TransMedics®
Organ Care System™ (OCS) Heart System

FDA Presentation for the April 6, 2021
Cardiovascular Devices Advisory Panel Meeting

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FDA Review Team

Clinical	John Sapirstein, MD
Engineering	Bridget Wildt, PhD
Statistics	Xuan Ye, PhD
In Vivo	Diane Cordray, VMD
Sterilization/Packaging	Angel Soler-Garcia, PhD
Biocompatibility	Pushya Potnis, PhD
Software	Luke Ralston, MS/Matt Hazelett, BS
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Battery	Charles Ho, MS
Post-approval Study	George Aggrey, MD, MPH
Pathology	Andrew Farb, MD
GMP	Angela Dixon-Allamby
BIMO	Janette Collins-Mitchell

FDA Team Presenters

Catherine Wentz. MS Eng

- Device Description; Clinical/Regulatory History; Summary of Non-clinical information; Proposed PAS; Panel Discussion Questions

Xuan Ye, PhD

- Statistics

John Sapirstein, MD

- Clinical

Andrew Farb, MD

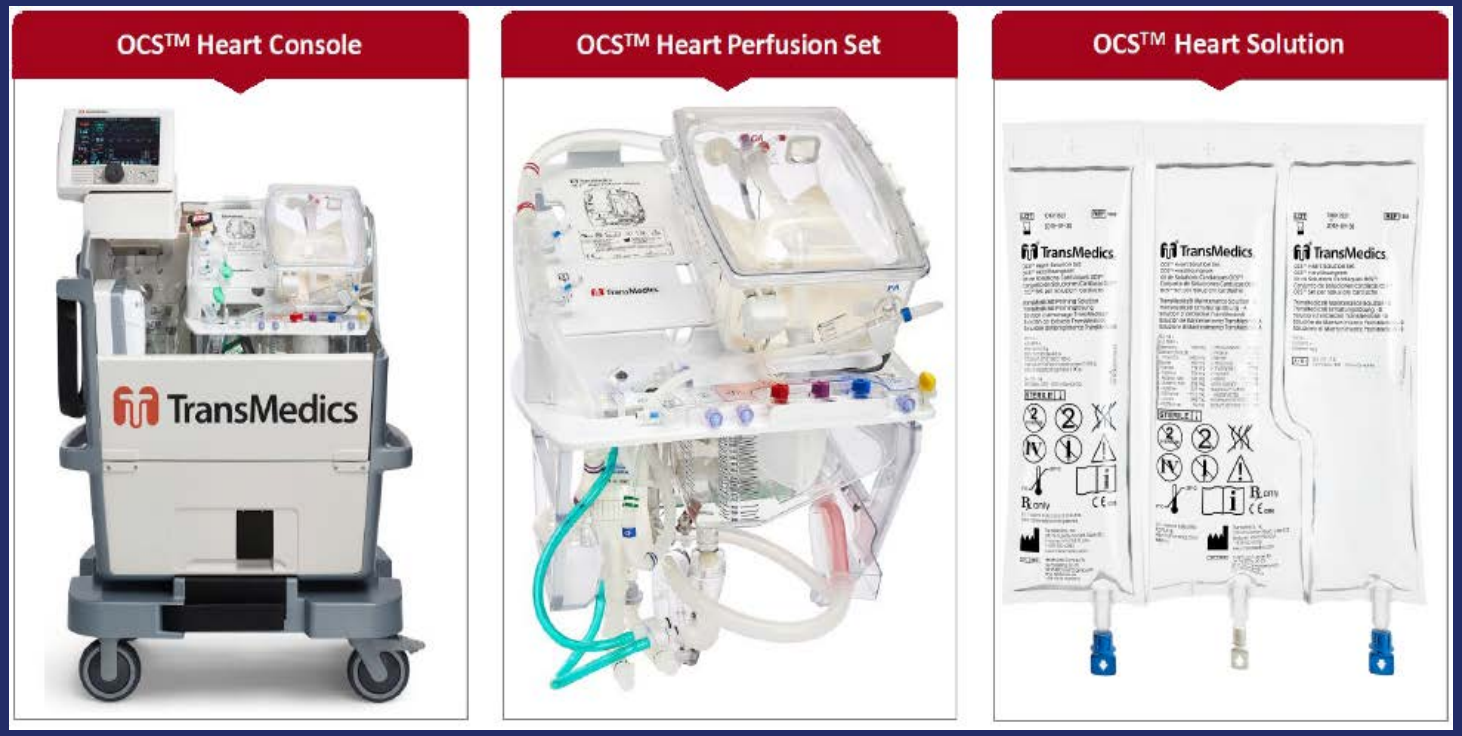
- Pathology

Fernando Aguel, MS Eng .- Assistant Division Director

- Clinical Summary

Device Description

- Console
- Heart Perfusion Set
- Heart Solution Set



Proposed Indications for Use

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

- Expected cross-clamp or ischemic time ≥ 4 hours due to donor or recipient characteristics (e.g., donor-recipient geographical distance, expected recipient surgical time); or
- Expected total cross-clamp time of ≥ 2 hours PLUS one of the following risk factors:
  - Donor Age ≥ 55 years; or
  - Donors with history of cardiac arrest and downtime ≥ 20 minutes; or
  - Donor history of alcoholism; or
  - Donor history of diabetes; or
  - Donor Left Ventricular Ejection Fraction (LVEF) ≤ 50% but ≥ 40%; or
  - Donor history of Left Ventricular Hypertrophy (LVH) (septal or posterior wall thickness of > 12 ≤ 16 mm); or
  - Donor angiogram with luminal irregularities but no significant coronary artery disease (CAD).

Clinical History

Both PROCEED II and EXPAND provide critical insights into the safety and effectiveness of the OCS Heart device

PROCEED II

- randomized (1:1) trial (n=128)
- n=62 OCS and n=66 SOC
- standard-criteria donor hearts
- March 2009 – October 2013
- Reasonable assurance of safety and effectiveness not determined

EXPAND

- single arm study (n=75)
- extended-criteria donor hearts
- September 2015 – March 2018
- Continued Access Protocol (CAP) (n=41) *May 2019 – July 2020*

Device Design Changes

PROCEED II vs EXPAND

- Oxygenator vs. oxygenator w/integral heat exchanger
- Addition of a Second compliance chamber and one-way valve
  - Later removed shortly after initial enrollment of EXPAND

Per Sponsor: Changes reflect *minor* design improvements based upon experience gained during the PROCEED II trial

Device Design Changes During EXPAND

Device modification	Number of Hearts Supported (transplanted)	Notes
Infusion Pump Automatic AOP mode	0 (0)	Users relied predominantly or fully on automatic mode in 50% of the turned-down hearts and 79% of the transplanted hearts
Removal of second compliance chamber and one-way valve	6 hearts supported (3 Tx)	Removal to harmonize US and OUS device designs
Increases in upper limits for AOP from 80 mmHg to 100 mmHg	17 hearts supported (12 Tx)	Conditions such as LVH or CAD may need higher aortic pressure

FDA does not believe that changes affected the poolability of the data

Regulatory History – Section 520(g)

In 2012, Congress revised Section 520(g) of the Food Drug and Cosmetic Act to state,

> **"***FDA will not disapprove an IDE because the investigational plan for a pivotal study may not support approval or clearance of a marketing application. However, if FDA believes modifications to the study are needed to achieve this objective, FDA will convey such considerations to the sponsor to provide greater clarity and predictability***."**

EXPAND Protocol Changes

Protocol Version (date)	Protocol Changes	Transplanted subjects per protocol	Notes
1.2		9	
1.3	AOP 40-100 mmHg CF 400-900 ml/min	41	Increased upper limits for AOP and CF to accommodate certain hearts
1.4	Enrollment increase (+20), stat plan and definition changes	25	• Missing data & poolability analyses added • Removal of PGD dysfunction scale • New definitions for protocol deviations

