vena cavae are sutured closed. The right atrium shows focal endocardial hemorrhage consistent with cannulation. The foramen ovale is closed. The tricuspid valve shows mild myxomatous degeneration with thickening and billowing. The right ventricle is within normal limits. The pulmonic valve is within normal limits. The main pulmonary artery is gathered by a blue purse-string type suture. The wall of the pulmonary artery is thin, especially in the proximal portion of the vessel, but is without evidence of dissection. The left atrium is unremarkable. The mitral valve shows moderate myxomatous degeneration with thickening and billowing. The left ventricle is mildly dilated and shows mild hypertrophy. Small areas of hemorrhage are present; otherwise there are no focal lesions in the left ventricular myocardium. The aortic valve shows mild myxomatous degeneration. The ascending aorta contains 4 pledgets near the cut edge. The aortic wall is thinned and contains focal fatty streaks, but is without evidence of dissection. Proximal to the pledgets, there is a transverse tear in the wall measuring 1.1 cm in length in the aortopulmonary window aspect of the aorta, likely secondary to attempted instrumentation on the OCS device. The diameter of the aorta at the cut edge is 2.0 cm; the wall thickness here is 1.5 mm. There is mild epiaortic hemorrhage. At the mid-ventricular level, the anterior wall of the left ventricle measures 2.0 cm, the lateral wall (exclusive of the papillary muscle) measures 1.9 cm, the posterior wall measures 2.1 cm, the interventricular septum measures 2.0 cm and the right ventricular free wall measures 0.5 cm. The coronary ostia arise normally from the sinuses of Valsalva of the right and left coronary cusps. The coronary arteries show only minimal atherosclerosis with no stenosis, thrombosis or acute plaque change. Microscopic sections are submitted as follows:

Micro 1:	Anterior left ventricle
Micro 2:	Lateral left ventricle
Micro 3:	Posterior left ventricle
Micro 4:	Interventricular septum
Micro 5:	Right ventricle
Micro 6:	Left ventricle
Micro 7:	Interventricular septum
Micro 8:	Right ventricle

Micro 9: Left coronary artery system
Micro 10: Right coronary artery system
Micro 11: Mitral valve
Micro 12: Aortic valve
Micro 13: Aorta
Micro 14: Pulmonary artery
Micro 15: Left atrium
Micro 16: Right atrium

Microscopic description:
The sections of aorta show areas of thinning and disorganization of the components of the media. There is loss of normal elastic lamination predominantly in the most thinned areas of the aorta, best seen on the elastic tissue stain. There is medial degeneration of the diffuse type, with smooth muscle cell dropout and accumulation of basophilic extracellular material between individual smooth muscle cells. There is focal atherosclerosis. There is no evidence of vasculitis, infection or dissection. The sections of pulmonary artery also show areas of thinning with pronounced disorganization of the components of the media. The sections of aortic valve and mitral valve show myxomatous degeneration. The sections of coronary artery show focal mild atherosclerosis with no significant stenosis, acute plaque change or thrombosis. The sections of myocardium show minimal acute or chronic pathology. There is mild edema, focal myocyte vacuolization, rare contraction bands and focal hemorrhage. There is mild myocyte hypertrophy with no significant interstitial fibrosis. There is no evidence of acute or remote myocardial infarction, vasculitis or infiltrative processes. There is no evidence of iron deposition, granulomatous disease, viral cytopathic changes or amyloidosis.

Interpretation and correlation:
By report, the aorta was extraordinarily fragile when an attempt was made to instrument the heart on the OCS device. The predominant pathology of the great vessels was diffuse medial degeneration with disorganization of the elastic fibers within the media. In addition, there was myxomatous degeneration of the mitral, tricuspid and, to a lesser extent, the aortic valve. The remainder of the pathologic examination was unremarkable, save for mild hypertrophy. The constellation of clinical and pathologic findings suggests a connective tissue abnormality, likely congenital. From the findings herein, the differential diagnosis includes Ehlers-Danlos disease and Lowes-Deitz syndrome, among others. Additional donor history may be useful in further defining the precise diagnosis. Clinical correlation is needed.

Annotated gross and microscopic images are attached in a PowerPoint file.

Respectfully submitted,

(b) (6)

Pathology Report – Turned Down Heart

Subject (b) (6)

(b) (6)

November 16, 2012

PROCEED II STUDY, SITE 11, SUBJECT (b) (6)

Gross examination:
The specimen is received in formalin in a container labeled "PROCEED II STUDY, Site #11, SUBJ (b) (6) . The specimen consists of a 340gm heart. A cannula spans the left atrium and mitral valve and terminates in the left ventricle. Cannulae are also in place in the aorta and pulmonary artery. The epicardial surface shows multiple petechiae diffusely; these do not involve the myocardium. The right atrium is within normal limits. The tricuspid valve has a small surface abrasion that is likely secondary to a central or pulmonary artery line. The right ventricle is mildly dilated and has a wall thickness of 0.4 cm (normal 0.25-0.3 cm). The pulmonic valve and pulmonary artery are normal. The left atrium and mitral valve are within normal limits. The left ventricular free wall thickness at the mid-ventricular level is 1.4 cm (normal 0.9-1.4 cm) and the interventricular septal thickness is also 1.4cm. The left ventricular chamber size is within normal limits. The myocardium of the left ventricle and interventricular septum contains multiple areas of hemorrhage ranging in size up to 0.8 x 0.4 x 0.4 cm. This focus is in the posterolateral left ventricle. The myocardium is otherwise tan-brown and without fibrosis. The aortic valve and ascending aorta are normal. The coronary arteries arise from the aorta in a normal configuration. There is no gross evidence of atherosclerosis, no thrombi and no myocardial bridging of the coronary arteries. Microscopic sections are submitted as follows:

Micro 1:	Posterior left ventricle with hemorrhage
Micro 2:	Posterior left ventricle with hemorrhage
Micro 3:	Anterior interventricular septum-right ventricle junction
Micro 4:	Anterior left ventricle
Micro 5:	Interventricular septum
Micro 6:	Lateral left ventricle
Micro 7:	Anterior right ventricle
Micro 8:	Lateral left ventricle
Micro 9:	Anterior left ventricle
Micro 10:	Posterior right ventricle
Micro 11:	Anterior left ventricle
Micro 12:	Lateral left ventricle
Micro 13:	Posterior left ventricle
Micro 14:	Posterior interventricular septum
Micro 15:	Anterior interventricular septum including left anterior descending
Micro 16:	Posterior left ventricle
Micro 17:	Lateral left ventricle

Micro 18: Interventricular septum
Micro 19: Anterior left ventricle
Micro 20: Lateral left ventricle and papillary muscles
Micro 21: Posterior left ventricle
Micro 22: Interventricular septum
Micro 23: Right ventricle
Micro 24: Right ventricle
Micro 25: Interventricular septum
Micro 26: Right ventricle
Micro 27: Right ventricle
Micro 28: Coronary arteries

Microscopic description:
The sections show multiple microscopic areas containing hemorrhage and myocardial contraction bands. There are additional microscopic areas that show only interstitial hemorrhage with adjacent viable myocytes with no specific pathologic change, and some microscopic areas that show contraction band necrosis without associated hemorrhage. Occasional foci of myocardial damage involving small clusters of myocytes are accompanied by inflammatory cells. There is diffuse mild edema. There is no evidence of granulation tissue or fibrosis. No microscopic emboli of thrombus or foreign material are seen. The underlying myocardium shows mild hypertrophy and no significant interstitial fibrosis. A single focus of incidental borderline myocarditis is present. The sections of coronary artery show no significant atherosclerosis or other pathology.

Interpretation and correlation:
The predominant pathologies in the heart were hemorrhage and necrosis; these were present in a patchy distribution predominantly in the left ventricle and interventricular septum, and were seen grossly. There were areas of hemorrhage without necrosis, and areas of necrosis without hemorrhage. Because there was no significant inflammation associated with these areas, these likely would have originated in the hours before procurement or on the OCS device. These areas are the likely source of the increasing lactate levels on the OCS device. In addition, there was evidence of necrosis of single myocytes or small groups of myocytes with an early inflammatory infiltrate. These likely originated from the time of the reported motor vehicle accident, code in the emergency department and subsequent resuscitation. This also correlates with the donor history of down time of 20 minutes and additional 20 minutes of CPR. Because these areas were very small overall compared to the areas of hemorrhage and acute necrosis, they likely did not contribute much to the rising lactate level. However, they do serve as evidence of some degree of myocardial damage around the time of the motor vehicle accident. The etiology of the areas of hemorrhage and necrosis are not apparent from the gross and microscopic assessment of the heart. It is possible, given the pre-existing injury, that the areas of hemorrhage and necrosis may represent a type of reperfusion injury on the OCS.

Respectfully submitted,

(b) (6)

OCS Heart EXPAND Trial Clinical Study Report

Appendix 5

Pathology Reports

(b) (6)

January 11, 2016

#03-(b)

UNOS (b) (6) (b) (6)

The specimen is received in formalin, labeled "Site #03, (b) (6) " and consists of a heart that has been transected transversely at the mid-ventricle.

Gross findings:

The fixed heart weight is 390 grams. There is moderate hemorrhage around the aorta and mild hemorrhage around the pulmonary artery. There is epicardial hemorrhage around the closure sites including the inferior vena cava, pulmonary veins and left atrial appendage. There is mild patchy epicardial hemorrhage over the ventricles, predominantly over the right ventricle.

Opening the heart reveals an unremarkable right atrium save for the epicardial hemorrhage in the areas of the inferior and superior vena cavae. The tricuspid valve is normally formed and without any lesions. The right ventricle shows mild hypertrophy (wall thickness 5 mm). The pulmonic valve is unremarkable. The left atrium is unremarkable save for the epicardial hemorrhage in the areas of the pulmonary veins. The mitral valve is normally formed and without any lesions. The left ventricle shows mild hypertrophy (wall thickness 16 mm), as does the interventricular septum (wall thickness 15 mm). The aortic valve is unremarkable. There is endocardial hemorrhage in the left ventricular outflow tract.

The myocardium of the right ventricle, interventricular septum and left ventricle shows multifocal hemorrhage. The largest intramyocardial hemorrhage is in the posterior right ventricle measuring 10 mm in greatest dimension. There are scattered intramyocardial hemorrhages in the septum and left ventricle measuring up to 5 mm. The anterior papillary muscle shows patchy discoloration without hemorrhage. There is an area with similar appearance in the subendocardium of the anterior left ventricular wall. There is no evidence of fibrosis or infiltrative disease.

The coronary arteries show patchy mild atherosclerosis without any stenosis. There is no evidence of thrombosis, plaque hemorrhage or erosion.

Microscopic findings:

The sections of the papillary muscle and anterior left ventricle show subendocardial infarctions that pre-date the time on OCS. There is hypereosinophilia, complete loss of nuclei and focal inflammation. This correlates with the areas of patchy discoloration seen grossly. These likely represent the sequelae of the downtime reported in the donor at the onset of death, which was about 3.5 days before heart retrieval.

The sections of the hemorrhagic areas identified grossly show intramyocardial hemorrhage without a clear underlying cause. The cardiac myocytes in these areas are viable with no evidence of hypereosinophilia or contraction bands. The areas that grossly demonstrate epicardial and adventitial hemorrhage show recent hemorrhage microscopically with no identifiable underlying pathology.

The background myocardium shows mild myocyte hypertrophy with no significant interstitial fibrosis or vascular changes. There is no myocarditis, iron deposition or infiltrative process.

Discussion:

The papillary muscle and anterior left ventricle showed a healing infarct that correlates with the arrest and downtime approximately 3.5 days prior to donor heart retrieval. The dead cardiac myocytes at this timeline should show dense hypereosinophilia, intracellular coagulative changes and loss of nuclei. The inflammatory infiltrate should be an early mononuclear cell one with some neutrophilic karyorrhectic debris. These are indeed the pathologic changes that were found in this donor heart.

There is nothing specific within the gross or microscopic evaluation of the heart that would prove that the initial arrest was secondary to drug use. However, there is no evidence of another clear cause of the arrest. Specifically, there was only mild myocyte hypertrophy and no significant interstitial fibrosis, no intramyocardial vascular changes, no remote myocardial infarction, no myocarditis, no infiltrative process or deposition disease, no congenital structural heart disease, no evidence of a genetic cardiomyopathy and no significant coronary artery disease. In cases with these findings when there is a reported history of drug use, this etiology must be considered a possibility as the cause of the arrest.

(b) (6)

June 23, 2017

#03-(b)

UNOS (b) (6) ; Site #03, (b) (6))
The specimen is received in formalin, labeled "Site #03, (b) (6) and consists of a heart that has been transected transversely at the mid-ventricle.

Gross findings:
The fixed heart weight is 300 grams. There is mild hemorrhage around the aorta and pulmonary artery. There is mild epicardial hemorrhage around the closure sites including the inferior vena cava, pulmonary veins and left atrial appendage. There is mild patchy epicardial hemorrhage over the ventricles, predominantly over the lateral left ventricle.

Opening the heart reveals an unremarkable right atrium save for the epicardial hemorrhage in the areas of the inferior and superior vena cavae. The tricuspid valve is normally formed and without any lesions. The right ventricle has a wall thickness of 4 mm with moderate dilation. The pulmonic valve is unremarkable. The left atrium is unremarkable save for the epicardial hemorrhage in the areas of the pulmonary veins. The mitral valve is normally formed and without any lesions. The left ventricle has a wall thickness of 12 mm at the anterior wall and 14 mm at the posterior wall. The thickness of the interventricular septum is 14 mm. The aortic valve is unremarkable. There is endocardial hemorrhage in the left ventricular outflow tract.

There is an area of discoloration in the anterolateral left ventricle measuring 1.0 x 0.8 x 0.6 cm suspicious for hemorrhage. There are occasional punctate areas of hemorrhage (0.1-0.2 cm) in the myocardium of the right ventricle, interventricular septum and left ventricle. The remainder of the myocardium is tan-brown, uniform and unremarkable. There is no evidence of fibrosis or infiltrative disease.

The coronary arteries show minimal atherosclerosis without any stenosis in this right-dominant system. There is no evidence of thrombosis, plaque hemorrhage or erosion.

Microscopic slide key:
1. Anterior left ventricle
2-4. Anterolateral area of discoloration
5. Lateral left ventricle
6. Posterior left ventricle
7. Posterior interventricular septum

8. Anterior interventricular septum
9. Anterior right ventricle
10. Posterior right ventricle
11. Left and right coronary arteries
12. Left atrium, aorta
13. Right atrium, pulmonary artery
14. Interventricular septum, papillary muscle

Microscopic description:

The sections of the anterolateral left ventricle show subendocardial infarction with evidence of reperfusion and hemorrhage. The myocytes are hypereosinophilic with contraction bands, focal loss of nuclei and no significant inflammation. This correlates with the area of discoloration seen grossly. The remainder of the sections of ventricular myocardium show occasional acute microinfarcts with hypereosinophilia, contraction bands, edema and hemorrhage secondary to reperfusion, and other similar-sized areas with hemorrhage in the absence of ischemic myocyte changes. This correlates with the smaller areas of discoloration seen grossly throughout the myocardium. There is no evidence of fibrosis or vascular changes. There is no myocarditis, iron deposition or infiltrative process. The sections of the right and left atria, pulmonary artery and aorta are unremarkable save for the epicardial hemorrhage with no identifiable underlying pathology. The sections of the coronary arteries only show minimal intimal proliferation.

Discussion:

There was no evidence of chronic cardiovascular pathology, with a normal heart weight, no structural heart disease, no hypertrophy, no fibrosis and no coronary artery disease. There is no evidence of subacute/healing pathology which would correlate with the time of the presentation of unresponsiveness secondary to an intracranial hemorrhage; this correlates with the pre-harvest laboratory data showing no elevation of troponin I during the donor hospital course. The predominant histologic changes were those of patchy acute ischemia and hemorrhage without any inflammation, likely representing changes occurring in the immediate pre-harvest or peri-OCS time.

(b) (6)

08/05/2016

RE: Pathology Report from Turned Down Heart – Transmedics EXPAND Trial

UNOS ID: (b) (6)
Explant Date: (b) (6)
Barcode Number: (b) (6)

(b) (6)

GROSS EVALUATION:

Shape/Size Characteristics:

Overall Shape	Normal
Height	14.0 cm
Width	9.0 cm
Length	8.0 cm
Weight	304.93 g

Anatomical Evaluation:

Epicardial Surface	Petechiae

Right Atrium		***Left Atrium***	
Primary Findings	Normal	Primary Findings	Normal
Secondary Findings	Normal	Secondary Findings	
Interventricular Septal Thickness	1.3 cm		
Right Ventricle		***Left Ventricle***	
Thickness	1.4 cm	Thickness	1.2 cm
Primary Findings	Normal	Primary Findings	Normal
Secondary Findings		Secondary Findings	
		Posterior Wall Thickness	1.2 cm
Tricuspid Valve		***Mitral Valve***	
Circumference	12.0 cm	Circumference	8.5 cm
Primary Findings	Normal	Primary Findings	Normal
Secondary Findings	Normal	Secondary Findings	
Aortic Valve		***Pulmonic Valve***	
Circumference	5.3 cm	Circumference	6.0 cm
Primary Findings	Other, see comment	Primary Findings	Normal
Secondary Findings		Secondary Findings	

Coronary Circulation Findings:

Coronary Circulation Dominance	Right
Narrowing of Left Coronary Artery	30 %
Narrowing of Left Circumflex	30 %
Narrowing of Right Coronary Artery	30 %
Narrowing of Posterior Coronary Artery	30 %

MICROSCOPIC EVALUATION:

Sections through the patchy mottling noted grossly (see image #7) in anterior-lateral left ventricle shows large areas of patchy myofiber hypereosinophilia, contraction-band and early coagulative-type necrosis combined with focal interstitial edema and hemorrhage, which is seen throughout the entire thickness, but worse near the endocardium. Occasional ischemically-damaged myocytes are devoid of nuclei and rare neutrophilic infiltration is seen (image #21). Altogether, these findings are consistent with an acute myocardial ischemia and subsequent reperfusion. Grossly this area occupies >15% of the left ventricular circumference at the mid-portion of the left ventricles - classifiable as "moderately sized" infarct/ischemic insult (C. Basso et al. / Cardiovascular Pathology 19 (2010) 22-28).

Sections through the coronary arteries (e.g. image #16) shows bland fibro-intimal hyperplasia resulting in ~30% luminal narrowing. A rare focus of peri-adentitial fibrosis of a penetrating artery is also seen.