Site #2 IRB Termination

The IRB at site #2 determined that based on -

"…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; further, the IRB decided, based on the history of non-compliance by the sponsor, that IRB approval is terminated for this study…"

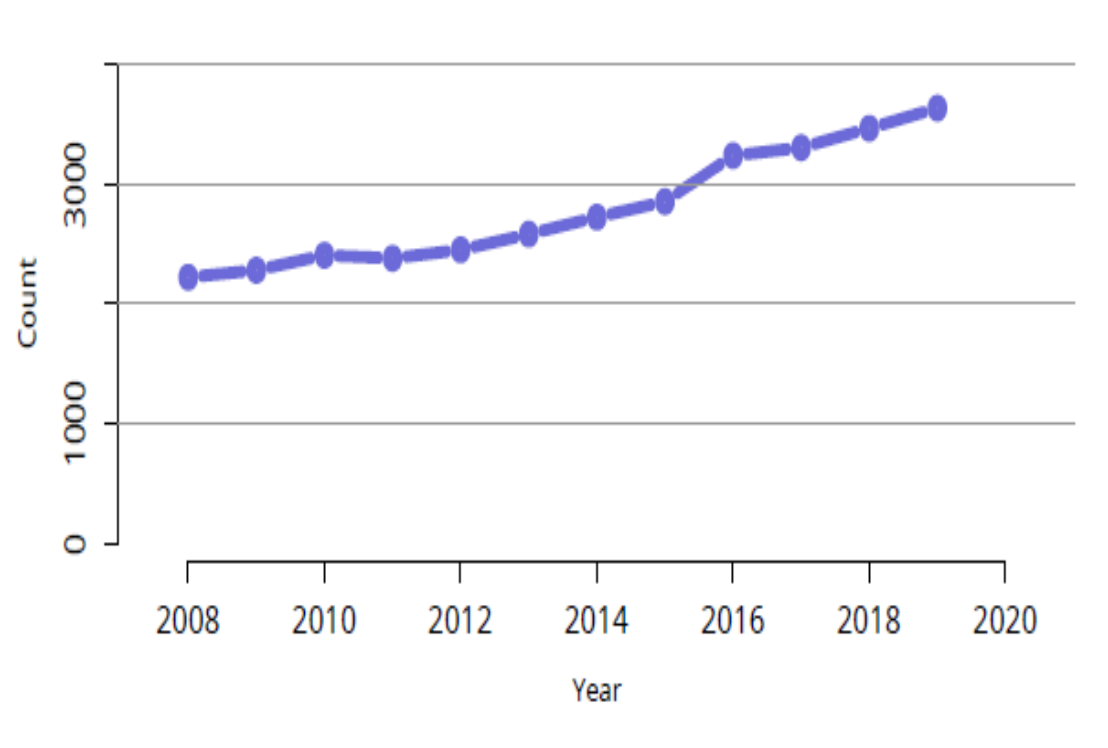
FDA's Study Design Considerations for EXPAND

- Non-randomized concurrent control group
- A pre-specified safety endpoint hypothesis test
- A clinically robust primary effectiveness endpoint
- Use of the ITT or mITT cohort as the primary analysis population

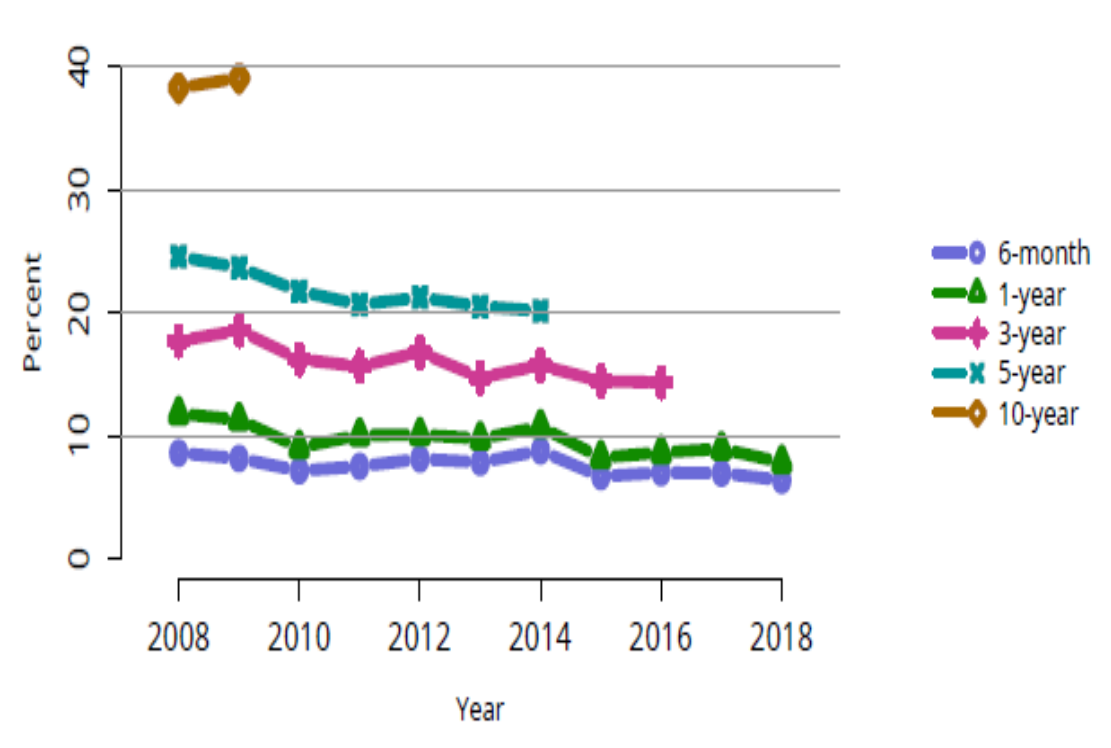
FDA's study design considerations not adopted by the Sponsor

Donor Heart/Survival Trends

Donor Heart Availability



Mortality Rate over Time



2019 SRTR Annual Report published 2021

Non-Clinical Testing

- Bench Testing
- Electrical Safety
- Electromagnetic Compatibility
- Sterilization
- Packaging
- Biocompatibility
- Batteries
- Software/cybersecurity

Current PMA Ex Vivo Animal Study

- Non-GLP
- No control hearts
- N = 2 porcine hearts preserved on the OCS Heart for 6 hours and transported for at least 30 minutes
- No histologic evaluation or other assessments of tissue viability
- ≈20% heart weight gain post-perfusion, consistent with tissue edema

	Pre-perfusion Weight (g)	Post-perfusion Weight (g)
Heart 1	343.3	417.4 *(+22%)*
Heart 2	357.2	426.9 *(+20%)*

No comprehensive animal studies on the final OCS Heart System design/function

Other Ex Vivo Animal Studies

4 small non-GLP porcine studies, focused on validating design changes

- No control groups (e.g., no cold static preservation group)
- No myocardial histologic studies provided to FDA
- Heart weight gain

No animal studies performed to evaluate myocardial preservation and injury patterns between the OCS-Heart device and standard of care static cold storage

Key Issues for Today's Panel

- Study Design
- Study Conduct
- Definition of Extended Criteria Hearts
- Lactate
- Survival
- OCS Heart Device Safety
- Impact of OCS Heart System

Clinical Data Sources and Predicted Survival

Xuan Ye, PhD
Mathematical Statistician
Division of Biostatistics
Office of Clinical Evidence and Analysis
CDRH/FDA

Clinical Data Sources Overview

- PROCEED II
  - Prospective, multicenter, randomized, controlled trial on standard criteria donor hearts
- EXPAND
  - Prospective, multicenter, single-arm study on extended criteria donor hearts
- EXPAND CAP
  - EXPAND Continued Access Protocol

PROCEED II

- Prospective, multicenter, 1:1 randomized, controlled trial
- OCS-Heart System (OCS: test group) vs. cold static cardioplegia standard of care (SOC: control group)
- Standard criteria donor hearts
- Planned Sample Size: 128 recipient patients
- Sites: 12 Enrolling Sites
- PROCEED II IDE trial conducted between March 2009 and October 2013