DIAGNOSIS:

DONOR HEART, CARDIECTOMY (305 GMS):
A. RIGHT-DOMINANT CORONARY ARTERY CIRCULATION WITH MILD CORONARY ARTERY FIBRO-INTIMAL HYPERPLASIA RESULTING IN ~30% LUMINAL NARROWING.
B. NEGATIVE FOR COMPLICATED/ULCERATED CORONARY ARTERY DISEASE AND THROMBOSIS.
C. PATCHY MID-PORTION, ANTERIOR-LATERAL LEFT VENTRICULAR ISCHEMIC INJURY WITH MYOFIBER HYPEREOSINOPHILIA, CONTRACTION BAND AND EARLY COAGULATIVE-TYPE NECROSIS WITH RARE NEUTROPHILIC INTERSTITIAL INFLAMMATION AND FOCAL HEMORRHAGE INVOLVING ~15% OF THE LEFT VENTRICULAR CIRCUMFERENCE (SEE COMMENT) - CONSISTENT WITH MODERATELY-SIZED ACUTE MYOCARDIAL INFARCT.
D. MILD AORTIC VALVE ATHEROSCLEROSIS CHANGES.

COMMENTS:

Overall, the heart is structurally normal with mild atherosclerotic coronary artery disease without any complicated plaques or coronary artery thrombosis. There is, however, definite evidence of recent ischemic injury involving primarily the subendocardial aspect of the mid-portion of the anterior-lateral left ventricle. The insult appears relatively recent: > than 12-18 hours and probably <48 hrs of time subjected to normothermic sanguinous circulation. This assertion is based on the presence of easily identifiable hypereosinophilia, contraction band necrosis, nuclear pyknosis, and early nuclear dissolution. However, the pacuity of neutrophils in lesional areas might be related to blood perfusate being leukocyte-poor, which would slightly UNDER-ESTIMATE the age

of infarct. The contraction bands occurs within minutes after reperfusion and interstitial hemorrhage associated with the areas of ischemic injury are indicative of sanguinous reperfusion after the initial ischemic insult. Similar changes might be seen with coronary occlusion/global ischemia, resuscitation attempts, catecholamine excess/aggresive inotrope use, intra-cranial hemorrhage, potassium or magnesium deficiency, electric shock, cobalt administration, and a wide variety of drugs (e.g. cocaine, polymyxin, neomycin, streptokinase, trypsin, and papain.

Case Completed: (b)(4)
Pathologist: (b) (6)

(b) (6)

10/13/2016

RE: Pathology Report from Turned Down Heart – Transmedics EXPAND Trial

UNOS ID: (b) (6) (b) (6)
Explant Date: (b) (6)
Barcode Number: (b) (6)

GROSS EVALUATION:

Shape/Size Characteristics:

Overall Shape	Normal
Height	6.0 cm
Width	10.5 cm
Length	14.5 cm
Weight	359.0 g

Anatomical Evaluation:

Epicardial Surface	Normal

Right Atrium

Primary Findings	Normal
Secondary Findings	
Interventricular Septal Thickness	1.3 cm

Left Atrium

Primary Findings	Normal
Secondary Findings	

Right Ventricle

Thickness	0.5 cm
Primary Findings	Normal
Secondary Findings	

Left Ventricle

Thickness	1.5 cm
Primary Findings	Myocardial Ischemic Injury / Paleness
Secondary Findings	Other, see comment
Posterior Wall Thickness	1.3 cm

Tricuspid Valve

Circumference	9.0 cm
Primary Findings	Normal
Secondary Findings	

Mitral Valve

Circumference	9.5 cm
Primary Findings	Normal
Secondary Findings	

Aortic Valve

Circumference	6.5 cm
Primary Findings	Normal
Secondary Findings	Other, see comment

Pulmonic Valve

Circumference	6.5 cm
Primary Findings	Normal
Secondary Findings	

Coronary Circulation Findings:

Coronary Circulation Dominance	Right
Narrowing of Left Coronary Artery	10 %
Narrowing of Left Circumflex	10 %
Narrowing of Right Coronary Artery	10 %
Narrowing of Posterior Coronary Artery	10 %

MICROSCOPIC EVALUATION:
Sections through the patchy mottling noted grossly (see image #8) involving the posterior left ventricle, but also the septum show large areas of patchy myofiber hypereosinophilia (images #9-14); edema and wavy fibers (images #15-17), and focal frank coagulative necrosis (images 19-22). The area of frank coagulative necrosis shows early loss of nuclei, but minimal to no neutrophilic infiltration is seen. Altogether, these findings are consistent with an acute myocardial ischemia and subsequent reperfusion.

DIAGNOSIS:
DONOR HEART, CARDIECTOMY (359 GMS):
A. RIGHT-DOMINANT CORONARY ARTERY CIRCULATION WITH MILD CORONARY ARTERY FIBRO-INTIMAL HYPERPLASIA RESULTING IN ~10% LUMINAL NARROWING.
B. NEGATIVE FOR COMPLICATED/ULCERATED CORONARY ARTERY DISEASE AND THROMBOSIS.
C. PATCHY LEFT POSTERIOR AND LATERAL VENTRICULAR AND INTERVENTRICULAR SEPTAL ISCHEMIC INJURY MANIFEST AS MYOFIBER HYPEREOSINOPHILIA; WAVY MYOFIBERS AND FOCAL INTERSTITIAL EDEMA; AND FOCAL FRANK COAGULATIVE-TYPE NECROSIS INVOLVING ~20% TISSUE SAMPLING FROM THE LEFT VENTRICLE (SEE COMMENT).

COMMENTS:
Overall, the heart is structurally normal with minimal atherosclerotic coronary artery disease without any complicated plaques or coronary artery thrombosis. There is, however, definite evidence of recent ischemic injury involving primarily the subendocardial aspect of the posterior and lateral left ventricle and interventricular septum. The insult is probably > 24 hours and <36 hrs before the time subjected to normothermic sanguinous circulation. This assertion is based on the presence of easily identifiable hypereosinophilia, frank coagulative necrosis and definite nuclear dissolution. However, the pacuity of neutrophils in lesional areas might be related to blood perfusate being leukocyte-poor, which would slightly UNDER-ESTIMATE the age of infarct.

The area of frank necrosis in images #19-22 was taken from a papillary muscle in the posterior left ventricle (see image # 8).

Left Ventricle comments: Circumferential Paleness, subendocardial hemorrhage below aortic valve

Aortic Valve comments: minimal atherosclerotic plaque

Extra specimens taken:
1) left anterior ventricular wall
2) left lateral ventricular wall
3) left posterior ventricular wall
4) hemorrhagic papillary muscle

Case Completed: (b)(4)
Pathologist: (b) (6)

(b) (6)

08/05/2016

RE: Pathology Report from Turned Down Heart – Transmedics EXPAND Trial

UNOS ID: (b) (6) (b) (6)
Explant Date: (b)
Barcode Number: (b) (6)

GROSS EVALUATION:

Shape/Size Characteristics:

Overall Shape	Normal
Height	12.8 cm
Width	11.0 cm
Length	11.0 cm
Weight	493.44 g

Anatomical Evaluation:

Epicardial Surface	Petechiae

Right Atrium

Primary Findings	Normal
Secondary Findings	N/A
Interventricular Septal Thickness	1.2 cm

Left Atrium

Primary Findings	Normal
Secondary Findings	

Right Ventricle

Thickness	0.5 cm
Primary Findings	Normal
Secondary Findings	

Left Ventricle

Thickness	1.4 cm
Primary Findings	Normal
Secondary Findings	Other, see comment
Posterior Wall Thickness	1.4 cm

Tricuspid Valve

Circumference	13.0 cm
Primary Findings	Normal
Secondary Findings	

Mitral Valve

Circumference	9.5 cm
Primary Findings	Normal
Secondary Findings	

Aortic Valve

Circumference	7.5 cm
Primary Findings	Normal
Secondary Findings	

Pulmonic Valve

Circumference	7.0 cm
Primary Findings	Normal
Secondary Findings	

Coronary Circulation Findings:

Coronary Circulation Dominance	Right
Narrowing of Left Coronary Artery	20 %
Narrowing of Left Circumflex	20 %
Narrowing of Right Coronary Artery	10 %
Narrowing of Posterior Coronary Artery	10 %

MICROSCOPIC EVALUATION:

Sections through the patchy mottling noted grossly (see images #3 and #4) involving the most of the left ventricular subendocardial circumference shows large areas of patchy myofiber hypereosinophilia, myofiber thinning, interstitial edema and pronounced contraction-band and early coagulative-type necrosis combined with focal interstitial hemorrhage. In areas, this process involves nearly the full thickness of the left ventricular and focally involves the septum. Occasional individual ischemically-damaged myocytes are also seen, along with rare myocytes devoid of nuclei.

Altogether, these findings are consistent with an acute myocardial ischemia with subsequent reperfusion. Grossly this area occupies >25% of the left ventricular circumference -predominantly subendocardial, but focally transmural and involving the interventricular septum

Sections through the coronary arteries (e.g. image #10) shows bland fibro-intimal hyperplasia resulting in generally <20% luminal narrowing. Mild patchy interstitial fibrosis is seen in the subvalvular sections of the left ventricular.

NOTE on Cassettes:
1) CoArtCSXS: Both the left circumflex and left coronary artery are in piece painted red. Blue is right coronary artery.

2)Myo Defect 1 -3: taken from anterior lateral left ventricle near the mid heart (see gross images).

DIAGNOSIS:

DONOR HEART, CARDIECTOMY (493 GMS):
A. RIGHT-DOMINANT CORONARY ARTERY CIRCULATION WITH GENERALLY MILD CORONARY ARTERY FIBRO-INTIMAL HYPERPLASIA RESULTING IN < 20% LUMINAL NARROWING.
B. NEGATIVE FOR COMPLICATED/ULCERATED CORONARY ARTERY DISEASE AND THROMBOSIS.
C. PATCHY, PREDOMINANTLY SUBENDOCARIAL, BUT FOCALLY TRANSMURAL AND SEPTAL ACUTE ISCHEMIC INJURY MANIFEST AS MYOFIBER HYPEREOSINOPHILIA, INTERSTITIAL EDEMA, AND MYOFIBER THINNING WITH LARGE AREAS OF CONTRACTION BAND AND FOCAL EARLY COAGULATIVE-TYPE NECROSIS, AND WIDESPREAD FOCAL HEMORRHAGE, BUT MINIMAL NEUTROPHILIC INFLAMMATION INVOLVING >20% OF THE LEFT VENTRICULAR CIRCUMFERENCE (SEE COMMENT) - CONSISTENT WITH MODERATELY-SIZED ACUTE MYOCARDIAL INFARCT.
D. MINIMAL PATCHY INTERSTITAL FIBROSIS IN SUBVALVULAR LEFT VENTRICLE.

COMMENTS:
Overall, the heart is structurally normal with very mild atherosclerotic coronary artery disease without any complicated plaques or coronary artery thrombosis. There is, however, evidence of recent and extensive ischemic injury involving primarily the subendocardial aspect of the mid-portion of the anterior-lateral left ventricle. The insult appears relatively recent: > than 12-18 hours and probably <48 hrs of time subjected to sanguinous circulation. This assertion is based on the presence of easily identifiable hypereosinophilia, extensive contraction band necrosis, nuclear pyknosis, and focal early nuclear dissolution. However, the pacuity/absence of neutrophils in lesional areas might be related to blood perfusate being leukocyte-poor, which would slightly UNDER-ESTIMATE the age of infarct. The contraction bands occur within minutes after reperfusion and interstitial hemorrhage associated with the areas of ischemic injury are indicative of sanguinous reperfusion after the initial ischemic insult.

Case Completed: (b)(4)
Pathologist: (b) (6)

(b) (6)

11/09/2016

RE: Pathology Report from Turned Down Heart – Transmedics EXPAND Trial

UNOS ID: (b) (6)
Explant Date: (b) (6)
Barcode Number: (b) (6)

(b) (6)

GROSS EVALUATION:

Shape/Size Characteristics:

Overall Shape	Normal
Height	12.0 cm
Width	10.0 cm
Length	7.5 cm
Weight	335.19 g

Anatomical Evaluation:

Epicardial Surface	Other, see comment

Right Atrium		***Left Atrium***	
Primary Findings	Normal	Primary Findings	Normal
Secondary Findings		Secondary Findings	
Interventricular Septal Thickness	1.2 cm		
Right Ventricle		***Left Ventricle***	
Thickness	0.5 cm	Thickness	1.4 cm
Primary Findings	Other, see comment	Primary Findings	Other, see comment
Secondary Findings		Secondary Findings	
		Posterior Wall Thickness	1.6 cm
Tricuspid Valve		***Mitral Valve***	
Circumference	9.5 cm	Circumference	9.0 cm
Primary Findings	Normal	Primary Findings	Normal
Secondary Findings		Secondary Findings	
Aortic Valve		***Pulmonic Valve***	
Circumference	5.5 cm	Circumference	6.0 cm
Primary Findings	Normal	Primary Findings	Normal
Secondary Findings	Other, see comment	Secondary Findings	

Coronary Circulation Findings:

Coronary Circulation Dominance	Right
Narrowing of Left Coronary Artery	10 %
Narrowing of Left Circumflex	10 %
Narrowing of Right Coronary Artery	10 %
Narrowing of Posterior Coronary Artery	10 %

MICROSCOPIC EVALUATION:
Nearly all sections from the left and right ventricles and interventricular septum show myofiber hypereosinophilia, focal contraction band necrosis, wavy myofibers, interstitial edema, focal frank coagulative necrosis. Area of coagulative necrosis shows early loss of nuclei, but minimal to no neutrophilic infiltration is seen. Altogether, these findings are consistent a widespread ischemic insult.

Sections through the coronary artery show generally mild, non-complicated fibro-intimal hyperplasia, which narrow the lumen by ~15%, which is slightly greater than estimated on gross examination.

Defects taken 5:
1 -
2- mottled
3- posterior right ventricle
4 - posterior right
5 - apex

DIAGNOSIS:
DONOR HEART, CARDIECTOMY (359 GMS):
A. RIGHT-DOMINANT CORONARY ARTERY CIRCULATION WITH MILD CORONARY ARTERY FIBRO-INTIMAL HYPERPLASIA RESULTING IN ~15% LUMINAL NARROWING (SEE MICROSCOPIC DESCRIPTION AND COMMENT).
B. NEGATIVE FOR COMPLICATED/ULCERATED CORONARY ARTERY DISEASE AND THROMBOSIS.
C. EXTENSIVE LEFT ANTERIOR, LATERAL, AND POSTERIOR, VENTRICULAR, INTERVENTRICULAR SEPTAL, AND RIGHT VENTRICULAR ISCHEMIC INJURY MANIFEST AS EXTENSIVE CONTRACTION BAND NECROSIS, MYOFIBER HYPEREOSINOPHILIA; WAVY MYOFIBERS AND INTERSTITIAL EDEMA; AND FOCAL FRANK COAGULATIVE-TYPE NECROSIS - ALTOGETHER INVOLVING ~30% TISSUE SAMPLING WITH FOCAL INTERSTITIAL HEMORRHAGE (SEE COMMENT).

COMMENTS:
When heart arrived, it had already been dissected with samples taken. This includes coronary arteries.

Epicardial surface: hemorrhagic

Right Ventricle: focal hemorrhage in posterior and lateral walls
Left Ventricle: mottled hemorrhagic mostly in left anterior and left lateral walls
Aortic Valve: tricuspid

The heart is structurally normal with minimal to focally mild atherosclerotic coronary artery disease without any complicated plaques or coronary artery thrombosis. There is, however, evidence of extensive ischemic injury involving both the left and right ventricles and interventricular septum (image #7-18). The insult is probably > 24 hours and <36 hrs before the time subjected to normothermic sanguinous circulation. This assertion is based on the presence of easily identifiable hypereosinophilia, frank coagulative necrosis and focal nuclear dissolution. The pacuity of neutrophils in lesional areas might be related to blood perfusate being leukocyte-poor, which would slightly UNDER-ESTIMATE the age of the ischemic damage.

Case Completed: (b)(4)
Pathologist: (b) (6)

(b) (6)

05/14/2018

RE: Pathology Report from Turned Down Heart – Transmedics EXPAND Trial

UNOS ID: (b) (6)
Explant Date: (b) (6)
Barcode Number: (b) (6)

(b) (6)

GROSS EVALUATION:

Shape/Size Characteristics:

Overall Shape	Normal
Height	6.5 cm
Width	10.5 cm
Length	13.5 cm
Weight	452.9 g

Anatomical Evaluation:

Epicardial Surface	Petechiae

Right Atrium

Primary Findings	Normal
Secondary Findings	

Left Atrium

Primary Findings	Normal
Secondary Findings	

Interventricular Septal Thickness	1.5 cm

Right Ventricle

Thickness	0.5 cm
Primary Findings	Normal
Secondary Findings	

Left Ventricle

Thickness	1.6 cm
Primary Findings	Other, see comment
Secondary Findings	
Posterior Wall Thickness	1.6 cm

Tricuspid Valve

Circumference	13.0 cm
Primary Findings	Normal
Secondary Findings	

Mitral Valve

Circumference	8.0 cm
Primary Findings	Normal
Secondary Findings	

Aortic Valve

Circumference	5.5 cm
Primary Findings	Normal
Secondary Findings	

Pulmonic Valve

Circumference	6.5 cm
Primary Findings	Normal
Secondary Findings	

Coronary Circulation Findings:

Coronary Circulation Dominance	Right
Narrowing of Left Coronary Artery	10 %
Narrowing of Left Circumflex	10 %
Narrowing of Right Coronary Artery	10 %
Narrowing of Posterior Coronary Artery	10 %

MICROSCOPIC EVALUATION:
Sections, especially from the myocardial defects (esp. defect #1 from the anterior lateral left ventricle) and from the superior left ventricle (LAMVLV section) show easily recognizable myofiber hypereosinophilia, wavy myofibers and intertitial edema. However, prominent monocyte infiltration or contraction band necrosis are not seen, but rare contraction bands are seen (image #17). Some hypereosinophilic myocytes are devoid of nuclei and one of two myocytes show early nuclear dissolution.

Representative sections through the coronary arteries show mild (~10%) fibro-intimal hyperplasia noticed on both the gross and microscopic examination.

DIAGNOSIS:
DONOR HEART, CARDIECTOMY (453 GMS):
A. MILD CORONARY ARTERY ATHEROSCLEROSIS WITH ~10% LUMINAL NARROWING (SEE GROSS AND MICROSCOPIC ANATOMICAL EVALUATION).
B. WIDESPREAD PATCHY ISCHEMIC-TYPE CARDIAC MYOCYTE INJURY PIMARILY INVOLVING THE ANTERIOR AND SUPERIOR LEFT VENTRICLE (SEE MICROSCOPIC DESCRIPTION AND COMMENT).
C. PATCHY FOCI OF INTERSTITIAL HEMORRHAGE.