PROCEED II Primary Effectiveness Endpoint

- Definition
  - 30-day patient survival following transplantation with the originally transplanted donor heart; *and*
  - No mechanical circulatory assist device at Day 30
- Non-inferiority test hypothesis

  H0: $\pi_{OCS} \leq \pi_{SOC} - \delta$

  H1: $\pi_{OCS} > \pi_{SOC} - \delta$

  where $\delta = 0.10$ is the non-inferiority margin, π_{OCS} and π_{SOC} are the respective proportions of subjects surviving at Day 30
- Pre-Specified Statistical Analysis
  - Normal approximation test with one-sided alpha = 0.05

PROCEED II Safety Endpoint

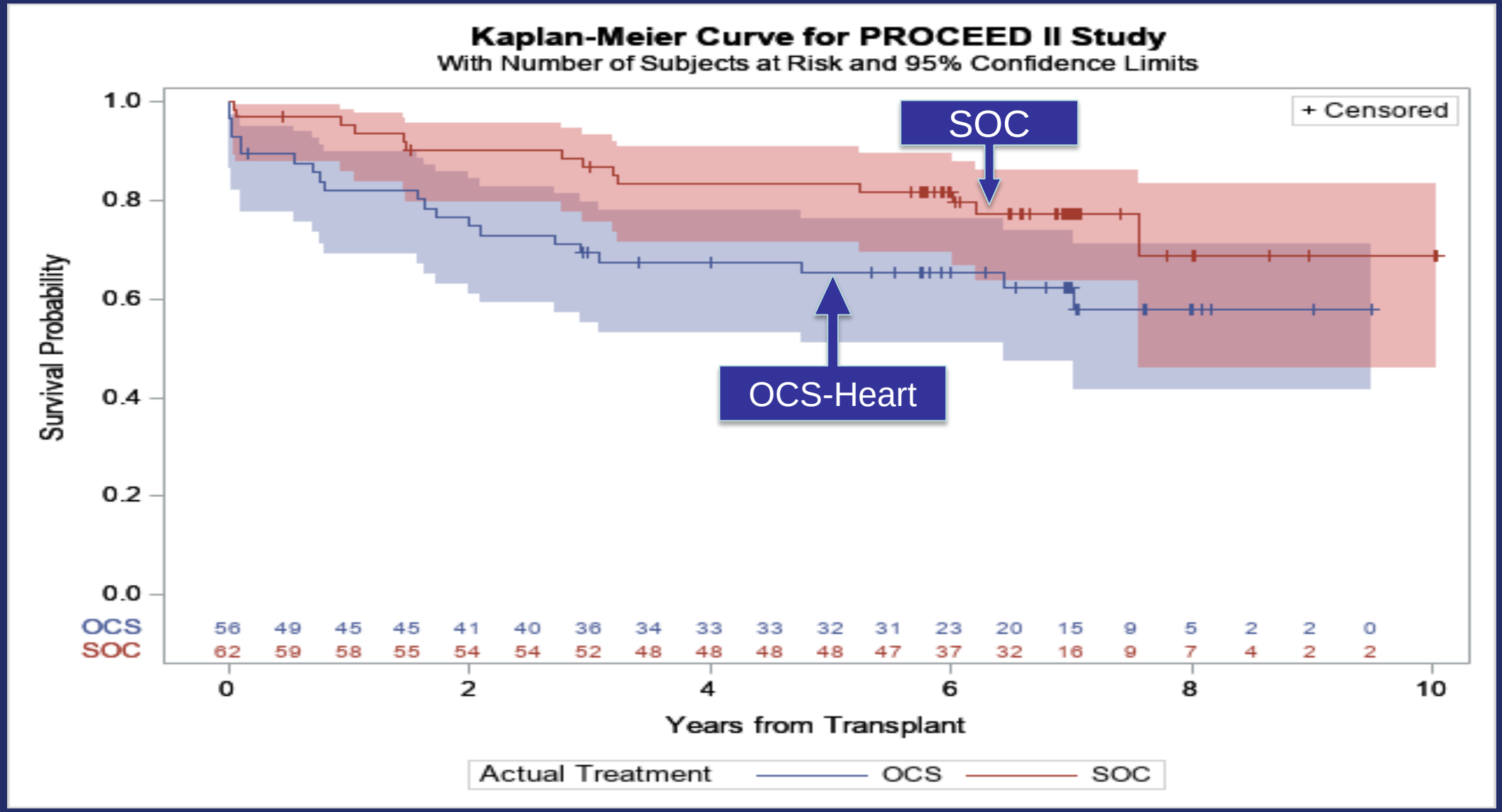
- Definition
  - Incidence of Clinical Events Committee (CEC)-adjudicated cardiac-related serious adverse events up to 30 days following transplantation
- Non-inferiority test hypothesis

  H0: $\tau_{OCS} \geq \tau_{SOC} + \delta$

  H1: $\tau_{OCS} < \tau_{SOC} + \delta$

  where δ=0.10 is the non-inferiority margin, τ_{OCS} and τ_{SOC} are the respective proportions of patients experiencing at least one cardiac-related adverse event up to 30 days following transplantation
- Statistical Analysis
  - Normal approximation test with one-sided alpha = 0.05

PROCEED II Long-Term Survival Analysis



EXPAND

- Prospective, multicenter, single-arm (OCS-Heart) study
- Extended criteria donor hearts
- Planned Sample Size: 75 transplanted heart recipients with the OCS preserved donor hearts
- Sites: 12 sites activated with 9 sites having transplanted heart recipients

EXPAND Primary Effectiveness Endpoint

- Definition
  - A composite of patient survival at Day 30 post-transplant; *and*
  - Freedom from severe PGD-LV or PGD-RV ISHLT primary graft dysfunction (PGD)
- Hypothesis

  H0: $\pi \leq 0.65$

  H1: $\pi > 0.65$

  where π is the true proportion of transplanted recipients survival at Day 30 and absence of severe PGD-LV or PGD-RV ISHLT PGD
- Pre-Specified Statistical Analysis
  - Exact binomial test with one-sided alpha = 0.05

EXPAND Safety Endpoint

Incidence of heart graft-related serious adverse events in the first 30 days post heart transplantation, defined as:

- Moderate or severe PGD-LV / PGD-RV (ISHLT); *or*
- Graft failure leading to re-transplantation