COMMENTS:
Comments from Dissection:
- Left ventricle: thick and mottled (picture)

Defect Samples taken:
1) Anterior lateral left ventricle
2) lateral left ventricle subendocardial region
3) posterior left ventricle

Additional Sections of Left Ventricle for Analysis Taken on 4/13/18:
2) Anterior Left Ventricle
3) Interventricular Septum

The timing of the insult based on morphology is difficult to determine because of the paucity of monocytes and neutrophils in the perfusate. However, definite areas of myofiber hypereosinophilia, interstitial edema, contraction band necrosis, and wavy myofibers are seen. Many hypereosinophlic myocytes are devoid of nuclei This suggests that the ischemic insult occured between 12 - 18 hrs before tissue fixation and subsequent sampling. However, the histopathological timing of the injury might have been influenced by the paucity of neutrophils and monocytes in the perfusate: this might

retard the development and thus the timing of changes because of less neutrophilic and monocytic enzymes released into the tissues.

Case Completed: (b)(4)
Pathologist: (b) (6)

(b) (6)

08/05/2016

RE: Pathology Report from Turned Down Heart – Transmedics EXPAND Trial

UNOS ID: (b) (6) (b) (6)
Explant Date: (b)
Barcode Number: (b) (6)

GROSS EVALUATION:

Shape/Size Characteristics:

Overall Shape	Normal
Height	14.0 cm
Width	4.5 cm
Length	12.0 cm
Weight	480.31 g

Anatomical Evaluation:

Epicardial Surface	Normal

Right Atrium

Primary Findings	Normal
Secondary Findings	
Interventricular Septal Thickness	1.2 cm

Left Atrium

Primary Findings	Normal
Secondary Findings	

Right Ventricle

Thickness	0.5 cm
Primary Findings	Normal
Secondary Findings	

Left Ventricle

Thickness	1.2 cm
Primary Findings	Normal
Secondary Findings	Other, see comment
Posterior Wall Thickness	1.2 cm

Tricuspid Valve

Circumference	11.0 cm
Primary Findings	Normal
Secondary Findings	

Mitral Valve

Circumference	9.0 cm
Primary Findings	Normal
Secondary Findings	

Aortic Valve

Circumference	5.5 cm
Primary Findings	Normal
Secondary Findings	

Pulmonic Valve

Circumference	7.5 cm
Primary Findings	Normal
Secondary Findings	

Coronary Circulation Findings:

Coronary Circulation Dominance	Right
Narrowing of Left Coronary Artery	10 %
Narrowing of Left Circumflex	10 %
Narrowing of Right Coronary Artery	10 %
Narrowing of Posterior Coronary Artery	10 %

MICROSCOPIC EVALUATION:

Sections through the patchy mottling noted grossly (see image #3) involving the anterior-lateral left ventricle shows large areas of patchy myofiber hypereosinophilia (image #7), wavy fibers (image #8), and focal contraction-band (image 10-12) and perhaps very early coagulative-type necrosis combined with focal interstitial edema and hemorrhage, which is seen throughout the entire thickness, but worse near the endocardium. Rare necrotic myocytes might be devoid of nuclei, but minimal to no neutrophilic infiltration is seen (image #21). Altogether, these findings are consistent with an acute myocardial ischemia and subsequent reperfusion.

Mottling grossly occupies ~20% of circumference of left anterior lateral ventricle (subendocardial) - 3 pieces taken for analysis (image 5)

DIAGNOSIS:

DONOR HEART, CARDIECTOMY (480 GMS):
A. RIGHT-DOMINANT CORONARY ARTERY CIRCULATION WITH MILD CORONARY ARTERY FIBRO-INTIMAL HYPERPLASIA RESULTING IN ~10% LUMINAL NARROWING.
B. NEGATIVE FOR COMPLICATED/ULCERATED CORONARY ARTERY DISEASE AND THROMBOSIS.
C. PATCHY MID-PORTION, ANTERIOR-LATERAL LEFT VENTRICULAR ISCHEMIC INJURY WITH MYOFIBER HYPEREOSINOPHILIA, CONTRACTION BAND AND EARLY COAGULATIVE-TYPE NECROSIS AND FOCAL HEMORRHAGE INVOLVING <10% OF THE LEFT VENTRICULAR CIRCUMFERENCE (SEE COMMENT).
D. MILD LEFT VENTRICULAR HYPERTROPHY: 1.6 CM

COMMENTS:

Overall, the heart is structurally normal with mild atherosclerotic coronary artery disease without any complicated plaques or coronary artery thrombosis. There is, however, definite evidence of recent ischemic injury involving primarily the subendocardial aspect of the mid-portion of the anterior-lateral left ventricle. The insult appears relatively recent: > than 8-12 hours and probably <36 hrs of time subjected to normothermic sanguinous circulation. This assertion is based on the presence of easily identifiable hypereosinophilia, contraction band necrosis, nuclear pyknosis, and early nuclear dissolution. However, the pacuity of neutrophils in lesional areas might be related to blood perfusate being leukocyte-poor, which would slightly UNDER-ESTIMATE the age of infarct. Contraction bands occur within minutes after reperfusion and interstitial hemorrhage associated with the areas of ischemic injury are indicative of sanguinous reperfusion after the initial ischemic insult. Similar changes might be seen with coronary occlusion/global ischemia, resuscitation attempts, catecholamine excess/aggresive inotrope use, intra-cranial hemorrhage, potassium or magnesium deficiency, electric

shock, cobalt administration, and a wide variety of drugs (e.g. cocaine, polymyxin, neomycin, streptokinase, trypsin, and papain.

Case Completed: (b)(4)
Pathologist: (b) (6) .

(b) (6)

03/27/2017

RE: Pathology Report from Turned Down Heart – Transmedics EXPAND Trial

UNOS ID: (b) (6)
Explant Date: (b) (6)
Barcode Number: (b) (6)

(b) (6)

GROSS EVALUATION:

Shape/Size Characteristics:

Overall Shape	Normal
Height	7.0 cm
Width	10.5 cm
Length	14.0 cm
Weight	414.82 g

Anatomical Evaluation:

Epicardial Surface	Normal

Right Atrium

Primary Findings	Normal
Secondary Findings	
Interventricular Septal Thickness	1.3 cm

Left Atrium

Primary Findings	Normal
Secondary Findings	

Right Ventricle

Thickness	0.5 cm
Primary Findings	Normal
Secondary Findings	

Left Ventricle

Thickness	1.7 cm
Primary Findings	Other, see comment
Secondary Findings	
Posterior Wall Thickness	1.7 cm

Tricuspid Valve

Circumference	11.0 cm
Primary Findings	Normal
Secondary Findings	

Mitral Valve

Circumference	10.0 cm
Primary Findings	Other, see comment
Secondary Findings	

Aortic Valve

Circumference	6.5 cm
Primary Findings	Other, see comment
Secondary Findings	

Pulmonic Valve

Circumference	7.0 cm
Primary Findings	Normal
Secondary Findings	

Coronary Circulation Findings:

Coronary Circulation Dominance	Other, see comment
Narrowing of Left Coronary Artery	10 %
Narrowing of Left Circumflex	10 %
Narrowing of Right Coronary Artery	10 %
Narrowing of Posterior Coronary Artery	10 %

MICROSCOPIC EVALUATION:
Sections from the left ventricular defects (esp. defect #5 from the anterior left ventricle including the papillary muscles show a variety of ischemic insults ranging from hypereosinophilia and wavy myofibers to contraction band necrosis to interstitial edema and focal frank coagulative necrosis with nuclear dissolution (images 21 and 22). However, very little neutrophilic inflammation is seen, which is likely related to the relative paucity of neutrophils in the perfusate.

DIAGNOSIS:
DONOR HEART, CARDIECTOMY (415 GMS):
A. MILD CORONARY ARTERY ATHEROSCLEROSIS WITH <20% LUMINAL NARROWING (SEE COMMENT).
B. FOCAL EARLY MITRAL VALVE CALCIFICATION (IMAGE #12).
C. WIDESPREAD PATCHY LEFT VENTRICULAR ISCHEMIC INJURY, FOCALLY SEVERE WITH AN INFARCT INVOLVING THE SUBENDOCARDIAL ANTERIOR LEFT VENTRICLE - PORBABLY PAPILLARY MUSCLE (SEE MICROSCOPIC DESCRIPTION, CARDIAC DEFECT #5; IMAGES #14, 21, AND 22 AND COMMENT).
D. PATCHY MILD SUBENDOCARDIAL FIBROSIS OF THE ANTERIOR LEFT VENTRICLE WITH FOCAL FIBROINTIMAL HYPERPLASIA OF PENETRATING CORONARY ARTERIES WITH NEARBY ARTERIAL ADVENTITIAL FIBROSIS.
E. PATCHY LEFT VENTRICULAR INTERSTITIAL HEMORRHAGE (IMAGE#20).

COMMENTS:
1) Mitral Valve - thickening (see picture), calcified?
2) Left Ventricle - normal but a little thick
3) aortic valve has atherosclerotic plaques (see picture)
4) coronary circulation is either co-dominant or left leaning
Sections from Defects:
1) hemorrhagic apex
2) posterior left ventricle
3) anterior left ventricle
4) lateral left ventricle near apex
5) anterior left ventricle with papillary muscle
COMMENT: the underlying cause of the focal subendocardial fibrosis, arterial intimal thickening, and adventitial fibrosis is uncertain. One possibility is that theese are age-related changes seen near papillary muscle tips (Anatomical Science International (2003) 78, 223-227). However, previous remote damage from arterial vasospasms or transient ischemic insult cannot be absolutely excluded.

Case Completed: (b)(4)

Pathologist: (b) (6)

(b) (6)

05/15/2017

RE: Pathology Report from Turned Down Heart – Transmedics EXPAND Trial

UNOS ID: (b) (6)
Explant Date: (b) (6)
Barcode Number: (b) (6)

(b) (6)

GROSS EVALUATION:

Shape/Size Characteristics:

Overall Shape	Normal
Height	7.0 cm
Width	12.0 cm
Length	15.0 cm
Weight	414.2 g

Anatomical Evaluation:

Epicardial Surface	Petechiae

Right Atrium		***Left Atrium***	
Primary Findings	Dilatation	Primary Findings	Normal
Secondary Findings		Secondary Findings	
Interventricular Septal Thickness	1.2 cm		
Right Ventricle		***Left Ventricle***	
Thickness	0.5 cm	Thickness	1.7 cm
Primary Findings	Normal	Primary Findings	Normal
Secondary Findings		Secondary Findings	
		Posterior Wall Thickness	1.5 cm
Tricuspid Valve		***Mitral Valve***	
Circumference	11.0 cm	Circumference	9.0 cm
Primary Findings	Normal	Primary Findings	Normal
Secondary Findings		Secondary Findings	
Aortic Valve		***Pulmonic Valve***	
Circumference	6.0 cm	Circumference	6.5 cm
Primary Findings	Normal	Primary Findings	Normal
Secondary Findings		Secondary Findings	Other, see comment

Coronary Circulation Findings:

Coronary Circulation Dominance	Right
Narrowing of Left Coronary Artery	20 %
Narrowing of Left Circumflex	10 %
Narrowing of Right Coronary Artery	15 %
Narrowing of Posterior Coronary Artery	10 %

MICROSCOPIC EVALUATION:
Sections through the coronary arteries show focally moderate atherosclerosis resulting in ~ 40% narrowing of the left anterior descending coronary, which appears worse microscopically than grossly, so the microscopic evaluation probably over-estimates the severity of narrowing. The left circumflex also shows atherosclerotic narrowing with focal intimal hemorrhage.

Sections through the myocardial defects show large areas of patchy interstitial edema and pronounced contraction-band necrosis (images #12-17) most severe in anterior left ventricle and left ventricular papillary muscles.

DIAGNOSIS:
DONOR HEART, CARDIECTOMY (414 GMS):
A. RIGHT-DOMINANT CORONARY ARTERY CIRCULATION WITH FOCALLY MODERATE CORONARY ARTERY FIBRO-INTIMAL HYPERPLASIA WITH ATHEROSCLEROTIC PLAQUE RESULTING IN ~40% LUMINAL NARROWING (SEE COMMENT).
B. NEGATIVE FOR COMPLICATED/ULCERATED CORONARY ARTERY DISEASE AND THROMBOSIS.
C. PATCHY LEFT VENTRICULAR PERIARTERIAL/ADVENTITIAL FIBROSIS.
D. PATCHY ISCHEMIC INJURY MANIFEST AS INTERSTITIAL EDEMA AND CONTRACTION BAND NECROSIS (ESPECIALLY DEFECTS #3 AND TO A LESSOR EXTENT DEFECT #4 FROM THE ANTERIOR LEFT VENTRICLE AND LEFT VENTRICULAR PAPILLARY MUSCLES; IMAGES #12-14 AND #16-17) AND EQUIVOCAL MONOCYTE INFILTRATION (SEE COMMENT).
E. STENT IN PULMONIC VALVE

COMMENTS:
COMMENT: gross and microscopic examination of the coronary arteries shows focally moderate atherosclerosis with atherosclerotic plaque formation and focal intra-intimal hemorrhage. This is associated with patchy peri-arterial/adventitial fibrosis and myocyte hypertrophic changes (image #15). The gross estimate of luminal narrowing is less than the 40% narrowing by microscopic examination. The ischemic damage is most severe in the defects #3 and, to a lessor extent #4, from the anterior left ventricle and left ventricular papillary muscles.

stent in pulmonic valve

right atrium dilated

myocardial defects:

1)mottled posterior/inferior left ventricle
2)lateral left ventricle
3)anterior left ventricle
4)left ventricle papillary muscle

Case Completed: (b)(4)
Pathologist: (b) (6)

(b)(4)

05/31/2017

RE: Pathology Report from Turned Down Heart – Transmedics EXPAND Trial

UNOS ID: (b) (6)
Explant Date: (b) (6) (b) (6)
Barcode Number: (b) (6)

GROSS EVALUATION:

Shape/Size Characteristics:

Overall Shape	Normal
Height	5.0 cm
Width	10.0 cm
Length	15.0 cm
Weight	297.9 g

Anatomical Evaluation:

Epicardial Surface	Petechiae

Right Atrium

Primary Findings	Normal
Secondary Findings	
Interventricular Septal Thickness	1.3 cm

Left Atrium

Primary Findings	Normal
Secondary Findings	Other, see comment

Right Ventricle

Thickness	0.5 cm
Primary Findings	Normal
Secondary Findings	

Left Ventricle

Thickness	1.2 cm
Primary Findings	Normal
Secondary Findings	
Posterior Wall Thickness	1.2 cm

Tricuspid Valve

Circumference	10.0 cm
Primary Findings	Normal
Secondary Findings	

Mitral Valve

Circumference	8.5 cm
Primary Findings	Normal
Secondary Findings	

Aortic Valve

Circumference	6.5 cm
Primary Findings	Normal
Secondary Findings	

Pulmonic Valve

Circumference	6.0 cm
Primary Findings	Normal
Secondary Findings	

Coronary Circulation Findings:

Coronary Circulation Dominance	Right
Narrowing of Left Coronary Artery	10 %
Narrowing of Left Circumflex	10 %
Narrowing of Right Coronary Artery	10 %
Narrowing of Posterior Coronary Artery	10 %

MICROSCOPIC EVALUATION:
Sections from the left ventricular defects (esp. defect #2 from the left lateral ventricle, but also in other defect sections) including the papillary muscles show a variety of ischemic insults. However, hypereosinophilia is the most prevalent finding combined with interstitial edema and focal wavy myofibers and contraction band necrosis. Although very little neutrophilic inflammation is seen, which is likely related to the relative paucity of neutrophils in the perfusate, there does appear to be a slight increase of monocytes. Prominent ischemic injury is not seen in the right ventricular sections.

DIAGNOSIS:
DONOR HEART, CARDIECTOMY (298 GMS):
A. MILD CORONARY ARTERY ATHEROSCLEROSIS WITH <15% LUMINAL NARROWING.
B. WIDESPREAD PATCHY LEFT VENTRICULAR ISCHEMIC INJURY, FOCALLY SEVERE, ESPECIALLY IN THE LEFT LATERAL VENTRICLE AND PAPILLARY MUSCLES, BUT ALSO PRESENT IN RANDOM SECTIONS OF THE POSTERIOR-SUPERIOR LEFT VENTRICLE AND SEPTUM (SEE MICROSCOPIC DESCRIPTION AMD IMAGES #22 AND 23).
C. PATCHY SUBENDOCARIDAL LEFT VENTRICULAR INTERSTITIAL HEMORRHAGE (E.G. IMAGE#22).
D. SUTURE IN LEFT ATRIUM, REASON UNCERTAIN.

COMMENTS:
left atrium had a suture present?

Myocardial Defect sections:
1) left anterior ventricle
2) left lateral ventricle - papillary muscle
3) left posterior ventricle
4) left inferior/posterior ventricle

The ischemic insult probably occurred > 12 hours hrs before the time subjected to normothermic sanguinous circulation. This assumption based on the presence of easily identifiable hypereosinophilia, frank coagulative necrosis, and early monocytic infiltration/activation. However, neutrophilic infiltration is not prominent, likely related to the paucity of PMNs in the perfusate.

Case Completed: (b)(4)
Pathologist: (b) (6)

(b) (6)

10/03/2017

RE: Pathology Report from Turned Down Heart – Transmedics EXPAND Trial

UNOS ID: (b) (6) (b) (6)
Explant Date: (b) (6)
Barcode Number: (b) (6)

GROSS EVALUATION:

Shape/Size Characteristics:

Overall Shape	Normal
Height	6.0 cm
Width	12.0 cm
Length	16.0 cm
Weight	445.21 g

Anatomical Evaluation:

Epicardial Surface	Petechiae

Right Atrium		***Left Atrium***	
Primary Findings	Normal	Primary Findings	Normal
Secondary Findings		Secondary Findings	
Interventricular Septal Thickness	1.5 cm		
Right Ventricle		***Left Ventricle***	
Thickness	0.5 cm	Thickness	1.6 cm
Primary Findings	Normal	Primary Findings	Other, see comment
Secondary Findings		Secondary Findings	
		Posterior Wall Thickness	1.7 cm
Tricuspid Valve		***Mitral Valve***	
Circumference	9.5 cm	Circumference	9.5 cm
Primary Findings	Normal	Primary Findings	Normal
Secondary Findings	Other, see comment	Secondary Findings	
Aortic Valve		***Pulmonic Valve***	
Circumference	6.5 cm	Circumference	5.5 cm
Primary Findings	Other, see comment	Primary Findings	Normal
Secondary Findings		Secondary Findings	

Coronary Circulation Findings:

Coronary Circulation Dominance	Right
Narrowing of Left Coronary Artery	10 %
Narrowing of Left Circumflex	10 %
Narrowing of Right Coronary Artery	10 %
Narrowing of Posterior Coronary Artery	10 %

MICROSCOPIC EVALUATION:
Section through the myocardial defects reveal the most significant changes in myocardial defects #1 and #2, which consist of interstitial edema, myofiber hypereosinophilia, wavy myofibers, and frank contraction band necrosis with foci of nuclear fragmentation (see images 12, 16-23, 25,26). Some of the changes seem worse in the immediate subendocardium of the left ventricle.

Representative sections through all of the coronary arteries show fibro-intimal hyperplasia with luminal narrowing, best estimated on the gross examine. However, the narrowing appears slightly worse/more significant in the histological sections. The left anterior descending coronary artery, painted red on the adventitia, also shows intimal calcification, but is negative for ulceration or thrombosis.

DIAGNOSIS:
DONOR HEART, CARDIECTOMY (445 GMS):
A. MILD CORONARY ARTERY ATHEROSCLEROSIS WITH UP TO ~20% LUMINAL NARROWING (SEE GROSS AND MICROSCOPIC ANATOMICAL EVALUATION: ESTIMATED DEGREE OF NARROWING).
B. FOCALLY CACLIFIED CORONARY ARTERY ATHEROSCLEROSIS OF THE LEFT ANTERIOR DESCENDING CORONARY ARTERY, BUT NEGATIVE FOR CORONARY ARTERY THROMBOSIS.
C. FOCAL ISHEMIC-TYPE CARDIAC MYOCYTE INJURY PIMARILY INVOLVING THE LEFT AND LEFT POSTERIOR AND LEFT ANTERIOR VENTRICULAR APEX, WORSE NEAR THE SUBENDOCARDIUM - ROUGHLY ESTIMATED AT ABOUT 10% OF THE LEFT VENTRICULAR SECTIONS (SEE MICROSCOPIC EVALUATION AND COMMENT).
D. MULTI-FOCAL SUBENDOCARDIAL INTERSITIAL HEMORRHAGE.

COMMENTS:
DISSECTION COMMENTS
Piece missing from heart upon arrival

Epidural Surface: mottled with petechiae
Tricuspid Valve: section missing at time of dissection
Left Ventricle: endocarium had mottled petechiae
Aortic Valve: minimal atherosclerosis

Sections of Defects taken from:
1) Left Anterior Apex
2) Posterior Left Ventricle
3) Anterior Interventricular Septum
4) Anterior Left Ventricle

The heart is structurally normal with generally mild, but focally calcified, coronary artery atherosclerosis. However, no ulcerated coronary artery plaques or thromboses are seen. There is, however, ischemic injury primarily involving the left ventricle, especially in the subendocardial regions (see images 16-20). The timing of the insult based on morphology is difficult to determine because of the paucity of neutrophils in the perfusate. However, definite areas of contraction bands are present and very early nuclear dissolution is seem in some areas. The insult, therefore, likley occurred between 12 and 24 hours before histopathological sampling. This assertion is based on the easily recognizable contractin band necrosis and very focal early nuclear dissolution but frank large areas of coagulative-typenecrosis are not seen. It is not possible, however, to determine whether the paucity of neutrophils in the perfusate might retard the development and thus the timing of changes because of less neutrophilic enzymes released into the tissues.

Timestamp of Diagnosis Data Used for Report: (b)(4)
Pathologist: (b) (6)

(b) (6)

12/08/2016

RE: Pathology Report from Turned Down Heart – Transmedics EXPAND Trial

UNOS ID: (b) (6)
Explant Date: (b) (6) (b) (6)
Barcode Number: (b) (6)

GROSS EVALUATION:

Shape/Size Characteristics:

Overall Shape	Normal
Height	6.5 cm
Width	10.5 cm
Length	11.0 cm
Weight	287.39 g

Anatomical Evaluation:

Epicardial Surface	Petechiae

Right Atrium

Primary Findings	Normal
Secondary Findings	N/A
Interventricular Septal Thickness	1.5 cm

Left Atrium

Primary Findings	Normal
Secondary Findings	N/A

Right Ventricle

Thickness	0.5 cm
Primary Findings	Normal
Secondary Findings	N/A

Left Ventricle

Thickness	1.5 cm
Primary Findings	Normal
Secondary Findings	N/A
Posterior Wall Thickness	1.5 cm

Tricuspid Valve

Circumference	8.0 cm
Primary Findings	Normal
Secondary Findings	N/A

Mitral Valve

Circumference	8.0 cm
Primary Findings	Normal
Secondary Findings	N/A

Aortic Valve

Circumference	4.5 cm
Primary Findings	Normal
Secondary Findings	N/A

Pulmonic Valve

Circumference	5.0 cm
Primary Findings	Normal
Secondary Findings	N/A

Coronary Circulation Findings:

Coronary Circulation Dominance	Right
Narrowing of Left Coronary Artery	0 %
Narrowing of Left Circumflex	0 %
Narrowing of Right Coronary Artery	0 %
Narrowing of Posterior Coronary Artery	0 %

MICROSCOPIC EVALUATION:
Nearly all sections from the left ventricles and interventricular septum show evidence of severe and extensive ischemic myofiber injury including hypereosinophilia, focal contraction band necrosis, wavy myofibers, interstitial edema, focal frank coagulative necrosis, and focal neutrophilic inflammation. Area of coagulative necrosis shows early loss of nuclei and early neutrophilic infiltration is seen (image#21). Altogether, these findings are consistent a widespread left ventricular ischemic insult.

Sections through the coronary artery show generally mild, non-complicated fibro-intimal hyperplasia, which narrow the lumen by <5% consistent with the gross examination.

DIAGNOSIS:
DONOR HEART, CARDIECTOMY (287 GMS):
A. MINIMAL TO NO EVIDENCE OF CORONARY ARTERY ATHEROSCLEROSIS WITH <5% OF LUMINAL NARROWING (SEE MICROSCOPIC DESCRIPTION AND COMMENT).
B. NEGATIVE FOR COMPLICATED/ULCERATED CORONARY ARTERY DISEASE AND THROMBOSIS.
C. EXTENSIVE CIRCUMFERENTIAL ISCHEMIC INJURY (MOST SEVERE IN THE INTERVENTRIBULAR SEPTUM) MANIFEST AS EXTENSIVE MYOFIBER HYPER-EOSINOPHILIA, CONTRACTION BAND NECROSIS, WAVY MYOFIBERS, FOCAL NEUTROPHILIC INFILTRATION (IMAGE #21), INTERSTITIAL EDEMA; AND FOCAL FRANK COAGULATIVE-TYPE NECROSIS WITH MYOFIBER DISSOLUTION INVOLVING THE ENTIRE CIRCUMFERENCE OF TEH LEFT VENTRICLE WITH FOCAL EARLY NEUTROPHILIC INFILTRATION AND FOCAL INTERSTITIAL HEMORRHAGE (SEE COMMENT).

COMMENTS:
Determining coronary artery dominance difficult because specimen was previously dissected.

HEMORRHAGE @ AORTA DUE TO MACHINE INSERT
LEFT VENTRICLE INTERNAL WALL IS HEMORRHAGIC
GROSSLY NORMAL

CASSETTE LABELED DEFECT #1 IS LEFT VENTRICLE WALL W/INTRA-MYOCARDIAL HEMMORRHAGE

CASSETTE LABELED DEFECT #2 IS PALE MYOCARDIAL WALL

The heart is structurally normal with minimal to focally mild atherosclerotic coronary artery disease without any complicated plaques or coronary artery thrombosis. There is,

however, evidence of extensive ischemic injury involving the entire circumference of the left ventricle, but worst in the interventricular septum. The insult is probably > 24 hours hrs before the time subjected to normothermic sanguinous circulation. This assertion is based on the presence of easily identifiable hypereosinophilia, frank coagulative necrosis, focal nuclear dissolution, and focal neutrophilic infiltration.

Case Completed: (b)(4)
Pathologist: (b) (6)

(b) (6)

02/01/2017

RE: Pathology Report from Turned Down Heart – Transmedics EXPAND Trial

UNOS ID: (b) (6) (b) (6)
Explant Date: (b) (6)
Barcode Number: (b) (6)

GROSS EVALUATION:

Shape/Size Characteristics:

Overall Shape	Normal
Height	15.0 cm
Width	6.5 cm
Length	9.0 cm
Weight	457.91 g

Anatomical Evaluation:

Epicardial Surface	Petechiae

Right Atrium		***Left Atrium***	
Primary Findings	Normal	Primary Findings	Normal
Secondary Findings		Secondary Findings	
Interventricular Septal Thickness	1.6 cm		
Right Ventricle		***Left Ventricle***	
Thickness	0.5 cm	Thickness	1.6 cm
Primary Findings	Other, see comment	Primary Findings	Other, see comment
Secondary Findings		Secondary Findings	
		Posterior Wall Thickness	1.6 cm
Tricuspid Valve		***Mitral Valve***	
Circumference	8.5 cm	Circumference	7.0 cm
Primary Findings	Normal	Primary Findings	Normal
Secondary Findings		Secondary Findings	
Aortic Valve		***Pulmonic Valve***	
Circumference	7.5 cm	Circumference	6.0 cm
Primary Findings	Other, see comment	Primary Findings	Normal
Secondary Findings		Secondary Findings	

Coronary Circulation Findings:

Coronary Circulation Dominance	N/A
Narrowing of Left Coronary Artery	0 %
Narrowing of Left Circumflex	0 %
Narrowing of Right Coronary Artery	0 %
Narrowing of Posterior Coronary Artery	0 %

MICROSCOPIC EVALUATION:
Sections from the left ventricular defects and random left ventricle sections severe ischemic myocyte injury, which seems worse near the endocardium. Changes include hypereosinophilia, contraction band necrosis, wavy myofibers, interstitial edema, and focal frank coagulative necrosis with nuclear dissolution. Again, however, very little neutrophilic inflammation is seen, which might be related to the relative paucity of neutrophils in the perfusate. The damage is especially severe in the secitons sampling the myocardial defects, but also focally present in the random section of the left ventricles. However, milder changes are seen in the section sampling the right ventricular defect (myocardial defect #3).

No sections of the coronary arteries were available for examination becuase they had been dissected away from the specimen before it was received.

DIAGNOSIS:
DONOR HEART, CARDIECTOMY (458 GMS):
A. CORONARY ARTERIES DISSECTED FROM SPECIMENS BEFORE EXAMINATION: THEREFORE, NOT POSSIBLE TO ACCURATELY DETERMINE DEGREE OF LUMINAL NARROWING (SEE COMMENT).
B. WIDESPREAD ISHEMIC-TYPE INJURY PIMARILY INVOLVING THE LEFT VENTRICLE (SEE MICROSCOPIC DESCRIPTION, IMAGES #8 - 18 AND COMMENT).
C. SMALL FOCI OF EARLY ISCHEMIC CHANGE INVOLVING THE RIGHT VENTRICLE (MYOCARDIAL DEFECT #3; IMAGES #17 AND 18).

COMMENTS:
- ORGAN RECEIVED EXTENSIVELY DISSECTED
- OVERALL SIZE CHARACTERISTICS MAY BE DISTORTED DUE TO PRIOR DISSECTION - SIZE APPEARS EXPANDED
- EPIDURAL SURFACE HAD OCCASSIONAL PETECHIAE
- RIGHT VENTRICLE WAS FOCALLY HEMORRHAGIC
- LEFT VENTRICLE HAD MOTTLED PAPILLARY MUSCLES; DID NOT EXPLICITY MEASURE THICKNESS OF POSTERIOR WALL (NEED TO REMEASURE?)
- AORTIC VALVE HAS PLAQUE - SEE PICTURE
- UNABLE TO DETERMINE CIRCULATION DOMINANCE OR NARROWING OF CORONARY/CIRCUMFLEX ARTERIES BECAUSE CUT OFF PRIOR TO ARRIVAL AT CORE; TEMPLATE REQUIRED INPUT OF VALUE --> NO SECTIONS OF COARTCSXS

SAMPLES OF DEFECTS TAKEN:
1) SEPTUM

2) CENTRAL LESION OF LEFT POSTERIOR VENTRICLE
3) RIGHT VENTRICULAR WALL
4) ANTERIOR INFERIOR LEFT VENTRICLE

NOTE: REPURPOSED CASSETTE LABELLED COARTCSXS FOR DEFECT 4 (LABELLED CHANGED WITH PENCIL BUT SOMETIMES WEARS OFF DURING PROCESSING)

The heart is structurally normal within the limits imposed by the previous dissection. There is, however, evidence of ischemic injury involving primarily the left ventricle, but also the right ventricle, and worse subendocardial regions of the left ventricle. The insult is probably > 24 hours hrs before the time subjected to normothermic sanguinous circulation - an assumption based on the presence of easily identifiable hypereosinophilia, frank coagulative necrosis, and focal nuclear dissolution. However, neutrophilic infiltration is not prominent.

Case Completed: (b)(4)
Pathologist: (b) (6)

(b) (6)

02/01/2017

RE: Pathology Report from Turned Down Heart – Transmedics EXPAND Trial

UNOS ID: (b) (6) (b) (6)
Explant Date: (b) (6)
Barcode Number: (b) (6)

GROSS EVALUATION:

Shape/Size Characteristics:

Overall Shape	N/A
Height	14.0 cm
Width	11.0 cm
Length	6.0 cm
Weight	325.04 g

Anatomical Evaluation:

Epicardial Surface	Petechiae

Right Atrium

Primary Findings	Normal
Secondary Findings	
Interventricular Septal Thickness	1.4 cm

Left Atrium

Primary Findings	Normal
Secondary Findings	

Right Ventricle

Thickness	0.6 cm
Primary Findings	Normal
Secondary Findings	

Left Ventricle

Thickness	1.5 cm
Primary Findings	Other, see comment
Secondary Findings	
Posterior Wall Thickness	1.5 cm

Tricuspid Valve

Circumference	9.0 cm
Primary Findings	Normal
Secondary Findings	

Mitral Valve

Circumference	9.0 cm
Primary Findings	Normal
Secondary Findings	

Aortic Valve

Circumference	6.5 cm
Primary Findings	Normal
Secondary Findings	

Pulmonic Valve

Circumference	6.0 cm
Primary Findings	Normal
Secondary Findings	

Coronary Circulation Findings:

Coronary Circulation Dominance	Right
Narrowing of Left Coronary Artery	10 %
Narrowing of Left Circumflex	10 %
Narrowing of Right Coronary Artery	10 %
Narrowing of Posterior Coronary Artery	10 %

MICROSCOPIC EVALUATION:
Nearly a sections from the myocardium show interstitial edema and at least focal wavy myofibers. In addition, sections from the left ventricular defects and left ventricle show evidence of severe and fairly extensive ischemic myocyte injury including hypereosinophilia, contraction band necrosis, wavy myofibers, interstitial edema, and focal frank coagulative necrosis and nuclear dissolution. However, very little neutrophilic inflammation is seen. The damage is especially severe in myocardial defects #1 (posterior anterior inferior left ventricle) and #3 (anterior inferior left ventricle; see images #7-15). These findings are consistent a widespread left ventricular ischemic insult.

Sections through the coronary artery show generally mild, non-complicated fibro-intimal hyperplasia. However, a tangentially sampled left descending coronary artery shows > 10% narrowing because of fibro-intimal hyperplasia (image #6).

DIAGNOSIS:
DONOR HEART, CARDIECTOMY (325 GMS):
A. MINIMAL TO NO EVIDENCE OF CORONARY ARTERY ATHEROSCLEROSIS WITH <10% OF LUMINAL NARROWING (SEE ANATOMICAL EVALUATION, MICROSCOPIC DESCRIPTION AND COMMENT).
B. NEGATIVE FOR COMPLICATED/ULCERATED CORONARY ARTERY DISEASE AND THROMBOSIS.
C. WIDESPREAD ISHEMIC-TYPE INJURY PIMARILY INVOLVING THE LEFT VENTRICLE (SEE MICROSCOPIC DESCRIPTION AND COMMENT).

COMMENTS:
- ALREADY EXTENSIVELY DISSECTED (MISSING PIECES)
- SHAPE AND SIZE CHARACTERISTICS MAY BE OFF DUE TO PRIOR DISSECTION - APPEARS TO HAVE DILATED CHAMBERS
- LEFT VENTRICLE HAS PETECHIAL HEMORRHAGING (NOTE - DID NOT RECORD SPECIFIC THICKNESS OF POSTERIOR WALL DURING DISSECTION - NEED TO REMEASURE?)
-NARROWING OF LEFT CORONARY ARTERY AND LEFT CIRCUMFLEX ARTERY ESTIMATED AS PORTION MISSING FROM PRIOR DISSECTION

NOTES ON BLOCKS:
1) IN COARTCSXS BLOCK - ONLY HAVE RED FOR LAD AND BLUE FOR RIGHT CORONARY ARTERY - NO GREEN, LEFT CIRCUMFLEX ARTERY MISSING

2) DEFECTS:
#1 - POSTERIOR LEFT VENTRICLE

#2 - ANTERIOR LEFT VENTRICLE
#3 - ANTERIOR INFERIOR LEFT VENTRICLE

The heart is structurally normal with minimal to focally mild atherosclerotic coronary artery disease without any complicated plaques or coronary artery thrombosis. There is, however, evidence of extensive ischemic injury involving primarily the left ventricle, but worse in the anterior and posterior left ventricle. The insult is probably > 24 hours hrs before the time subjected to normothermic sanguinous circulation. This assertion is based on the presence of easily identifiable hypereosinophilia, frank coagulative necrosis, and focal nuclear dissolution; neutrophilic infiltration is not prominent.