No pre-specified hypothesis testing for the safety endpoint

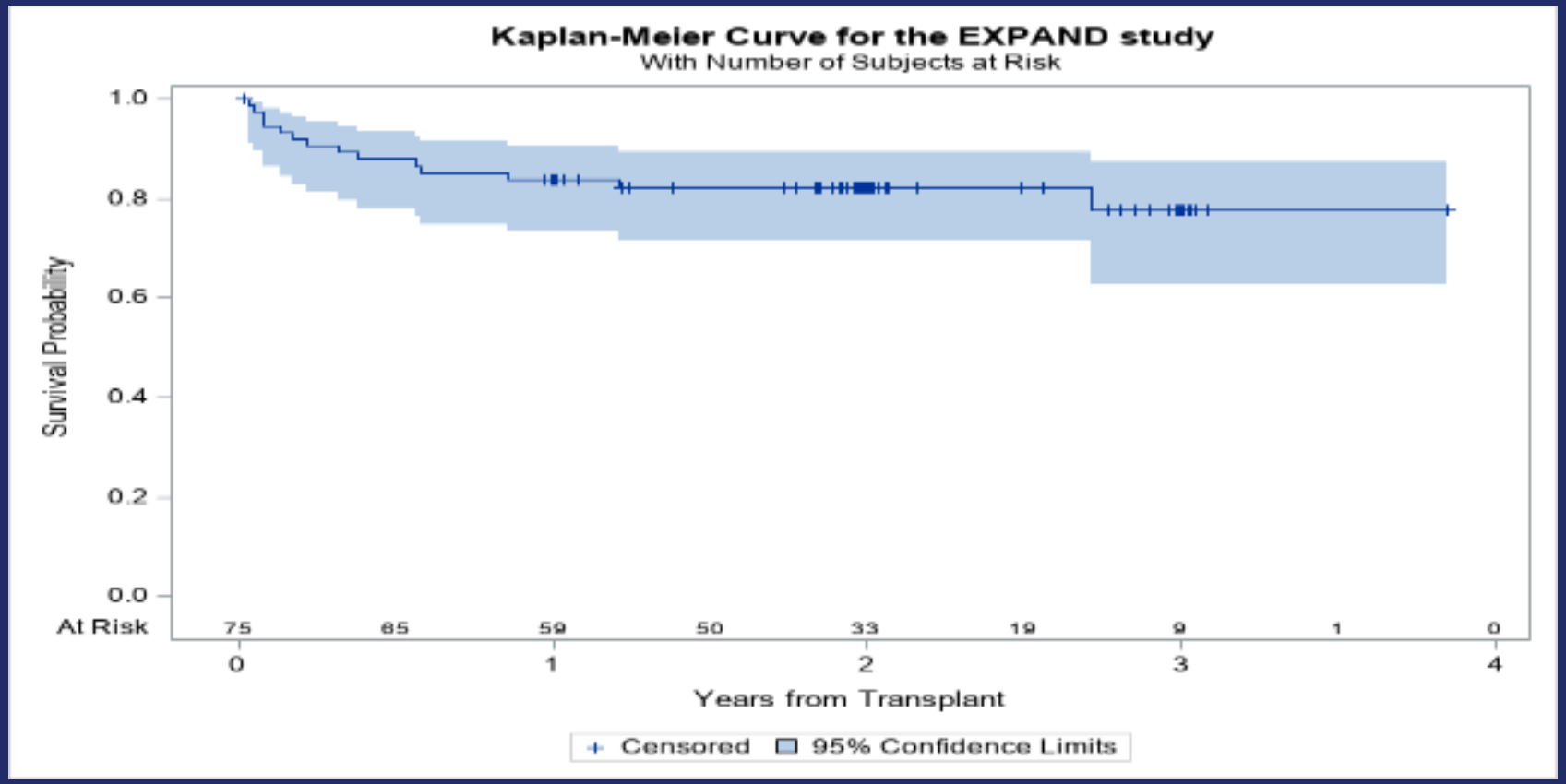
EXPAND Continued Access Protocol (CAP)

- CAP approved for up to 75 OCS-Heart perfused donor hearts meeting the EXPAND-defined extended donor heart criteria
- Sites: Approved for up to 8 sites
- 41 transplanted recipients with OCS-Heart who reached at least 30 days post-transplantation as of the August 2020 database lock
- No predefined hypotheses; data analyzed descriptively

Longer-Term Survival Prediction

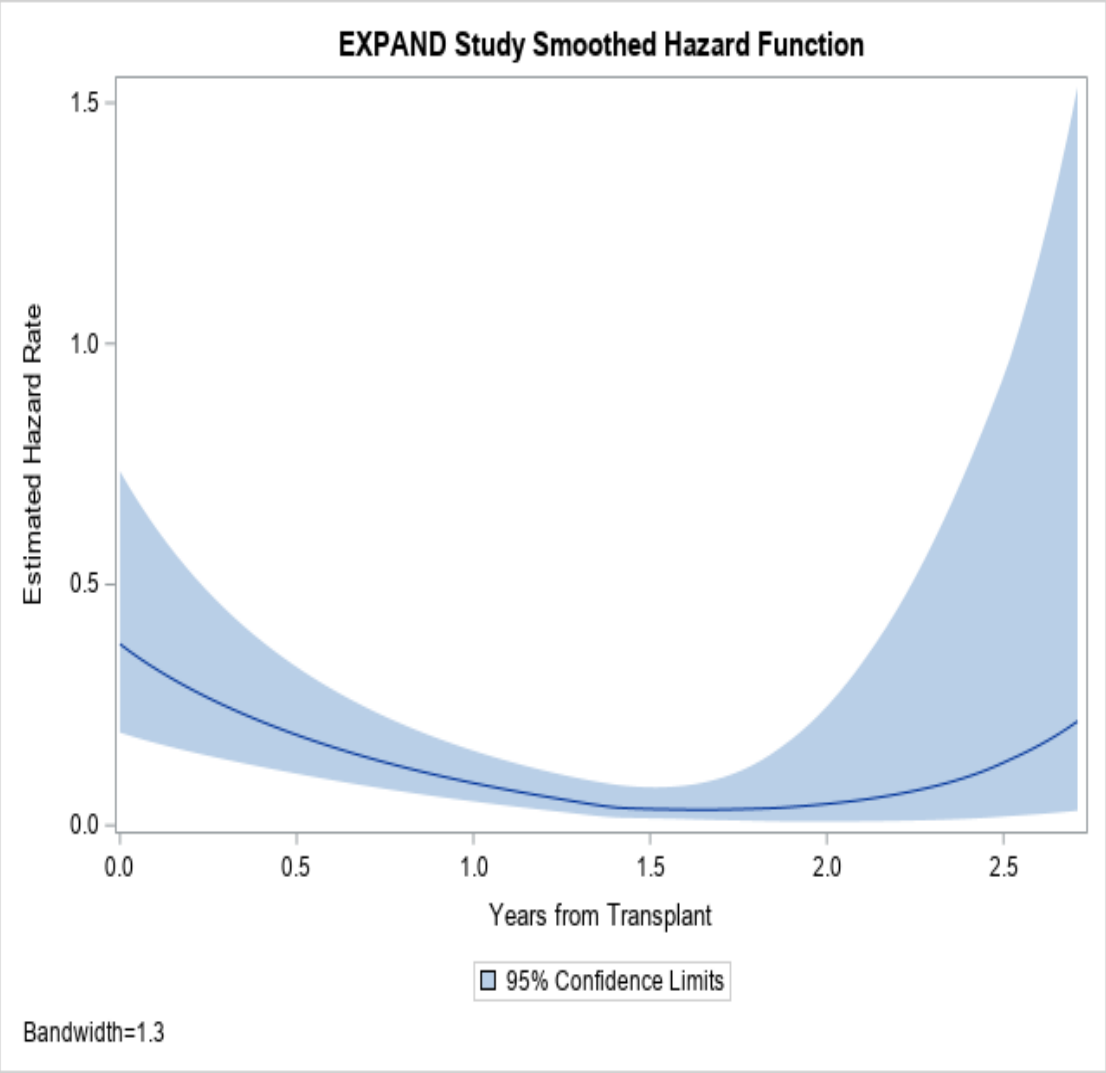
- PROCEED II raised concerns about longer-term survival probabilities among patients receiving hearts preserved with OCS-Heart
- Limited survival data beyond 2 years available for OCS Heart in EXPAND study patients
- Kaplan-Meier analysis can be used to estimate the survival probabilities for up to three years
- FDA built parametric models using available EXPAND study data to predict longer-term (at 4 and 5 years) survival

EXPAND Study Survival Curve (N=75)



Time	Day 0	Year 0.5	Year 1	Year 1.5	Year 2	Year 2.5	Year 3	Year 4
Number At-Risk	75	65	59	50	33	19	9	0

EXPAND Estimated Hazard Function

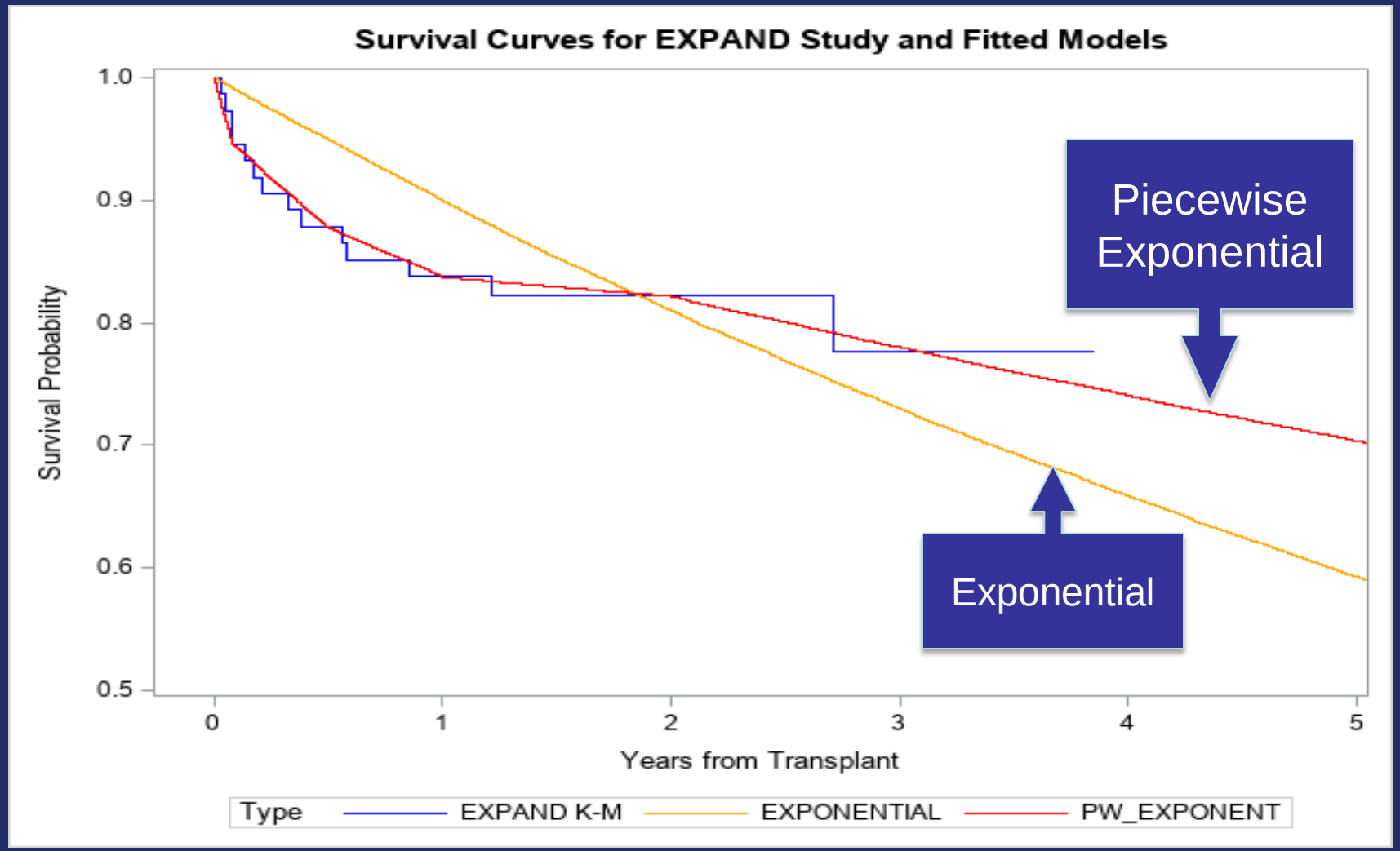


- Hazard is also known as failure rate or force of mortality
- Hazard function was estimated from the observed survival data
- Hazard function appears to be U-shaped

Exponential and Piecewise Exponential Models

- Two parametric models were used to extrapolate longer-term survival probabilities of the OCS-Heart recipients beyond three years
  - Exponential model: Assumes that survival time follows an exponential distribution with constant hazard rate
  - Piecewise exponential model: Assumes that the hazard rate is constant within specified time intervals and may be different across intervals
- Estimated hazard rates in two models were utilized to extrapolate longer-term survival probabilities

EXPAND Study Survival Curve and Models



EXPAND Survival Prediction

Time Post-transplant (at-risk N=75)	Survival Probability (%) (95% CI)		
	Exponential Model	Piecewise Exponential Model	Kaplan-Meier Survival Analysis
1 Year (at-risk=59)	90.1 (83.9, 94.0)	83.8 (74.7, 91.2)	83.8 (73.2, 90.5)
2 Years (at-risk=33)	81.2 (70.3, 88.4)	82.1 (72.8, 90.0)	82.2 (71.4, 89.3)
3 Years (at-risk=9)	73.1 (59.0, 83.1)	78.0 (65.5, 87.8)	77.7 (62.7, 87.2)
4 Years	65.9 (49.4, 78.1)	74.1 **(55.4, 86.8)**	-
5 Years	59.4 (41.5, 73.4)	70.4 **(46.1, 86.1)**	-

Uncertainty

Uncertainty

Survival Prediction Limitations

- Strong Model Assumptions
  - Assume constant Hazard rate within specified time intervals
  - Model prediction depends on model parameters
- Sparse longer-term follow-up data
  - Original sample size = 75
  - Subjects at risk at Year 2 = 33
- Large variability in predicted survival

FDA Clinical Review
TransMedics Organ Care System
Heart System

John S. Sapirstein, M.D.

Office of Cardiovascular Devices
Center for Devices and Radiological Health
Food and Drug Administration

Outline of Presentation

- Background for FDA focus
  - PROCEED II – donor hearts broadly
    FDA review under P14----
    Marketing application
  - EXPAND – donor hearts considered extended-criteria
    FDA review under P18----
    EXPAND CAP data (Q4 2020)
- Overview of IDE protocols and trials execution
  - Limitations identified by FDA
- Review results of both trials
  - Primary Effectiveness Endpoints
  - Key Secondary Endpoints
  - Adjunctive and *post hoc* analyses

OCS Heart System IDE Clinical Studies
Primary Objectives

- PROCEED II

  "…to compare the safety and effectiveness of the OCS Heart System with the existing cold static cardioplegia standard of care for the preservation of donor hearts."

  - Not explicitly limited to "standard-criteria" donor hearts
    - Not principally designed to show clinical superiority of OCS Heart

OCS Heart System IDE Clinical Studies
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  "…to compare the safety and effectiveness of the OCS Heart System with the existing cold static cardioplegia standard of care for the preservation of donor hearts."

  - Not explicitly limited to "standard-criteria" donor hearts
    - Not principally designed to show clinical superiority of OCS Heart

- EXPAND

  "…to evaluate the safety and effectiveness of the [OCS-Heart] to improve the utilization of donor hearts."

  - Limited to pre-defined "extended-criteria" donor hearts
    - Not principally designed for assessment of longer-term benefit:risk

Current PMA

- Intended Use of OCS Heart System (EXPAND IDE)

  "…intended to recruit, preserve and assess certain donor hearts that do not meet standard acceptance criteria for transplantation because of concerns that these donor hearts may be more likely to experience significant time-dependent ischemia injuries associated with cold storage preservation."