Case Completed: (b)(4)
Pathologist: (b) (6)

(b) (6)

07/13/2017

RE: Pathology Report from Turned Down Heart – Transmedics EXPAND Trial

UNOS ID: (b) (6) (b) (6)
Explant Date: (b) (6)
Barcode Number: (b) (6)

GROSS EVALUATION:

Shape/Size Characteristics:

Overall Shape	Normal
Height	6.5 cm
Width	10.0 cm
Length	11.0 cm
Weight	395.53 g

Anatomical Evaluation:

Epicardial Surface	Petechiae

Right Atrium		***Left Atrium***	
Primary Findings	Other, see comment	Primary Findings	Normal
Secondary Findings		Secondary Findings	
Interventricular Septal Thickness	1.7 cm		
Right Ventricle		***Left Ventricle***	
Thickness	0.5 cm	Thickness	1.4 cm
Primary Findings	Normal	Primary Findings	Other, see comment
Secondary Findings		Secondary Findings	
		Posterior Wall Thickness	1.4 cm
Tricuspid Valve		***Mitral Valve***	
Circumference	7.5 cm	Circumference	6.5 cm
Primary Findings	Normal	Primary Findings	Normal
Secondary Findings		Secondary Findings	
Aortic Valve		***Pulmonic Valve***	
Circumference	6.5 cm	Circumference	6.0 cm
Primary Findings	Other, see comment	Primary Findings	Normal
Secondary Findings		Secondary Findings	

Coronary Circulation Findings:

Coronary Circulation Dominance	Right
Narrowing of Left Coronary Artery	10 %
Narrowing of Left Circumflex	20 %
Narrowing of Right Coronary Artery	10 %
Narrowing of Posterior Coronary Artery	25 %

MICROSCOPIC EVALUATION:
Sections throughout all of the myocardial defects noted grossly show severe and extensive (~25% of myocyte area) changes of ischemic injury that range from contaction band to coagulative-type necrosis with microscopic foci of tissue dissolution in the center of the damaged areas. The damage is most severe in myocardial defects 2 and 3 from the left lateral ventricle and near the septum where early tissue dissolution is seen, but can be seen in nearly all defect and non-defect heart tissue samplings. Rare neutrophils can be seen, but are likely limited by the perfusate. The ischemically damaged nuclei also focally show nuclear pyknosis, nuclear loss, and dissolution of the entire cells exposing the underlying matrix framework. However, nearly all sections from the heart, including "non-lesional" areas show some evidence of ischemic damage.

Cross-sections of the coronary arteries show un-ulcerated atherosclerotic change (images 26-28), which display the most severe involved areas.

DIAGNOSIS:
DONOR HEART, CARDIECTOMY (395 GMS):
A. MILD CORONARY ARTERY ATHEROSCLEROSIS WITH UP TO ~25% LUMINAL NARROWING (SEE ANATOMICAL EVALUATION: ESTIMATED DEGREE OF NARROWING).
B. NEGATIVE FOR COMPLICATED/ULCERATED CORONARY ARTERY DISEASE AND THROMBOSIS.
C. WIDESPREAD ISHEMIC-TYPE INJURY PIMARILY INVOLVING THE LEFT AND RIGHT VENTRICLES AND INTERVENTRICULAR SEPTUM (SEE MICROSCOPIC EVALUATION AND COMMENT).
D. FOCAL SUBENDOCARDIAL HEMORRHAGE (IMAGE #23).

COMMENTS:
Right Atrium Findings: subendocardial hemorrhage
Left Ventricle Findings: subendocardial hemorrhage
Aortic Valve: tricuspid

Myocardial Defect 1 Block: posterior left ventricle
Myocardial Defect 2 Block: lateral left ventricle
Myocardial Defect 3 Block: near septum
Myocardial Defect 4 Block: anterior left ventricle

The heart is structurally normal with at least focally mild atherosclerotic coronary artery disease without any complicated plaques or coronary artery thrombosis. There is, however, evidence of extensive ischemic injury involving primarily the left and right ventricules and interventricular septum ventricle, but worse in the left lateral ventricle

and near septal samplings. Although timing of the insult based on morphology is affected by the paucity of neutrophils in the perfusate, the insult is likley > 36 hrs or more before before histopathological sampling. This assertion is based on the presence of frank coagulative necrosis, focal nuclear pyknois and dissolution; and focal early dissolution of the tissue at the center of the necrotic areas, exposing the underlying matrix framework (see image #29).

Case Completed: (b) (4)
Pathologist: (b) (6)

Note to File
MEMORANDUM

TITLE	International Trial to Evaluate the Safety and Effectiveness of The Portable Organ Care System (OCS™) Heart For Preserving and Assessing Expanded Criteria Donor Hearts for Transplantation (EXPAND Heart Trial)
PI	
DATE	

Regarding: Turn down organ for returned to Medical Examiner in and not to Core Lab.

We are writing this memo note to file to document that the donor heart for subject was returned to the Medical Examiner's Office of because the cause of death of the donor was an accident-Drowning. Because of this, the medical examiner has requested the donor heart be sent back to for medico-legal post-mortem examination. The site complied with the medical examiner's request and therefore did not send the turned down heart to the Core Lab. For examination.

(b) (6)

02/20/2018

RE: Pathology Report from Turned Down Heart – Transmedics EXPAND Trial

UNOS ID: (b) (6) (b) (6)
Explant Date: (b) (6)
Barcode Number: (b) (6)

GROSS EVALUATION:

Shape/Size Characteristics:

Overall Shape	Normal
Height	7.5 cm
Width	10.0 cm
Length	14.0 cm
Weight	339.32 g

Anatomical Evaluation:

Epicardial Surface	Petechiae

Right Atrium		***Left Atrium***	
Primary Findings	Normal	Primary Findings	Other, see comment
Secondary Findings	Other, see comment	Secondary Findings	
Interventricular Septal Thickness	1.3 cm		
Right Ventricle		***Left Ventricle***	
Thickness	0.5 cm	Thickness	1.5 cm
Primary Findings	Normal	Primary Findings	Normal
Secondary Findings		Secondary Findings	
		Posterior Wall Thickness	1.4 cm
Tricuspid Valve		***Mitral Valve***	
Circumference	9.5 cm	Circumference	8.5 cm
Primary Findings	Normal	Primary Findings	Normal
Secondary Findings		Secondary Findings	
Aortic Valve		***Pulmonic Valve***	
Circumference	5.0 cm	Circumference	6.0 cm
Primary Findings	Other, see comment	Primary Findings	Normal
Secondary Findings		Secondary Findings	

Coronary Circulation Findings:

Coronary Circulation Dominance	Right
Narrowing of Left Coronary Artery	10 %
Narrowing of Left Circumflex	10 %
Narrowing of Right Coronary Artery	10 %
Narrowing of Posterior Coronary Artery	10 %

MICROSCOPIC EVALUATION:
Section throughout the heart, including the multiple myocardial defects reveal show patchy areas of myofiber hypereosinophilia, wavy myofibers, intertitial edema, focal monocyte infiltration, contraction band necrosis and small foci of myocyte nuclear and total myocyte dissolution. The most severe damage is seen in myocardial defect #3 (posterior left ventricle near apex), but also present in many other sections.

Representative sections through the coronary arteries show minimal to no fibro-intimal hyperplasia with < 10% luminal narrowing using either the gross and/or microscopic examination.

DIAGNOSIS:
DONOR HEART, CARDIECTOMY (339 GMS):
A. MINIMAL TO NO EVIDENCE OF CORONARY ARTERY ATHEROSCLEROSIS WITH <10% LUMINAL NARROWING (SEE GROSS AND MICROSCOPIC ANATOMICAL EVALUATION).
B. WIDESPREAD PATCHY ISHEMIC-TYPE CARDIAC MYOCYTE INJURY PIMARILY INVOLVING THE LEFT POSTERIOR VENTRICLE NEAR THE APEX, BUT ALSO SEEN FOCALLY IN THE RIGHT AND LEFT VENTRICLES AND INTER-VENTRICULAR SEPTUM.
C. PATCHY FOCI OF INTERSTITIAL HEMORRHAGE.

COMMENTS:
Dissection Notes:
- very little fat on epidural surface
- vena cava sewn shut
- left atrium had subendocardial petechiae
- aortic valve had minimal plaque (image taken)
- Sections of "defects":
  1) left leteral ventricle midsection
  2) IV septum
  3) posterior left ventricle near apex
  4) anterior left ventricle mid portion

The heart is structurally normal with generally minimal to no evidence of coronary artery atherosclerosis. No ulcerated coronary artery plaques or thromboses are seen. There is, however, wide patchy foci of ischemic-type myocyte injury and focal interstitial hemorrhage, primarily involving left posterior ventricle near the apex, but present throught both ventricles and the septum, especially in the subendocardial regions (see images 11-26).

The timing of the insult based on morphology is difficult to determine because of the

paucity of neutrophils in the perfusate. However, definite areas of contraction bands are present; very early nuclear and rare myocyte dissolution is occuring in some areas; and focal interstitial edema and infiltration with monocytes/macrophages are observed. Based on these findings, the insult likely occurred > 24 - 48 hours before histopathological sampling. However, the histopathological timing of the injury might have been influenced by the paucity of neutrophils in the perfusate: this might retard the development and thus the timing of changes because of less neutrophilic enzymes released into the tissues.

Case Completed: (b)(4)
Pathologist: (b) (6)

(b) (6)

11/25/2019

RE: Pathology Report from Turned Down Heart – Transmedics EXPAND CAP or Heart DCD Trial

UNOS ID: (b) (6)
Explant Date: (b) (6)
Barcode Number: (b) (6)

GROSS EVALUATION:

Shape/Size Characteristics:

Overall Shape	Normal
Height	8.0 cm
Width	10.0 cm
Length	11.0 cm
Weight	508.66 g

Anatomical Evaluation:

Epicardial Surface	Fat

Right Atrium

Primary Findings	Normal
Secondary Findings	N/A
Interventricular Septal Thickness	1.5 cm

Left Atrium

Primary Findings	Other, see comment
Secondary Findings	N/A

Right Ventricle

Thickness	0.3 cm
Primary Findings	Normal
Secondary Findings	N/A

Left Ventricle

Thickness	1.6 cm
Primary Findings	Normal
Secondary Findings	
Posterior Wall Thickness	1.5 cm

Tricuspid Valve

Circumference	9.0 cm
Primary Findings	Normal
Secondary Findings	N/A

Mitral Valve

Circumference	8.5 cm
Primary Findings	Normal
Secondary Findings	N/A

Aortic Valve

Circumference	6.0 cm
Primary Findings	Normal

Pulmonic Valve

Circumference	6.5 cm
Primary Findings	Normal

Secondary Findings	Other, see comment	Secondary Findings	N/A

Coronary Circulation Findings:

Coronary Circulation Dominance	Right
Narrowing of Left Coronary Artery	10 %
Narrowing of Left Circumflex	10 %
Narrowing of Right Coronary Artery	10 %
Narrowing of Posterior Coronary Artery	10 %

MICROSCOPIC EVALUATION:

The section through the coronary arteries revealed focal eccentric fibrointimal hyperplasia resulting in approximately 10-20% luminal narrowing (image#11).

Sections through the myocardium reveal patchy areas of slight myofiber hypereosinophilia. In these areas it is difficult to determine wether the observed changes represent true ischemic injury or represents a subtle staining variation (images #12, 13). However, definite areas of contraction band necrosis with early myocyte nuclear degeneration are seen, primarily in the left ventricle. For example, the superior left ventricle section taken to include the left ventricle and aortic valve(images #13-15) contains foci of contraction band necrosis. Patchy interstitial hemorrhage is also appreciated, but is quite mild.

In addition, there are patchy areas of old/remote replacement-type (see section of myocardial defects 2 and 7; images 16, 17, 21) and patchy interstitial (see section of myocardial defect 3; image 20) fibrosis in the left ventricle. The small foci are suggestive of a previous small infarct (see section of myocardial defect 2) that has healed by fibrosis. The small focus of replacement-type fibrosis in myocardial defect 7 is surrounded by myocytes showing contract band necrosis and focal nuclear dissolution. There are also wavy myofibers (images #18 and #19).

Finally, the are abnormally-shaped vessels with hyper- and abnromal muscularization of the wall, which results in luminal narrowing. In some vessels it is difficult to distinguish arteries from veins, but the former is favored. Additional studies would be needed for further characterization.

DIAGNOSIS:

DONOR HEART, CARDIECTOMY (509 GMS):
A. MINIMAL TO MILD CORONARY ARTERY ATHEROSCLEROSIS WITH ~10 - 20% LUMINAL NARROWING (SEE GROSS DESCRIPTION AND IMAGE #11).
B. LEFT ATRIAL PLAQUE WITH NIPPLE (SEE IMAGE #5; SEE COMMENTS).
C. MILD ATHEROSCLEROTIC CHANGES OF AORTIC ROOT AND VALVE
D. FOCI OF REPLACEMENT-TYPE FIBROSIS INVOLVING THE PAPILLARY MUSCLES IN THE LEFT VENTRICLE (SEE IMAGE#16) WITH NEARBY CONTRACTION BAND NECROSIS AND MYOCYTE NUCLEAR DISSOLUTION (IMAGES #21 AND #22; SEE COMMENT).
E. FOCI OF ISOLATED CONTRACTION BAND NECROSIS AND WAVY MYOFIBERS, INDICATIVE OF ISCHEMIC INJURY (SEE MICROSCOPIC DESCRIPTION AND COMMENT).

E. OCCASIONAL VESSELS, PROBABLY ARTERIES WITH FIBRO-INTIMAL HYPERPLASIA ABNORMAL MURAL MUSCULARIZAITON AND LUMINAL NARROWING (IMAGES #23, 24, 25; SEE COMMENT).

COMMENTS:
Although the coronary arteries showed only mild, non-occlusive atherosclerotic change, there were several small foci of replacement-type fibrosis located mostly in the papillary muscles and subendocardial of the left ventricle, which was also slightly thickened (1.6 cm). These foci likely represent remote and healed/fibrotic "micro-infarcts". In addition, there was definite evidence of recent ischemic injury including myocyte hyper- eosinophilia, contraction band necrosis, and focal coagulative-type necrosis with early nuclear dissolution, suggestive of an insult of approximately 12 to 24 hours before histopathologic examination. It is difficult, however, to precisely time the insult because of the relative paucity of leukocytes in the perfusion solution and some anticoagulation, both of which would contribute to the evolution of the histopathological findings associated with ischemic injury.

The underlying cause(-s) of the pre-existing (old) areas of replacement-type fibrosis without significant coronary artery disease is uncertain. No evidence of active inflammatory coronary arteritis was seen. However, several penetrating vessels, which were assumed to be arteries (but veins cannot be excluded) show mis-shapened and hypertrophied walls that resulted in luminal narrowing (image #25). It is uncertain whether these vessels were the cause or the result of the small areas of scarring and replacement-type fibrosis. The former is favored, but perhaps both possibilities contributed. Moreover, some of the worst areas of definite acute myocyte ischemic injury are located immediately adjacent to the older areas of scarring.

Possible causes of the changes would include foci of fibromuscular dysplasia; patchy microinfarcts and interstitial fibrosis can also be seen with cocaine use (J Clin Pathol 2008;61:848-850) and with other causes of arterial vasospasm. Correlation with the donor profile might provide additional useful information.

Finally, the nature or origin of the perfectly round plaque/patch (image #5) in the left atrium is uncertain, but likely related to a previous procedure.

Notes from Grossing:
1) Left atrium had plaque inside with nipple (see image)
2) atherosclerosis on aortic root and valve
3) petechia near/under aortic valve
4) heart over all small, deformed from fixation

Additional Cassettes Taken:
Myo Defect 1 - Left Anterior Ventricle
Myo Defect 2 - Left Lateral Ventricle
Myo Defect 3 - Left Posterior Ventricle
Myo Defect 4 - Anterior Inferior Left Ventricle (discoloration/hemorrhaging)

Additional sections taken on 10/28/19:
Myo Defect #5 - anterior inferior left ventricle
Myo Defect #6 - posterior inferior left ventricle
Myo Defect #7 - left lateral inferior wall
Myo Defect #8 - septum
Myo Defect #9 - anterior apex
Myo Defect #10 - anterior left ventricle mid portion

Case Completed: (b)(4)
Pathologist: (b) (6)

Case Updated: (b)(4)
Pathologist: (b) (6)

Report Prepared by: (b) (6)
Date (b)(4)

(b) (6)

01/16/2020

RE: Pathology Report from Turned Down Heart – Transmedics EXPAND CAP or Heart DCD Trial

UNOS ID: (b) (6)
Explant Date: (b) (6)
Barcode Number: (b) (6)

GROSS EVALUATION:

Shape/Size Characteristics:

Overall Shape	Normal
Height	5.5 cm
Width	11.0 cm
Length	14.0 cm
Weight	463.02 g

Anatomical Evaluation:

Epicardial Surface	Other, see comment

Right Atrium

Primary Findings	Normal
Secondary Findings	N/A
Interventricular Septal Thickness	1.2 cm

Left Atrium

Primary Findings	Normal
Secondary Findings	N/A

Right Ventricle

Thickness	0.5 cm
Primary Findings	Normal
Secondary Findings	N/A

Left Ventricle

Thickness	1.3 cm
Primary Findings	Normal
Secondary Findings	N/A
Posterior Wall Thickness	1.3 cm

Tricuspid Valve

Circumference	8.0 cm
Primary Findings	Normal
Secondary Findings	N/A

Mitral Valve

Circumference	9.0 cm
Primary Findings	Normal
Secondary Findings	N/A

Aortic Valve

Circumference	6.0 cm
Primary Findings	Other, see comment
Secondary Findings	N/A

Pulmonic Valve

Circumference	5.5 cm
Primary Findings	Normal
Secondary Findings	N/A

Coronary Circulation Findings:

Coronary Circulation Dominance	Right
Narrowing of Left Coronary Artery	10 %
Narrowing of Left Circumflex	10 %
Narrowing of Right Coronary Artery	10 %
Narrowing of Posterior Coronary Artery	10 %

MICROSCOPIC EVALUATION:

Sections through the coronary arteries reveal minimal uncomplicated fibro-intimal hyperplasia/atherosclerosis resulting about 10% luminal narrowing.

Sections through the myocardial defects, especially defect #7 (left anterior ventricle) shows large foci of ischemic myocardial injury manifest as hypereosinophilia, widespread contraction band necrosis, early coagulative necrosis, nuclear pyknosis, focal nuclear loss, and cytoplasmic dissolution (images 11 - 14). There is also foci of interstitial edema and wavy myofibers. Contraction band necrosis is also seen in defect #6 (left lateral ventricle; IMAGE #15). However, very little inflammation is seen in or near the foci of ischemic myocyte injury, which might be related to the composition of the perfusate.

DIAGNOSIS:

DONOR HEART, CARDIECTOMY (463.02 GMS):
A. MINIMAL UNCOMPLICATED CORONARY ARTERY ATHEROSCLEROSIS RESULTING IN ~10% LUMINAL NARROWING.
B. PATCHY INTERSTITIAL HEMORRHAGE, MORE PROMINENT IN THE SUBENDOCARDIUM.
C. WIDESPREAD PRIMARILY ISCHEMIC MYOCYTE INJURY MANIFEST AS FOCI OF MYOFIBER HYPEREOSINOPHILIA, INTERSTITIAL EDEMA, CONTRACT BAND NECROSIS, EARLY COAGULATIVE NECROSIS WITH FOCAL NUCLEAR LOSS AND EARLY CYTOPLASMIC DISSOLUTION, PRIMARILY INVOLVING THE LEFT ANTERIOR AND LEFT LATERAL VENTRICLES.