- PROCEED II and EXPAND both informative to safety and effectiveness assessment

PROCEED II

- Randomized multicenter trial
  - 1:1 randomization, OCS Heart and cold static preservation (SOC)
  - Complexities of organ procurement and transplantation
    - Unblinded
    - Enrollment after randomization, after in-chest acceptance
      Randomization arm known prior to organ procurement
  - Testing for non-inferiority
    First-of-kind device

PROCEED II
Effectiveness Endpoints

Primary Study Endpoint

Composite of patient and graft survival at Day 30 post-transplantation in the absence of mechanical circulatory support (MCS)

Non-inferiority of proportions

δ = 10%

Secondary Endpoints

1. Moderate-severe acute rejection (biopsy-proven 2R/3R or clinically symptomatic) up to 30 days

   Non-inferiority of proportions

   δ = 10%

2. Initial ICU stay after transplantation

   Non-inferiority of median stay length

   δ = 12 hours

PROCEED II
Secondary Endpoint (Safety)

Incidence (number of events/subject) of Clinical Events Committee (CEC)-adjudicated cardiac-related serious adverse events (CRSAEs) up to 30 days

Non-inferiority of incidence

$\delta = 10\%$

CRSAEs*

- Graft failure leading to listing for re-transplantation
- Graft failure requiring MCS
- LV or RV heart failure
- Myocardial infarction or moderate-to-severe MR

* Modified by Steering Committee/CEC during trial

Other Effectiveness Measures Requested by FDA

- Longer-term survival of subjects (Kaplan-Meier analyses)
  - Scientific Registry of Transplant Recipients (SRTR)
    US Health Resources and Services Administration

- *Post hoc* analyses
  - Comparison to Organ Procurement and Transplantation Network (OPTN)/SRTR data Annual Reports (2018, 2019)
    All US waiting list patients and transplant recipients

  - Turned-down donor organs
    Sensitivity analyses for Primary Study Endpoint
    Pathology review

PROCEED II
Recipient Inclusion/Exclusion Criteria

Recipient	
	PROCEED II
Inclusion Criteria	
Heart transplant	Primary
Age	≥ 18 years
Informed consent	≠ enrollment
Exclusion Criteria	
Prior transplant	Not excluded
Concurrent transplant	Excluded → Renal Tx allowed
Prior sternotomy	> 4 → > 2
Ventilator	Excluded
VAD > 30 days (+ sepsis/hemorrhage/HITT)	Excluded
PRA	> 40%
Renal dysfunction	• Chronic serum creatinine >3.0 mg/dl • Hemodialysis

PROCEED II
Donor Inclusion/Exclusion Criteria

Inclusion

- < 60 years old
- MAP > 60 mmHg at final in-chest assessment
- Satisfactory echocardiography:
  - Ejection fraction > 40%
  - Absence of severe segmental wall motion abnormalities
  - Absence of LVH: IVS and PW thickness < 13 mm)
  - Absence of valve abnormalities ($\bar{x}$ regurg. > mod)

Exclusion

- Abnormal angiography (> 50% stenosis, needing CABG)
- Donor-to-recipient body weight ratio of < 0.6
- Vasoactive support at final in-chest assessment
- Any criterion based on site standard practice

PROCEED II
Pre-specified Analysis Populations

Recipients

Per Protocol (PP)

All randomized subjects who are transplanted per randomization, no recipient/donor criteria violations

Primary analysis for Primary Study Endpoint

Intention-to-Treat (ITT or mITT)

All randomized subjects for whom a matching and eligible heart is identified and confirmed at donor site

Supplemental analysis for Primary Study Endpoint

Recommended as primary analysis for Primary Endpoint

Safety/As Treated (AT)

All subjects who receive a transported donor heart

Primary analysis for secondary endpoints

Completed Treatment (CT)

AT subjects who complete study

"complete study" not prospectively defined

Donor Hearts

OCS Heart (OCS-H)

All donor hearts instrumented onto and transported with the OCS Heart System.

PROCEED II
Pre-specified Analysis Populations

Recipients

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All randomized subjects who are transplanted per randomization, no recipient/donor criteria violations

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Donor Hearts

OCS Heart (OCS-H)

All donor hearts instrumented onto and transported with the OCS Heart System.

PROCEED II
FDA Preference for ITT

- Maintains benefit of randomization
  - Accounts for “screen failure” after randomization
  - Accounts for crossover
    - Not part of PP
  - Incorporates post-preservation turn-down
    - OCS Heart arm more susceptible to turn-down after preservation
      An additional “screening” of one randomization arm

- PROCEED II’s ITT population actually *modified* ITT (mITT)
  - “Treatment” ≡ procurement → preservation → transplantation

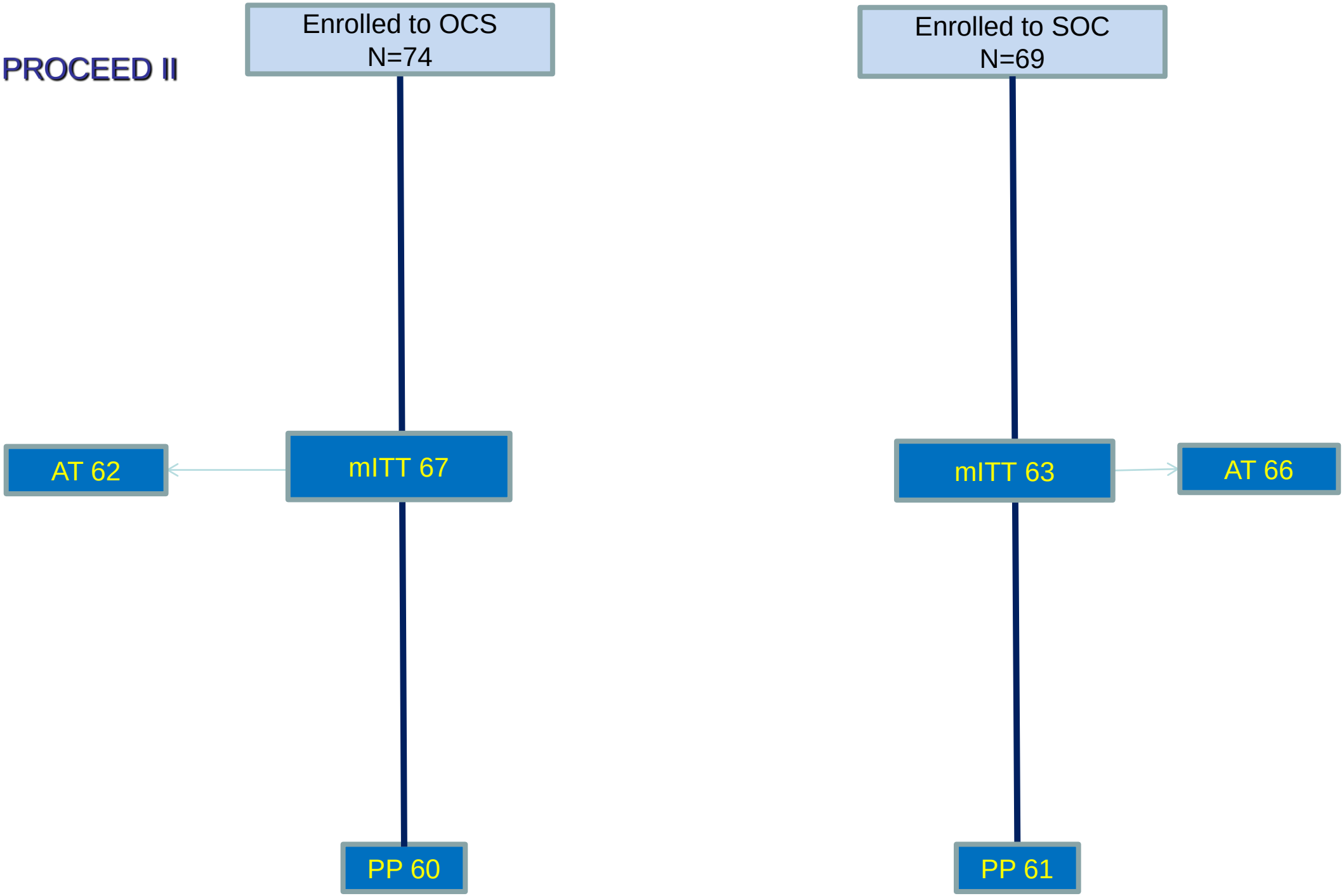
PROCEED II
Recipient Enrollment

Site Name	Country	SOC	OCS	# Randomized Patients
	USA	8	8	16
	USA	20	22	42
	USA	10	8	18
	USA	1	0	1
	USA	2	1	3
	USA	4	6	10
	FR	3	4	7
	USA	20	20	40
	UK	0	1	1
	UK	1	3	4
	IT	0	1	1
	USA	0	0	0
Total		**69**	**74**	**143**

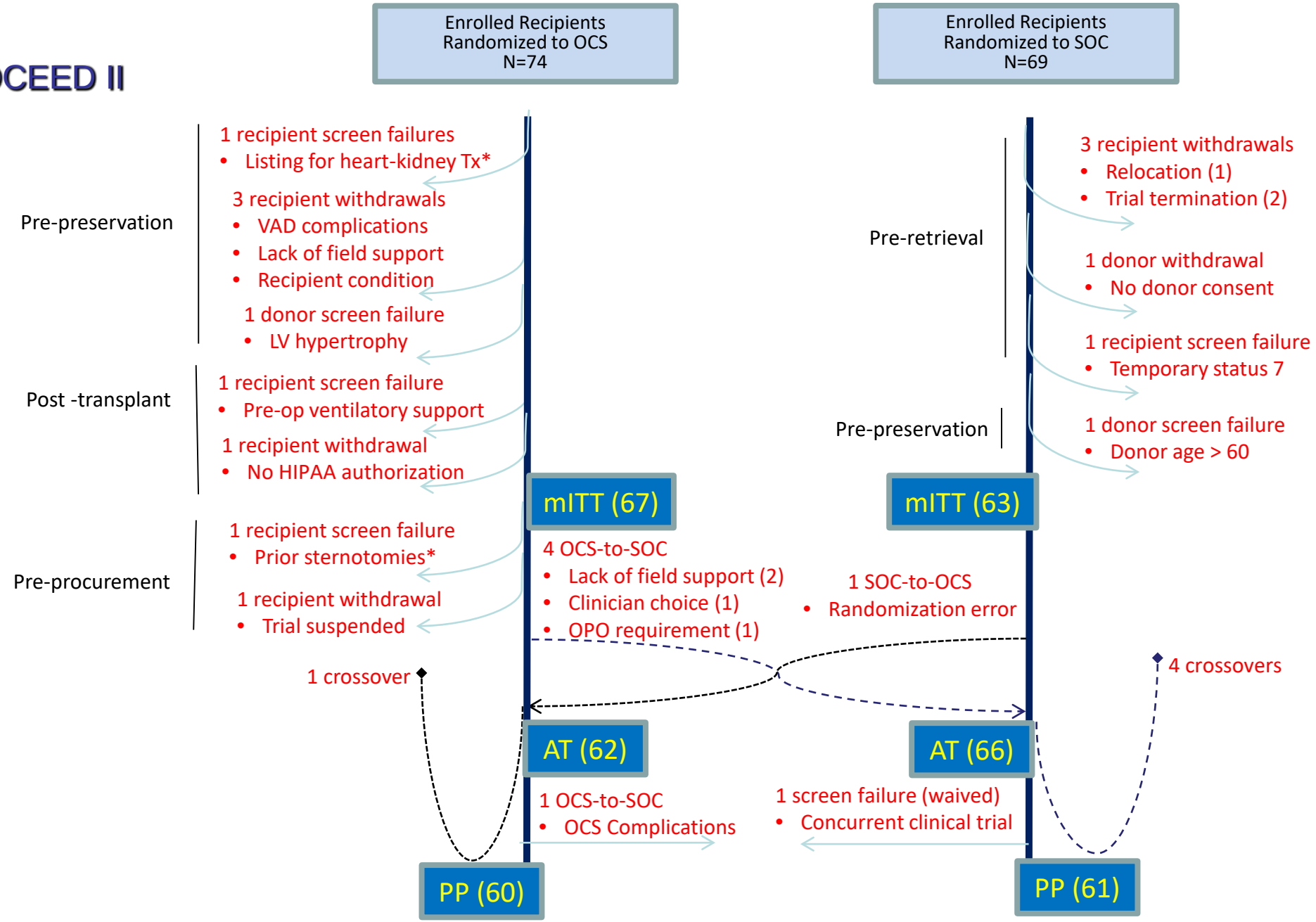
143 recipients enrolled/randomized
- March, 2009 – October, 2013

- 12 enrolling sites
  - 8 US
    Enrolled 91% of subjects
- Highest enrollers: 29% & 28%
- Post-enrollment screen failure & withdrawal
  - OCS: 12%
  - SOC: 9%
- Post-enrollment crossover
  - OCS-to-SOC: 7%
  - SOC-to-OCS: 1%
- 7% OCS-H hearts turned-down after preservation

PROCEED II

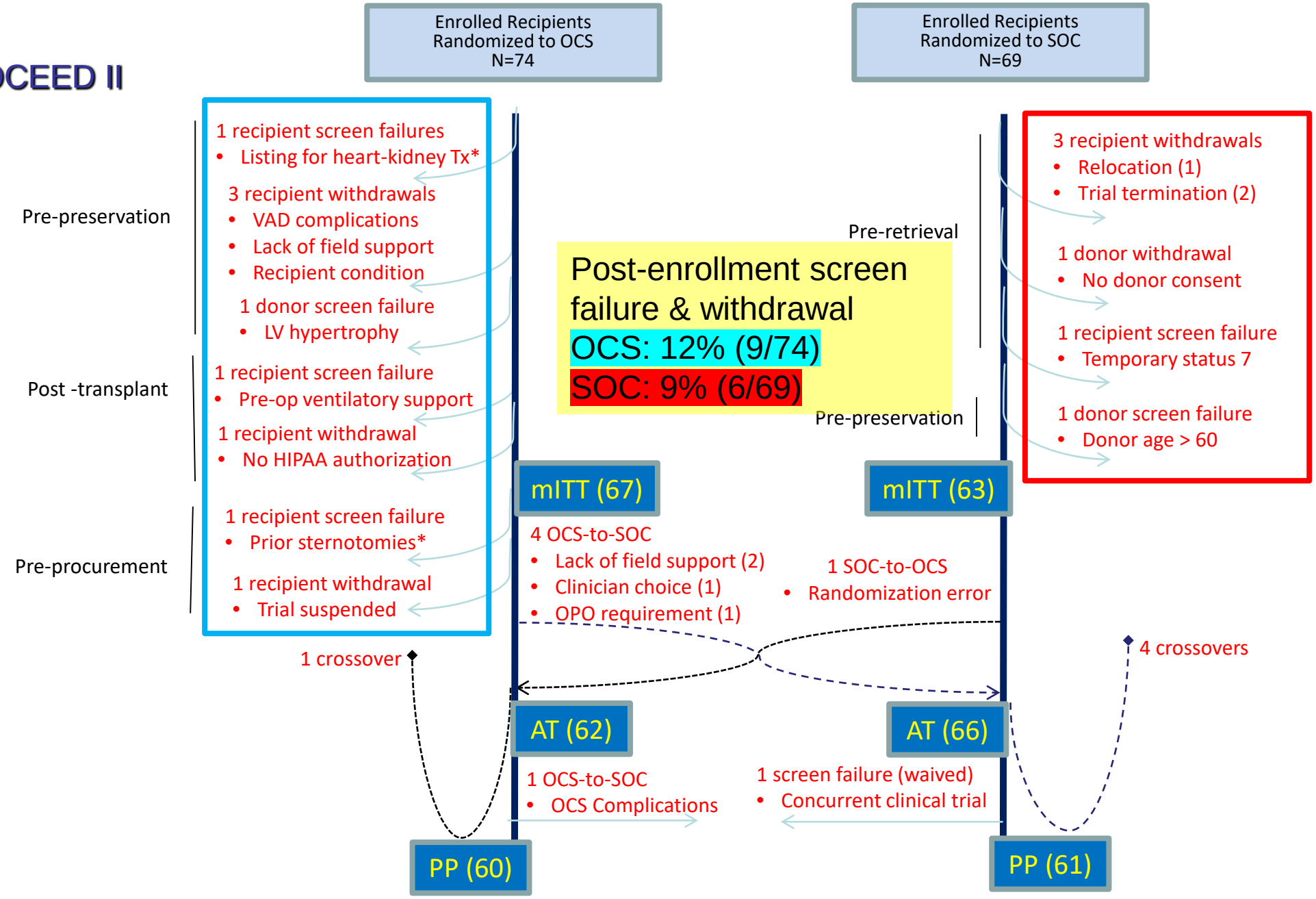

Enrolled to OCS
N=74
Enrolled to SOC
N=69
AT 62
mITT 67
mITT 63
AT 66
PP 60
PP 61