COMMENTS:

Despite minimal, clinically insignificant, uncomplicated coronary artery atherosclerotic changes, sections through grossly recognizable ventricular defect (especially left anterior and left lateral ventricular free wall) reveal interstitial edema, wavy myofibers, extensive, primarily contract band necrosis, early coagulative-type necrosis, but minimal evidence of neutrophilic or monocytic inflammation. Many ischemically damaged myocytes show nuclear pyknosis and others have lost nuclei. There is also focal, early dissolution of the myocyte cytoplasm. These findings suggest an ischemic insult between 8 and 24 hours before heart fixation and histopathological sampling. However, the histopathological dating might not be accurate considering the nature of the perfusate (less neutrophils and anti-coagulation). The interstitial hemorrhage is focally prominent, mostly subendocardial, and this is frequently associated with myocyte injury (see gross images # 1 - 3). Similar changes might be seen, or worsened by, coronary occlusion/global ischemia, resuscitation attempts, catecholamine excess/aggresive inotrope use, intra-cranial hemorrhage, potassium or magnesium deficiency, electric shock, cobalt

administration, and a wide variety of drugs (e.g. cocaine, polymyxin, neomycin, streptokinase, trypsin, and papain). Correlation with clinical sequence of events is suggested.

Notes from Grossing:
1) May be a portion missing?
2) Epidural surface whas hemorrhagic
3) Key for CoArtCSXS:
  -- red: LAD
  -- black: right
  -- orange: left circumflex
4) Aortic valve is tricuspid
5) Additional Cassettes:
  -- MyoDefect 1: Post Left Ventricle
  -- MyoDefect 2: Left lateral ventricle
  -- MyoDefect 3: Left anterior ventricle
  -- MyoDefect 4: Left anterior ventricle near apex

Case Completed: (b)(4)
Pathologist: (b) (6)

Report Prepared: (b)(4)
Lab Member: (b) (6)

(b) (6)

10/29/2019

RE: Pathology Report from Turned Down Heart – Transmedics EXPAND CAP or Heart DCD Trial

UNOS ID: (b) (6)
Explant Date: (b) (6)
Barcode Number: (b) (6)

GROSS EVALUATION:

Shape/Size Characteristics:

Overall Shape	Normal
Height	8.0 cm
Width	12.0 cm
Length	13.0 cm
Weight	525.05 g

Anatomical Evaluation:

Epicardial Surface	Other, see comment

Right Atrium

Primary Findings	Normal
Secondary Findings	N/A
Interventricular Septal Thickness	1.0 cm

Left Atrium

Primary Findings	Normal
Secondary Findings	N/A

Right Ventricle

Thickness	0.5 cm
Primary Findings	Normal
Secondary Findings	N/A

Left Ventricle

Thickness	1.7 cm
Primary Findings	Other, see comment
Secondary Findings	
Posterior Wall Thickness	1.7 cm

Tricuspid Valve

Circumference	8.0 cm
Primary Findings	Normal
Secondary Findings	N/A

Mitral Valve

Circumference	8.5 cm
Primary Findings	Normal
Secondary Findings	N/A

Aortic Valve

Circumference	6.5 cm
Primary Findings	Normal
Secondary Findings	N/A

Pulmonic Valve

Circumference	6.5 cm
Primary Findings	Normal
Secondary Findings	N/A

Coronary Circulation Findings:

Coronary Circulation Dominance	Right
Narrowing of Left Coronary Artery	10 %
Narrowing of Left Circumflex	10 %
Narrowing of Right Coronary Artery	10 %
Narrowing of Posterior Coronary Artery	10 %

MICROSCOPIC EVALUATION:

Sections from the myocardial defects (esp. defects #3 and #4 from the left anterior lateral and left anterior ventricle), but also from the right ventricle and interventricular septum show easily recognizable myofiber hypereosinophilia, intertitial edema, and large areas of contraction band necrosis with nuclear pyknosis and myocyte fragmentation and dissolution (myocytolysis). In some areas the myocyte damage is worse immediately subjacent to the endocardium, but significant damage can be seen throughout the muscular wall thickness, especially in the left ventricular defects (#3 and #4).

Representative sections through the coronary arteries show focal mild (<15%) non-concentric fibro-intimal hyperplasia noticed on both the gross and microscopic examination.

DIAGNOSIS:

DONOR HEART, CARDIECTOMY (525 GMS):
A. MILD CORONARY ARTERY ATHEROSCLEROSIS WITH < 15% LUMINAL NARROWING (SEE GROSS AND MICROSCOPIC ANATOMICAL EVALUATION).
B. LARGE AND WIDESPREAD AREAS OF ISCHEMIC-TYPE CARDIAC MYOCYTE INJURY WITH CONTRACTION BAND NECROSIS, NUCLEAR PYKNOSIS AND NUCLEAR AND MYOCYTE FRAGMENTATION AND DISSOLUTION (MYOCYTOLYSIS) THAT IS MOST PRONOUNCED IN THE LEFT ANTERIAL AND LEFT ANTERIOR LATERAL VENTRICLE, BUT SMALL AREAS ALSO PRESENT IN THE INTERVENTRICULAR SEPTUM AND RIGHT VENTRICLE (SEE MICROSCOPIC DESCRIPTION AND COMMENT).
C. PATCHY FOCI OF INTERSTITIAL HEMORRHAGE.

COMMENTS:

Notes from Grossing:
1) Epidural Surface had noticeable hemorrhages.
2) Left Ventricle had hemorrhagic mottling of septum, interior, posterior, and lateral walls.
3) Myocardial Defect Sections Taken:
    1 - Left Posterior Ventricle
    2 - Left Lateral Ventricle
    3 - Left Anterior Lateral Ventricle
    4 - Left Anterior Ventricle

The timing of the insult based on morphology is difficult to determine because of the paucity of monocytes and neutrophils in the perfusate. However, definite large areas of myofiber hypereosinophilia, interstitial edema, contraction band necrosis, and wavy myofibers are seen. Many hypereosinophlic myocytes showing contraction band necrosis are devoid of nuclei and some myocytes are undergoing fragmentation and dissolution (myocytolysis). These findings suggest that the ischemic insult occured

between > 12 - 18 hrs before tissue fixation and subsequent sampling. However, the histopathological timing of the injury might have been influenced by the paucity of neutrophils and monocytes in the perfusate: this might retard the development and thus the timing of changes because of less neutrophilic and monocytic enzymes released into the tissues.

Case Completed: (b)(4)
Pathologist: (b) (6)

Report Prepared by: (b) (6)
Date: (b)(4)

(b) (6)

01/21/2020

RE: Pathology Report from Turned Down Heart – Transmedics EXPAND CAP or Heart DCD Trial

UNOS ID: (b) (6)
Explant Date: (b) (6)
Barcode Number: (b) (6)

GROSS EVALUATION:

Shape/Size Characteristics:

Overall Shape	Normal
Height	5.5 cm
Width	9.0 cm
Length	8.0 cm
Weight	270.21 g

Anatomical Evaluation:

Epicardial Surface	Petechiae

Right Atrium

Primary Findings	Normal
Secondary Findings	N/A
Interventricular Septal Thickness	1.3 cm

Left Atrium

Primary Findings	Normal
Secondary Findings	N/A

Right Ventricle

Thickness	0.5 cm
Primary Findings	Normal
Secondary Findings	N/A

Left Ventricle

Thickness	1.4 cm
Primary Findings	Other, see comment
Secondary Findings	N/A
Posterior Wall Thickness	1.4 cm

Tricuspid Valve

Circumference	0.3 cm
Primary Findings	Normal
Secondary Findings	N/A

Mitral Valve

Circumference	8.0 cm
Primary Findings	Normal
Secondary Findings	

Aortic Valve

Circumference	6.0 cm
Primary Findings	Normal
Secondary Findings	N/A

Pulmonic Valve

Circumference	4.5 cm
Primary Findings	Normal
Secondary Findings	N/A

Coronary Circulation Findings:

Coronary Circulation Dominance	Right
Narrowing of Left Coronary Artery	15 %
Narrowing of Left Circumflex	15 %
Narrowing of Right Coronary Artery	15 %
Narrowing of Posterior Coronary Artery	15 %

MICROSCOPIC EVALUATION:

The sections through the coronary arteries revealed focal eccentric fibrointimal hyperplasia resulting in approximately 20% luminal narrowing (image #3) in the left anterior descending coronary artery.

Sections through the myocardium reveal patchy areas of interstitial hemorrhage, which in some regions are subendocardial and associated with myofiber hypereosinophilia and contraction band necrosis (e.g image #4). There are also relatively large areas of myofiber hypereosinophilia, wavy myofibers, and contraction band necrosis near the epicardial and endocardial surfaces (myocardial defects #1, 2; images # 8 - 14). Some of the necrotic myocytes show nuclear and focal cytoplasmic dissolution/loss with slight margination of PMNs (image #19), but minimal interstital inflammation is seen. Myocardial defect #3 shows more substantial subepicardial hemorrhage, whereas myocardial defect #4 shows more substantial subendocardial hemorrhage.

DIAGNOSIS:

DONOR HEART, CARDIECTOMY (270 GMS):
A. MILD CORONARY ARTERY ATHEROSCLEROSIS WITH ~20% LUMINAL NARROWING IN THE WORST AREAS (LEFT ANTERIOR DESCENDING CORONARY ARTERY; SEE GROSS DESCRIPTION AND IMAGE #3).
B. PATCHY FOCI OF SUBENDOCARDIAL (image #17) AND SUBEPICARDIAL (image #15) INTERSTITIAL HEMORRHAGE.
C. LARGE FOCI OF CONTRACTION BAND NECROSIS WITH FOCAL NUCLEAR AND EARLY CYTOPLASMIC DISSOLUTION, AND INTERSTITIAL EDEMA PRIMARILY INVOLVING THE LEFT ANTERIOR LATERAL WALL NEAR THE APEX (MYOCARDIAL DEFECT #1 AND #2; images #8 - 14)).

COMMENTS:

The coronary arteries showed only mild, non-occlusive, uncomplicated atherosclerotic change. However, there are relatively large areas of subepicardial and subendocardial interstitial hemorrhage. There is also definite evidence of recent ischemic injury including myocyte contraction band necrosis, wavy myofibers, nuclear and early cytoplasmic dissolution, interstitial edema and hemorrhage, but without significant inflammation. These findings are suggestive of an ischemic insult of approximately 12 to 24 hours before histopathologic examination. It is difficult, however, to precisely time the insult because of the relative paucity of leukocytes in the perfusion solution and some anticoagulation, both of which would contribute to the evolution of the histopathological findings associated with ischemic injury. The interstitial hemorrhage might be related to the ischemic injury

COMMENTS FROM DAY OF GROSSING:
A) Heart arrived gross with evidence of sections missing - observation herein provided based on what is present
B) Left ventricle had area of subendocardial hemorrhage (MyoDefect 4)
C) Key for MyoDefects sampled:

(1) Left anterior lateral wall near apex
(2) Left anterior ventricle apex
(3) Septum Mid-portion
(4) Left ventricle area of subendocardial hemorrhage

Case Completed: (b)(4)
Pathologist: (b) (6)

Report Prepared: (b)(4)
Lab Member: (b) (6)

Corrected Report Issued: (b)(4)
Lab Member: (b) (6)
Nature of Correction: IV septal thickness corrected from 0.3 cm to 1.3 cm. A data entry error occurred during database input. Diagnosis was not altered.

APPENDIX H: Post-Approval Study

Executive Summary – OCS Heart Post Approval Study Considerations

Note: The inclusion of a Post-Approval Study section in this summary should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA. The presence of a post-approval study plan or commitment does not alter the requirements for premarket approval and a recommendation from the Panel on whether the benefits of the device outweigh the risks. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered. The issues noted below are FDA's comments regarding potential post-approval studies, for the Panel to include in the deliberations, should FDA find the device approvable based upon the premarket data.

If the OCS Heart System is approved, FDA recommends that additional data collection be required as a condition of approval for this first of a kind device, to evaluate the short, mid, and long-term (through 5 years) safety and effectiveness outcomes such as patient survival and graft survival. TransMedics has proposed to conduct two post-approval studies to evaluate the performance of the OCS Heart if the device is approved as follows:

1. OCS Heart Post Approval Registry
2. OCS Heart EXPAND trial Post Approval Follow-Up Data Analysis

An overview of each post approval proposal is presented below followed by FDA comments.

1. <u>OCS Heart Post Approval Registry</u>

Study Objectives

The objective of this registry is to collect additional data on the use of the OCS™ Heart System in a post-approval and real-world setting.

Study Design and Study Population

This is a single-arm, prospective, multicenter, observational post-approval registry. Donors and recipients will be consistent with the approved indication for use and will reflect the eligibility criteria of the Heart EXPAND study. Patients will be followed 12 months post-transplantation. Patient outcomes will be evaluated months 24 - 60 post-transplantation by accessing data from the UNOS database.

The UNOS Donor IDs for all transplanted patients in the Heart EXPAND trial will be submitted to OPTN/SRTR to obtain clinical outcomes for years 2 through 5 post-transplantation.

Study Primary Endpoints and Hypothesis

The 12-month patient survival from cardiac graft related death (freedom from cardiac graft-related death) post transplantation with a donor heart preserved on the OCS Heart Systems will be greater than a performance goal (PG) based on the OPTN survival estimate of 98% and a margin of 12%, resulting in a PG of 86% (i.e. 98%-12% = 86%).

The hypothesis is stated as follows:

$H0: \pi OCS \leq 86\%$
$Ha: \pi OCS > 86\%$

where πOCS is the true freedom from cardiac graft-related death for subjects transplanted using the OCS Heart System in the post-approval study, and 86% is the performance goal.

The national average for survival reflects standard criteria donor hearts preserved on cold storage, while recipients in the registry will receive extended criteria donor hearts. Thus a 12% margin was proposed that resulted in a PG of 86%.

Safety Endpoints

The following safety endpoints will be assessed within 30 days post-transplant to allow comparison with standard UNOS statistics as well as results of the EXPAND study:

Incidence of:

- Patient death (all cause)
- Primary graft failure requiring re-transplantation

Other Endpoints

Additional endpoints include the following:

- Freedom from cardiac graft-related death (1, 24, 36, 48 and 60 months), and the following outcomes at 1, 12, 24, 36, 48 and 60 months:
    - Freedom from all-cause death
    - Freedom from re-transplantation
- Donor heart utilization rate, defined as the number of eligible donor hearts successfully transplanted divided by the total number of eligible donor hearts preserved on the OCS Heart System

Schedule of Assessments and Data Collection

Tables H.1 and H.2 show the schedule of assessments and data collection for the donor and recipients, respectively.

Table H.1: Donor Schedule of Assessments

Evaluations	Data Collected
Donor Organs UNOS ID	X
Demographics/Risks factors*	X
Eligibility	X
Donor Medical/Social History	X
Donor Cause of Death	X
Cross Clamp Time	X
OCS Trend File	X
Clinical reasons for donor heart not transplanted after OCS™ Heart System Preservation (if applicable)	X
*Donor risk factors include luminal irregularities, downtime, LV septal wall thickness, LVEF	

Table H.2: Recipient Schedule of Assessments

Evaluation	Characteristics & Risk Factors	0 to 30 Days	12 Months*
Informed Consent	X		
Donor organ & Recipient UNOS ID	X		
Demographic and Medical History	X		
Eligibility	X		
Primary Etiology of Heart Failure (Indication for transplantation)	X		
Transplant Details	X	X	
Patient Survival	X	X	X
Graft Survival	X	X	X
*Recipient outcome data for 24, 36, 48, and 60 months follow-up will be obtained directly from UNOS database to minimize burden on participating sites and maximize registry enrollment.			

The following additional information will be assessed and collected for all PAS consented recipients who are transplanted with an OCS Heart System-preserved donor heart:

- Circulatory Mechanical Support: Document if the recipient is on mechanical circulatory support on the day of transplant
- Renal Status: Confirm that the patient is not on renal replacement dialysis, hemofiltration, or peritoneal dialysis

Enrollment and Follow-Up

Subjects that meet eligibility criteria will be enrolled in the registry. The inclusion/exclusion criteria for recipients and donors are as follows:

Donor Eligibility Criteria

Inclusion

- Expected total cross-clamp time of ≥ 4 hours; **OR**
- Expected total cross-clamp time of ≥ 2 hours **PLUS** one of the following risk factors:
  - Donor age 45-55 years old with no coronary catheterization data
  - Donor age ≥ 55 years old
  - Left ventricular septal or posterior wall thickness of > 12 ≤ 16 mm
  - Reported down time of ≥ 20 min, with stable hemodynamics at time of final assessment
  - Left heart ejection fraction (EF) ≥ 40 ≤ 50%
  - Donor angiogram with luminal irregularities with no significant coronary artery disease (CAD)
  - History of carbon monoxide poisoning with good cardiac function at time of donor assessment
  - Social history of alcoholism with good cardiac function at time of donor assessment
  - History of diabetes combined with negative coronary angiogram for CAD

Exclusion

- Angiogram proven CAD with > 50% stenosis
- Cardiogenic shock or myocardial infarction
- Sustained terminal EF of < 40%
- Significant valve disease except for competent bicuspid aortic valve
- Donor after circulatory death (DCD donor)

Recipient Eligibility Criteria

Inclusion

- Registered male or female primary Heart transplant candidate
- Age ≥ 18 years old
- Obtained consent and authorization to access and disclose protected health information

Exclusion

- Prior solid organ or bone marrow transplant
- Multi-organ transplant recipient
- Chronic use of hemodialysis or diagnosis of chronic renal failure requiring dialysis

Follow-up data collection will be conducted by phone (or office visit per the site standard of care) at 12 months (± 60 days) post-transplant for graft and patient survival status.

The UNOS database will be queried directly to obtain recipients outcomes data at 24, 36, 48 and 60 months.

Sample Size Determination

A total of 175 patients transplanted with OCS Heart System-preserved hearts will be enrolled at up to 35 US sites.

The sample size estimation is as follows: The estimated one-year freedom from cardiac graft-related death for standard criteria donor hearts in the US per the Organ Procurement Transplant Network (OPTN) is 98% by the Kaplan-Meier method. Given that the OCS Heart Registry will enroll donor hearts with one or more risk factors and considering the variability of the real-world clinical use environment, a 12% margin is proposed, resulting in a performance goal of 86%. Using the assumptions below:

- Two-sided alpha = 0.1
- Power = 80%
- True proportion = 0.93

A sample size of 135 subjects is required and provides approximately 80% power based on the exact method for a single binomial proportion. The sample size is increased to 175 to allow for the potential enrollment of subjects that do not meet eligibility criteria. Missing outcomes for the primary endpoint assessment are not expected.

Statistical Methods

Analysis Populations

There will be two analysis populations:

1) Primary Analysis Population - defined as subjects who meet the recipient eligibility criteria and are transplanted with hearts that meet the donor eligibility criteria. All pre-specified hypothesis testing will be performed on this population when all recipients have completed 1 year of follow-up.

2) Full Analysis Population - defined as all recipients in the registry. All analyses will be repeated on the Full Analysis Population when these recipients have completed 12 months of follow-up, except that is no formal hypothesis testing is planned on this population.

Analysis of Endpoints

The comparator for the primary endpoint is a performance goal that is based on the current national average for heart transplant recipients who receive a standard criteria donor heart preserved on standard of care cold storage.

The primary endpoint of patient survival from cardiac graft-related death will be calculated based on the binomial method (simple proportion). The primary objective will be met if the

lower 90% exact binomial (Clopper-Pearson) confidence bound of the survival proportion exceeds the performance goal of 86%.

The safety endpoint results will be reported as descriptive statistics (n, mean, standard deviation, median, minimum, maximum, and 95% confidence interval based on the t-distribution).

Other endpoints such as freedom from cardiac graft-related mortality, and freedom from all-cause mortality through 60 months will be reported using Kaplan-Meier survival curves with survival estimates for all timepoints. Patients not having the event of interest will be censored at the date of last contact in the Kaplan-Meier estimate.

The incidence of re-transplantation will be estimated with 95% exact binomial (Clopper-Pearson) confidence intervals.

Donor heart utilization rate will be reported with descriptive statistics (n, mean, standard deviation, median, minimum, maximum, and 95% confidence interval based on the t-distribution).

Handling of Missing Data
Per the proposal, missing data (including lost to follow-up) for the primary endpoint are not expected. However, in order to report the most complete and accurate outcomes in this patient population, the UNOS database will be queried for outcomes for missing patients.

Adjudication of Data
A Clinical Event Committee (CEC) comprised of at least three (3) heart transplant experts will provide review of specific data throughout the OCS Heart Registry. The primary responsibility of the CEC is to review and adjudicate all primary causes of death in the trial through the first 12 months and determine cardiac graft-related deaths.

FDA Comments on the Proposed Registry

Study Objectives
FDA believes that if the device is approved (i.e., reasonable assurance of safety and effectiveness is demonstrated), additional device monitoring and surveillance is needed for this first-of-a-kind device, to provide a better understanding of device performance in a real world setting in the US population.

Study Design and Population
The proposed registry will lead to the collection of additional data on short and longer term (through 5 years) safety and effectiveness of the OCS Heart System for the preservation of extended criteria donor hearts. FDA agrees with TransMedics' proposal to leverage existing infrastructure, i.e., the UNOS registry, to monitor the device performance through surveillance. Since data on patient survival, cause of death, and other important endpoints are already being captured in the UNOS database, a surveillance approach is acceptable for addressing appropriate post-market questions.

Study Endpoint and Hypothesis

The primary endpoint for the proposed registry is patient survival from cardiac graft-related death at 12 months. In addition, the sponsor proposes to assess primary graft failure and patient death (all-cause) within the initial 30 days post-transplant as a safety endpoint. Other endpoints to be evaluated are freedom from cardiac graft-related death, freedom from all-cause death, freedom from re-transplantation through 5 years and donor utilization rate.

Cardiac graft-related death at 12 months was a non-adjudicated, post-hoc analysis performed by the sponsor for (b)(4). FDA's major concerns with the OCS Heart System are longer-term survival and injury to donor organs that might otherwise been well-preserved for transplant using standard of care cold static preservation. As such, FDA recommends evaluating *both* patient survival and graft survival at 1 year as a composite primary endpoint.

The applicant proposes to conduct a hypothesis test to demonstrate that 12-month patient survival from cardiac graft-related death in this registry study is greater than a performance goal (PG) of 86%. The proposed PG is based on OPTN data of 1-year freedom from cardiac graft-related death for standard criteria donor hearts preserved on cold storage (98%). TransMedics has proposed a margin of 12% from the U.S. national average for survival from cardiac graft related death at 1 year and this results in a PG of 86% (i.e.,98% -12%).

FDA does not believe that survival from cardiac graft-related death at 12 months is an appropriate primary endpoint for a post-approval study for the OCS Heart System. In addition, FDA also believes that a PG of 86% is inappropriately low since a post-hoc, unadjudicated analysis of cardiac graft-related survival at 12 months in the EXPAND Trial produced a 95% survival rate.

The Panel will be asked to discuss the proposed PAS, including whether the endpoints, the performance goal, and other follow-up assessments will provide a better understanding of OCS Heart device short and long-term safety and effectiveness of the in a real world setting.

Enrollment and Follow-up

At least 135 donors and recipients expected to enroll and be similar to patients enrolled in the EXPAND study. Although patient follow -up will be conducted by phone or office visit, the follow-up schedule did not include assessment at 6 months.

FDA recommends a 6 months post-transplant assessment (as was done in EXPAND).

Sample Size Determination

The OCS Heart Registry is expected to enroll a total 175 patients from up to 35 U.S sites. Of these patients, 135 would meet eligibility criteria for the heart EXPAND trial and reflect the approved indication for use of the device. Using PASS 2019 statistical software, a true cardiac graft-related survival of 93.3% at 1 year (and not 93% as stated in the proposal) and a 2-sided alpha of 0.01, a sample size of 135 patients will provide 80% power to evaluate the primary endpoint.

Analysis of Endpoints
The primary endpoint of patient survival from cardiac graft related death at 12-month will be tested against a PG of 86%. Per the applicant's proposal, missing outcomes for the primary endpoint are not expected. However, the applicant plans to query the UNOS database for outcomes of missing patients.

Although the applicant states that missing data are not expected, given the proportion of subjects lost-to-follow-up at 18 months in the EXPAND study, FDA recommends that sensitivity analyses be conducted to examine how missingness impacts the test results of the primary endpoint, if there is evidence of missing data for the primary endpoint.

Per the analysis plan, freedom from cardiac graft-related mortality, freedom from all-cause death and freedom from re-transplantation through 5 years will be analyzed using Kaplan Meier method. Incidence of re-transplantation at all timepoints through 60 months will be presented with 95% confidence interval (Clopper- Pearson) and donor utilization rate as descriptive statistics.

FDA agrees that that the outcomes for freedom from cardiac graft-related mortality, freedom from all-cause death and freedom from re-transplantation be presented as Kaplan Meier survival estimates, but these analyses should include the 95% confidence intervals.

2. OCS Heart EXPAND Post Approval Follow-Up Data Analysis

Study Objectives

The objectives of this post-approval study is to evaluate long-term outcomes of the OCS™ Heart EXPAND Trial subjects.

Study Design and Population

This is a single-arm, prospective, observational post-approval study in which outcomes obtained from the existing national Scientific Registry of Transplant Recipients (SRTR)/OPTN database for subjects transplanted in the Heart EXPAND Trial will be analyzed. The study population will be comprised of the 75 transplanted recipient population in the Heart EXPAND trial.

The UNOS Donor IDs for all transplanted patients in the Heart EXPAND trial will be submitted to OPTN/SRTR, and Central IRB approval will be obtained to access clinical outcomes for years 2, 3, 4 and 5 post-transplantation.

Study Primary Endpoint
The primary effectiveness endpoint is patient survival from cardiac graft-related death (freedom from cardiac graft-related mortality) through 5 years post-transplantation.

Other Endpoints

Additional endpoints to be evaluated from 2 through 5 years post-transplantation are the following:

- Patient survival (freedom from all-cause mortality) from 2 through 5 years post-transplantation
- Graft Survival (freedom from re-transplantation)

Enrollment, Sample Size and Follow-Up

There are no new enrollments for this study. This study will analyze all survival and re-transplant data available in the SRTR/OPTN database for subjects in the transplanted recipient population in the EXPAND study through 5 years post-transplant.

Statistical Analysis Plan

Kaplan Meier survival analysis results will be reported for the primary endpoint of patient survival from cardiac graft-related mortality through 5 years. The additional endpoints (patient survival from all-cause mortality and graft survival/freedom from re-transplant through 5 years post-transplant) will also be reported as Kaplan Meier survival analyses.

FDA Comments on the OCS Heart EXPAND Post Approval Follow-up Study

Study Design and Population

FDA agrees with leveraging transplant recipient data from the OCS Heart EXPAND trial to evaluate 5-year outcomes. Per the proposal, EXPAND transplant recipients in the OPTN/SRTR database will be identified, under a central IRB approval, using the UNOS Donor IDs to obtain long-term (2-5 years) outcome data. However, it is unclear if EXPAND patients were consented for 5-years of follow-up. TransMedics will need to obtain a new central IRB approval and reconsent the patients, if patients were not consented for 5-year follow-up, which could present challenges of selection bias, whereby the longer-term results could potentially contain fewer patients with less favorable outcomes.

Study Endpoints and Analyses

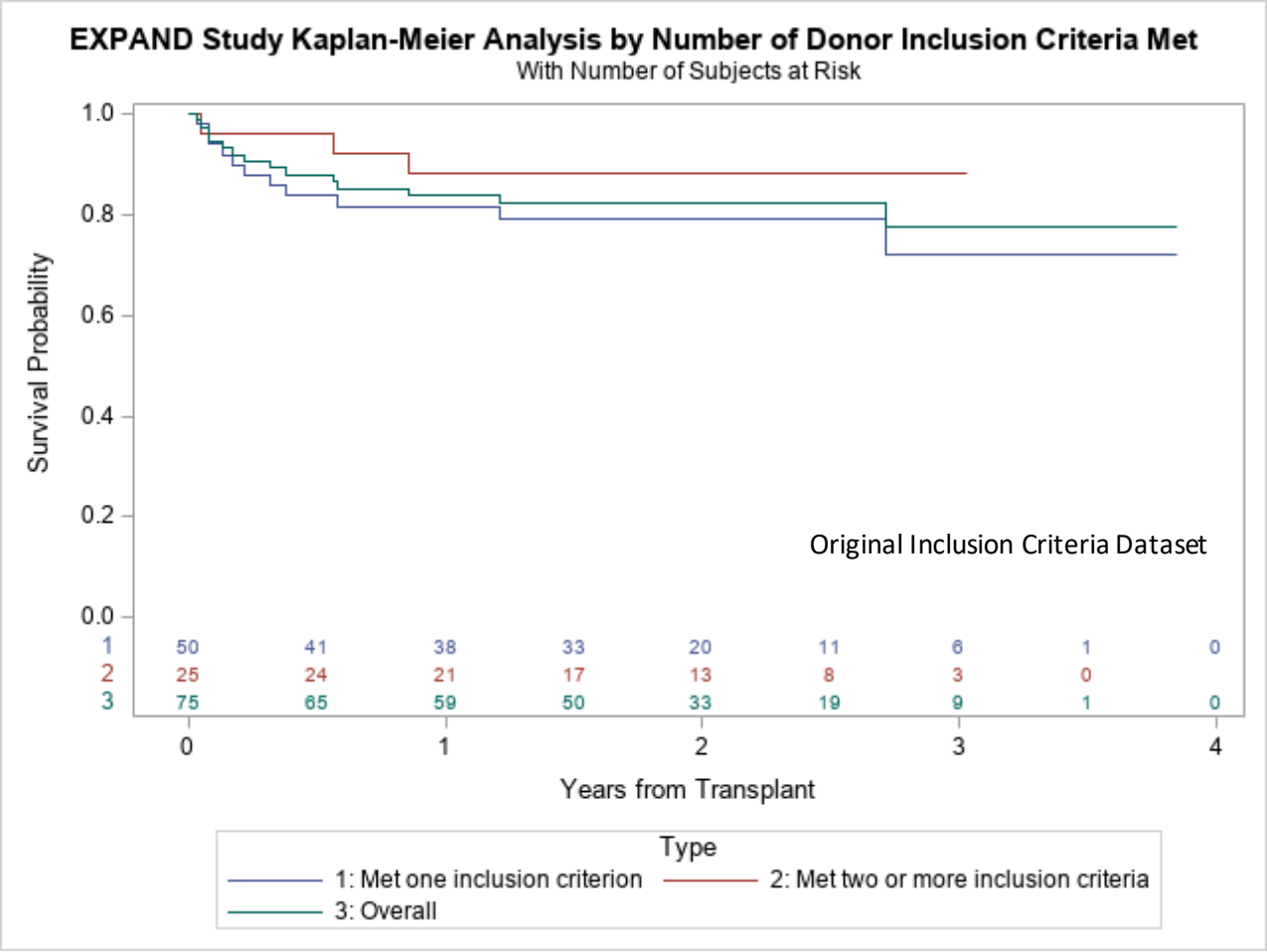
FDA agrees with the long-term endpoints of survival from cardiac graft-related death, patient survival (freedom from all cause-mortality), and graft survival as well as endpoint analysis using the with Kaplan Meier survival method. FDA recommends that the results be reported with confidence intervals for the KM estimates.

APPENDIX I: EXPAND Selected Post Hoc Subgroup Analyses

Post Hoc Analysis: Stratification by Donor Inclusion Criteria

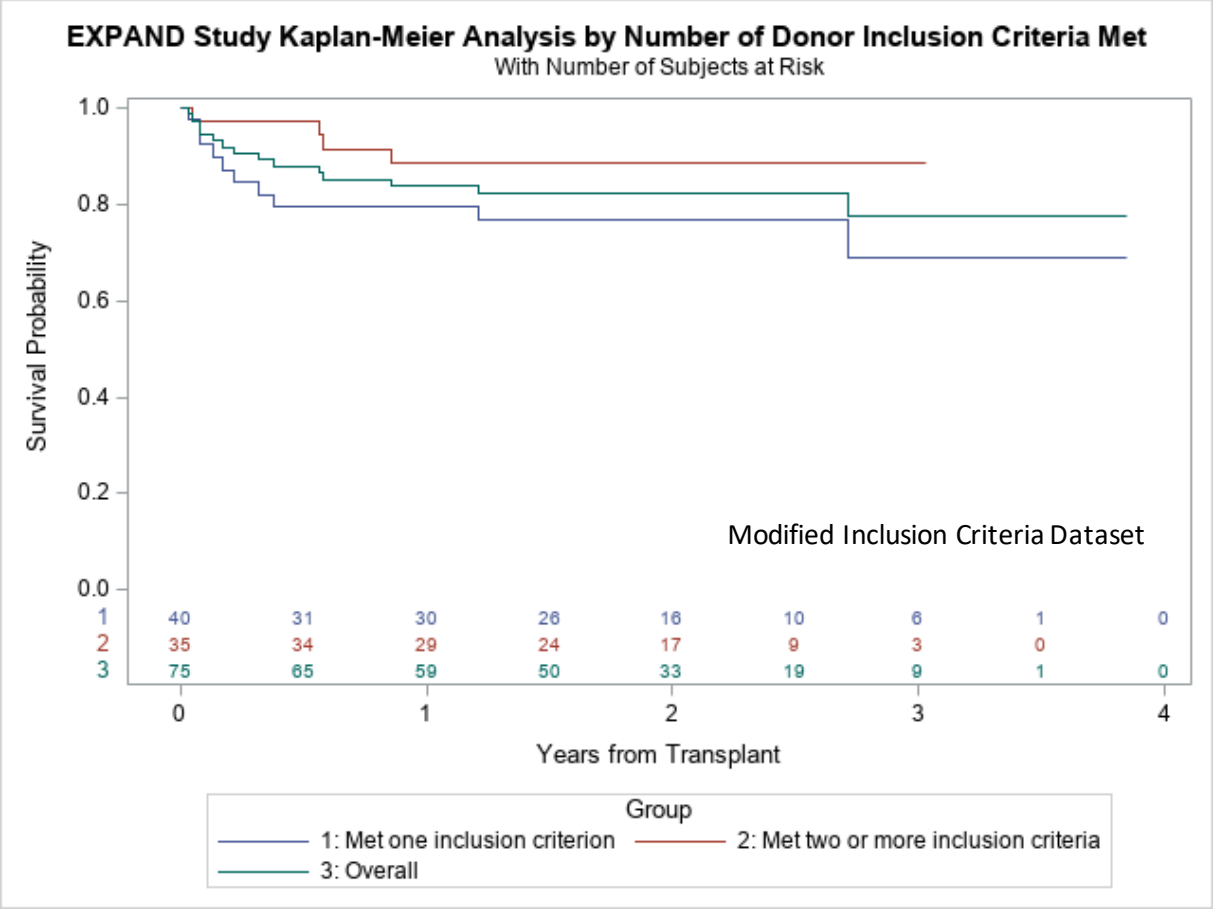
Using the investigator-identified inclusion criteria from the CRFs, FDA stratified survival by number of inclusion criteria met. Two-thirds of TR donor hearts (50/75) were single criterion donor organs, and the most common single criterion was ECCT ≥ 4.

Figure I.1– Kaplan-Meier EXPAND by Number of Donor Inclusion Criteria (Original) Met



FDA also evaluated survival trends stratified by number of inclusion criteria met using the sponsor's revised inclusion criteria dataset. The sponsor's revision shifted the proportion of single-criterion donor hearts in EXPAND downward to 53%. The revised analysis yielded somewhat decreased survival estimates in the first year for single-criterion donor organs, but multiple criteria donor organ survival did not change appreciably (Figure I.2).

Figure I.2 – Kaplan-Meier by Number of Donor Inclusion Criteria (Modified) Met



FDA-requested survival stratified by the individual inclusion criteria (modified inclusion criteria dataset). The sample sizes for some of the strata are very small, and inferences should be made with caution.

Multiple Criteria

Figure I.3 shows the aggregated survival of donor heart entered into the study with multiple criteria.

Figure I.3– Survival for Subjects with Multiple Criteria Donor Hearts

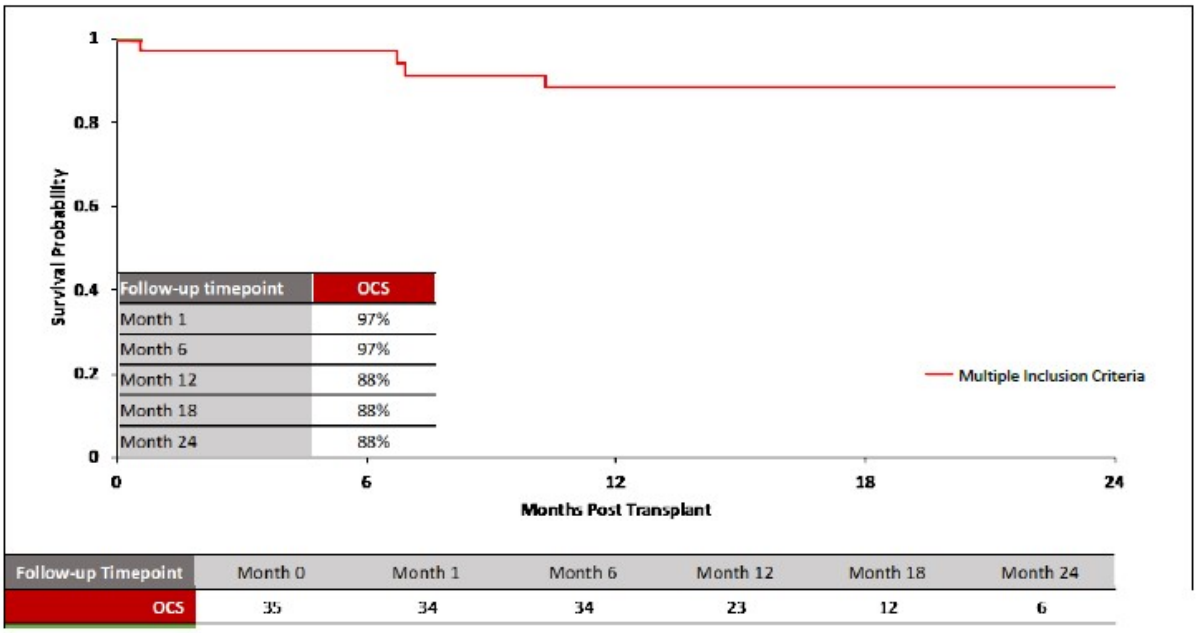
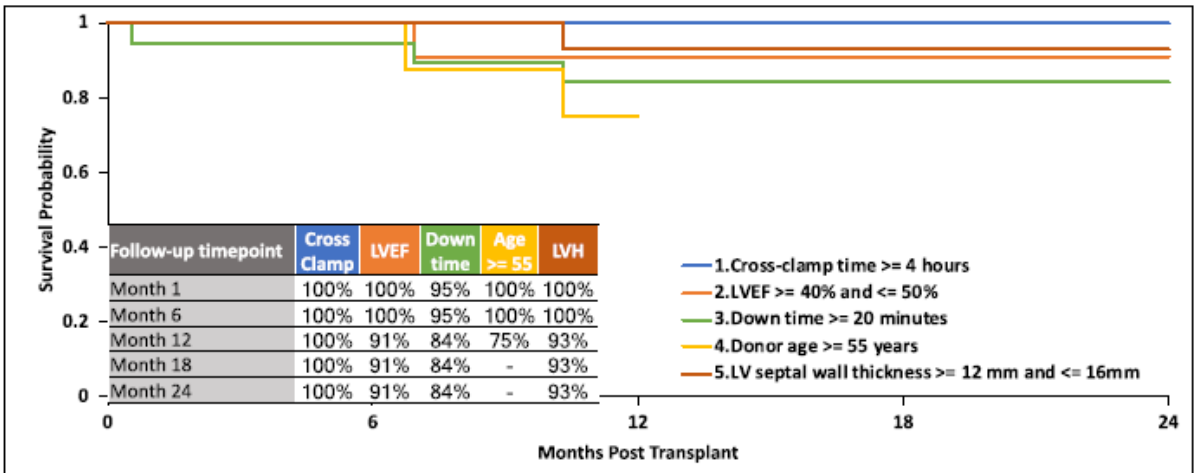


Figure I.4 stratifies the multiple criteria survival by presence of the indicated criterion.

Figure I.4 – Survival for Subjects with Multiple Criteria Donor Hearts, Stratified by Criterion



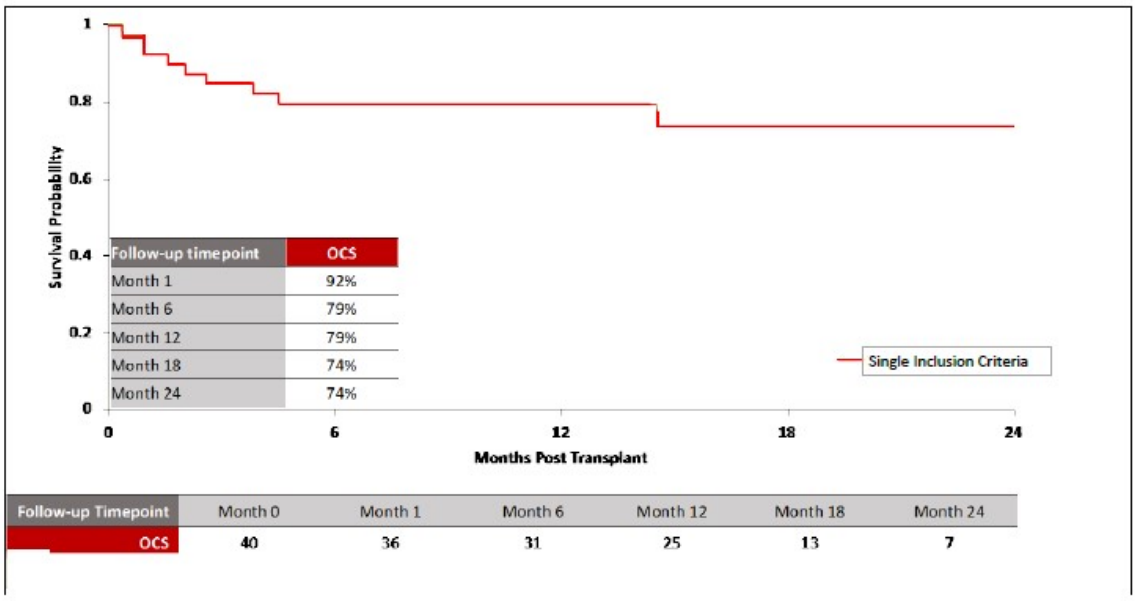
Follow-up timepoint	Cross Clamp	LVEF	Down time	Age >= 55	LVH
Month 1	100%	100%	95%	100%	100%
Month 6	100%	100%	95%	100%	100%
Month 12	100%	91%	84%	75%	93%
Month 18	100%	91%	84%	-	93%
Month 24	100%	91%	84%	-	93%

Subjects Remaining (Not Censored and Alive)						
Follow-up Timepoint	Month 0	Month 1	Month 6	Month 12	Month 18	Month 24
Cross-Clamp Time >= 4 hr	10	10	10	8	4	2
LVEF 40-50%	11	11	11	5	2	1
Downtime >= 20 min	19	18	18	14	7	4
Age >= 55	8	8	8	3	0	0
LVH	14	14	14	13	7	3

Single Criterion

Figure I.5 presents the aggregate survival of donor hearts entered into the study with a single criterion

Figure I.5 – Survival for Subjects with Single Criterion Donor Hearts (All)

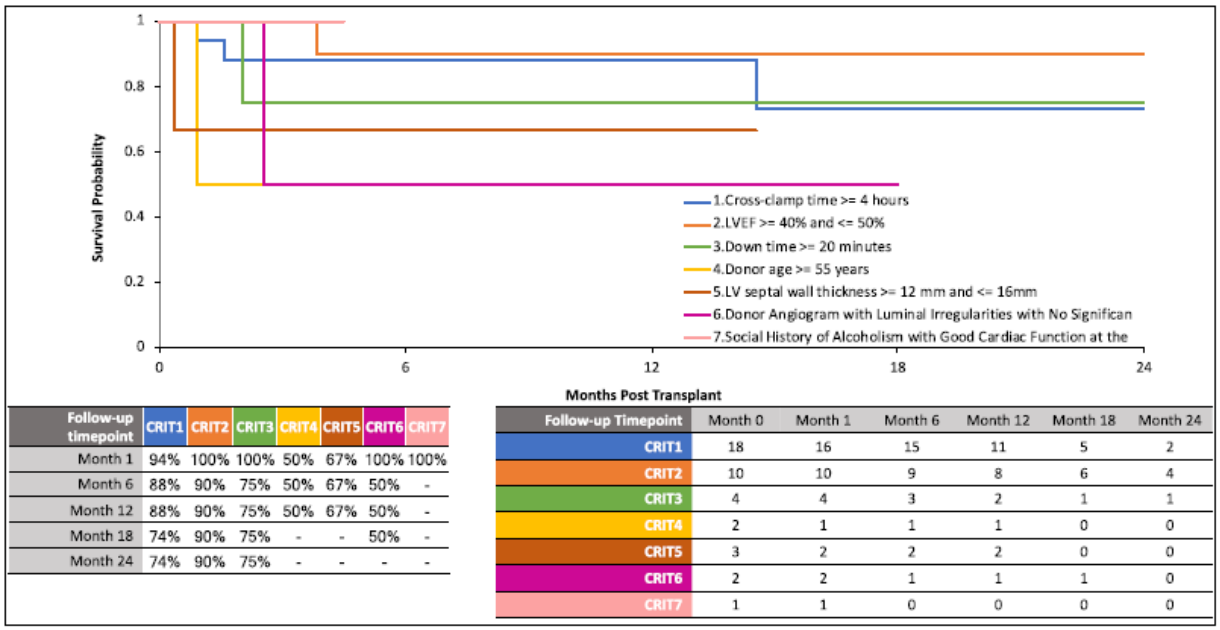


Follow-up timepoint	OCS
Month 1	92%
Month 6	79%
Month 12	79%
Month 18	74%
Month 24	74%

Follow-up Timepoint	Month 0	Month 1	Month 6	Month 12	Month 18	Month 24
OCS	40	36	31	25	13	7

Figure I.6 presents the survival stratified by the individual criterion.

Figure I.6 – Survival for Subjects with Single Criterion Donor Hearts, Stratified by Criterion



Follow-up timepoint	CRIT1	CRIT2	CRIT3	CRIT4	CRIT5	CRIT6	CRIT7
Month 1	94%	100%	100%	50%	67%	100%	100%
Month 6	88%	90%	75%	50%	67%	50%	-
Month 12	88%	90%	75%	50%	67%	50%	-
Month 18	74%	90%	75%	-	-	50%	-
Month 24	74%	90%	75%	-	-	-	-

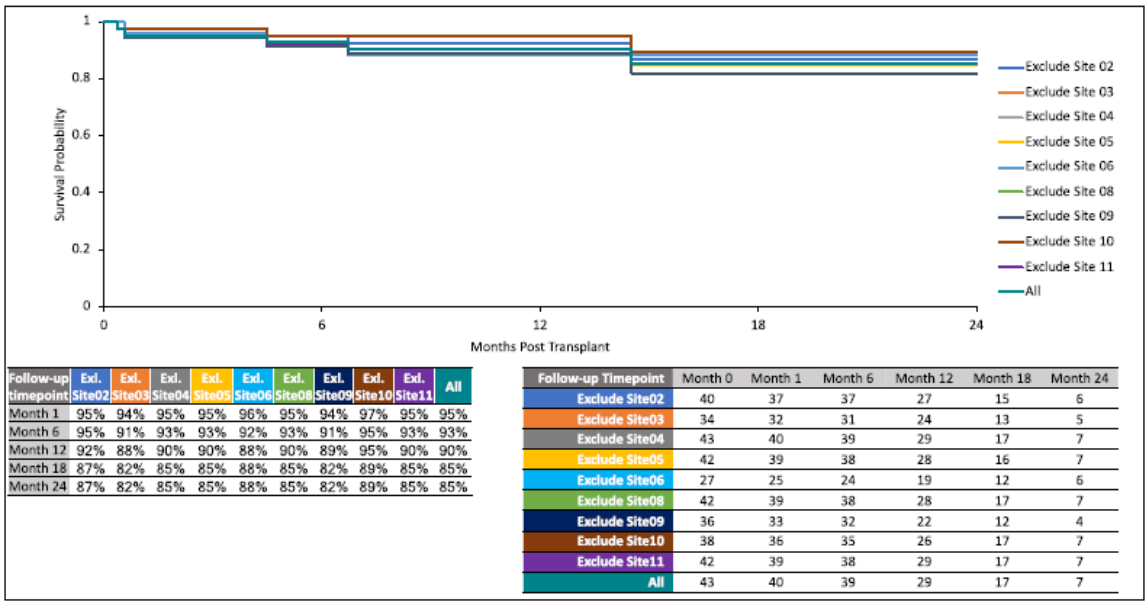
Follow-up Timepoint	Month 0	Month 1	Month 6	Month 12	Month 18	Month 24
CRIT1	18	16	15	11	5	2
CRIT2	10	10	9	8	6	4
CRIT3	4	4	3	2	1	1
CRIT4	2	1	1	1	0	0
CRIT5	3	2	2	2	0	0
CRIT6	2	2	1	1	1	0
CRIT7	1	1	0	0	0	0

Post Hoc Analysis: Stratification by Donor Preservation Time

FDA asked the sponsor to conduct a *post hoc* analysis using categorical groups defined by the mean/median cross-clamp times in this study (6 hours). The sponsor further stratified the analysis by censoring individual site's contribution, because there was a general site effect for survival (log-rank test, p=0.0185). The pre-specified poolability analysis, for the Primary Effectiveness Endpoint, determined no adjustment for site was necessary (p=0.8784, Fisher's exact test). The results are shown in Figures H.7 and H.8. Subjects who received donor hearts preserved > 6 hours had an 85% 2-year survival, and subjects with ≤ 6 hours preservation time had a 75% 2-year survival.

Cross-Clamp Time > 6 hours

Figure I.7– Survival for Donor Hearts with CCT> 6 hours

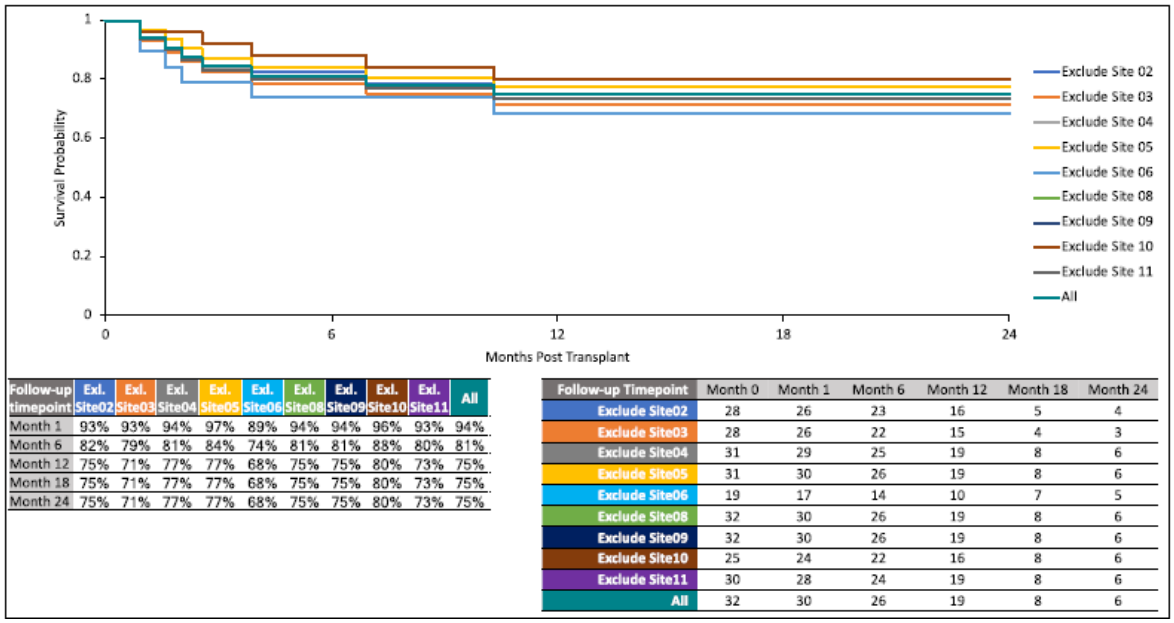


Follow-up timepoint	Excl. Site02	Excl. Site03	Excl. Site04	Excl. Site05	Excl. Site06	Excl. Site08	Excl. Site09	Excl. Site10	Excl. Site11	All
Month 1	95%	94%	95%	95%	96%	95%	94%	97%	95%	95%
Month 6	95%	91%	93%	93%	92%	93%	91%	95%	93%	93%
Month 12	92%	88%	90%	90%	88%	90%	89%	95%	90%	90%
Month 18	87%	82%	85%	85%	88%	85%	82%	89%	85%	85%
Month 24	87%	82%	85%	85%	88%	85%	82%	89%	85%	85%

Follow-up Timepoint	Month 0	Month 1	Month 6	Month 12	Month 18	Month 24
Exclude Site02	40	37	37	27	15	6
Exclude Site03	34	32	31	24	13	5
Exclude Site04	43	40	39	29	17	7
Exclude Site05	42	39	38	28	16	7
Exclude Site06	27	25	24	19	12	6
Exclude Site08	42	39	38	28	17	7
Exclude Site09	36	33	32	22	12	4
Exclude Site10	38	36	35	26	17	7
Exclude Site11	42	39	38	29	17	7
All	43	40	39	29	17	7

Cross-Clamp Time ≤ 6 hours

Figure I.8 – Survival for Donor Hearts with CCT≤ 6 hours



Follow-up timepoint	Excl. Site02	Excl. Site03	Excl. Site04	Excl. Site05	Excl. Site06	Excl. Site08	Excl. Site09	Excl. Site10	Excl. Site11	All
Month 1	93%	93%	94%	97%	89%	94%	94%	96%	93%	94%
Month 6	82%	79%	81%	84%	74%	81%	81%	88%	80%	81%
Month 12	75%	71%	77%	77%	68%	75%	75%	80%	73%	75%
Month 18	75%	71%	77%	77%	68%	75%	75%	80%	73%	75%
Month 24	75%	71%	77%	77%	68%	75%	75%	80%	73%	75%

Follow-up Timepoint	Month 0	Month 1	Month 6	Month 12	Month 18	Month 24
Exclude Site02	28	26	23	16	5	4
Exclude Site03	28	26	22	15	4	3
Exclude Site04	31	29	25	19	8	6
Exclude Site05	31	30	26	19	8	6
Exclude Site06	19	17	14	10	7	5
Exclude Site08	32	30	26	19	8	6
Exclude Site09	32	30	26	19	8	6
Exclude Site10	25	24	22	16	8	6
Exclude Site11	30	28	24	19	8	6
All	32	30	26	19	8	6