PROCEED II



Randomization prior to enrollment
* screening failure for exclusion criterion subsequently removed from protocol

PROCEED II



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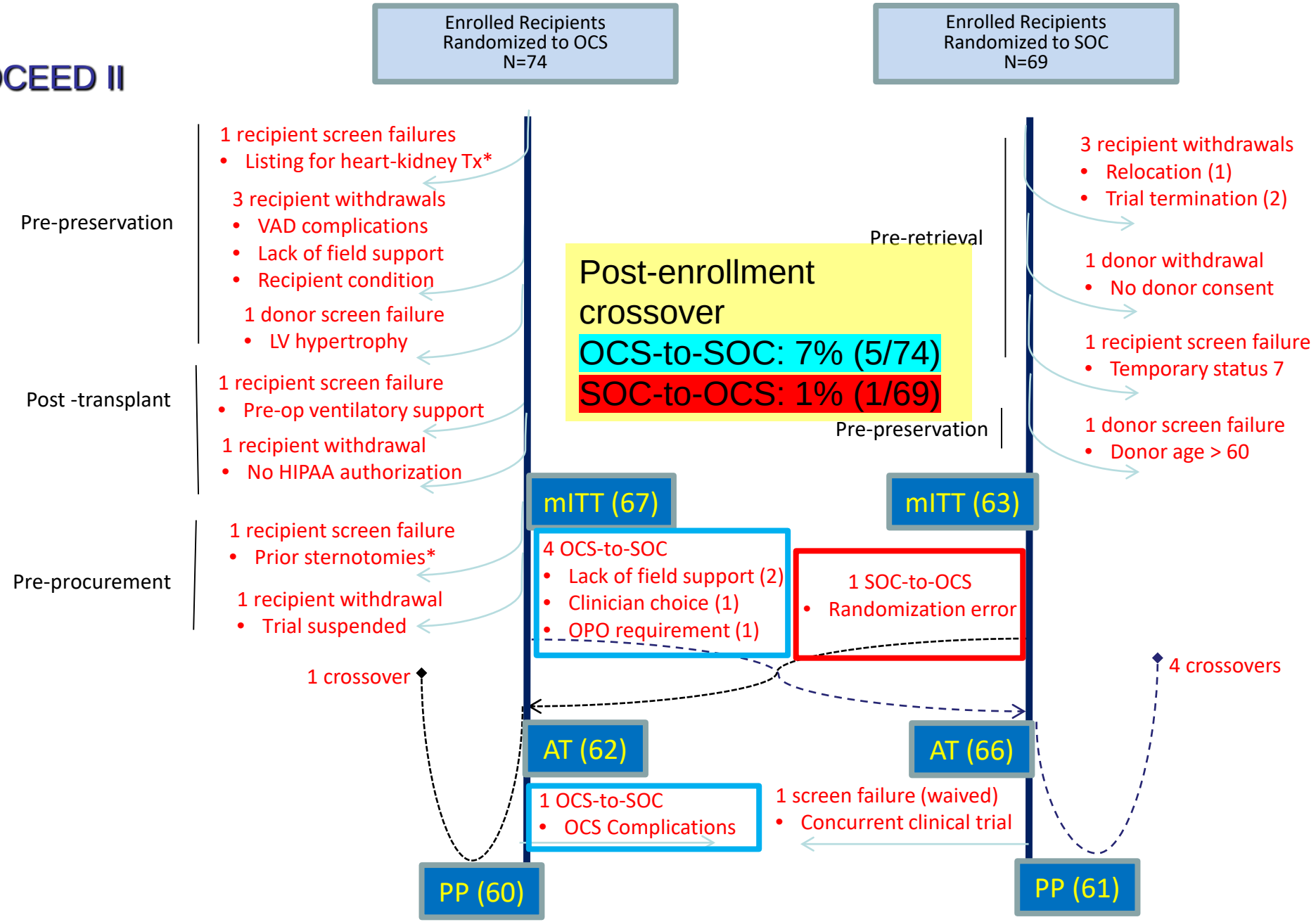

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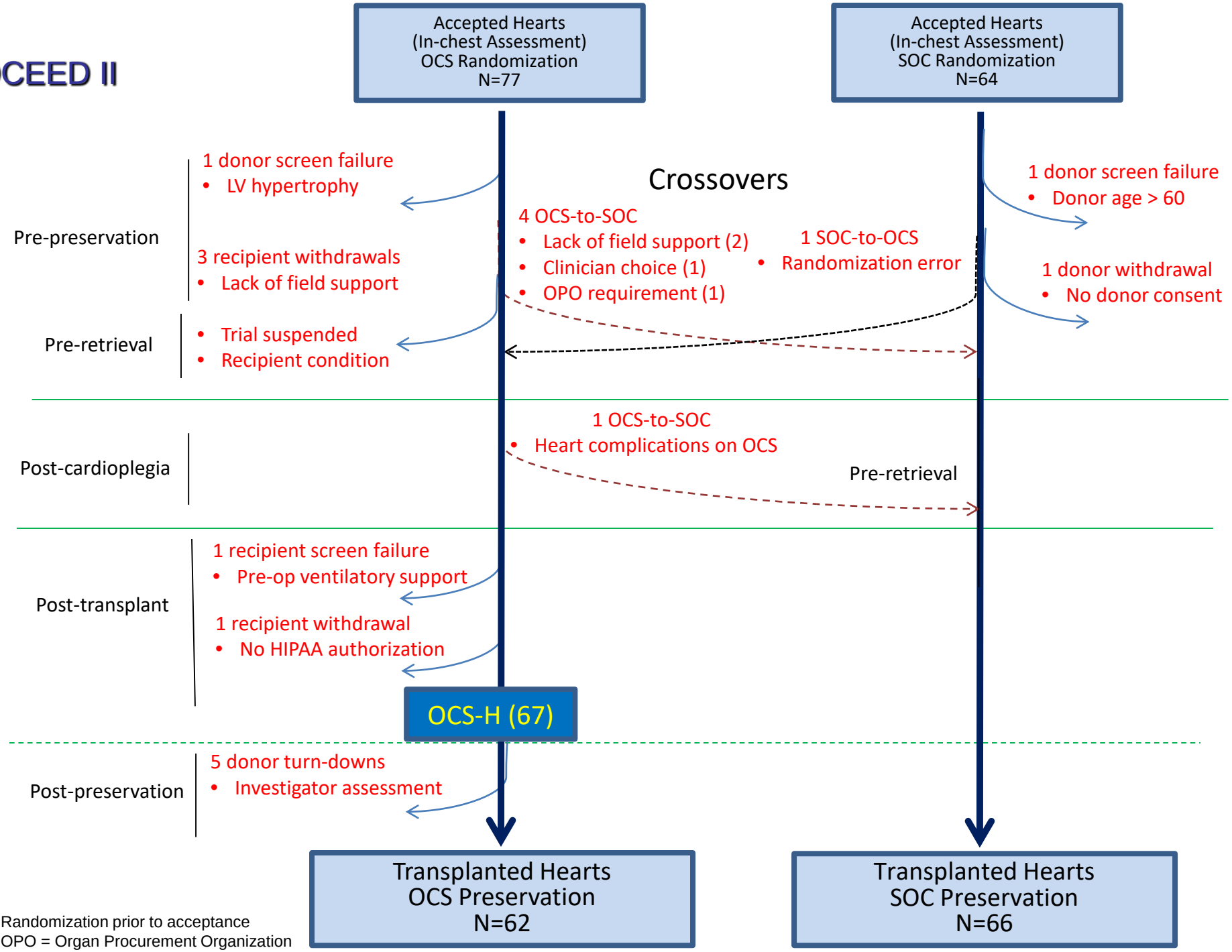
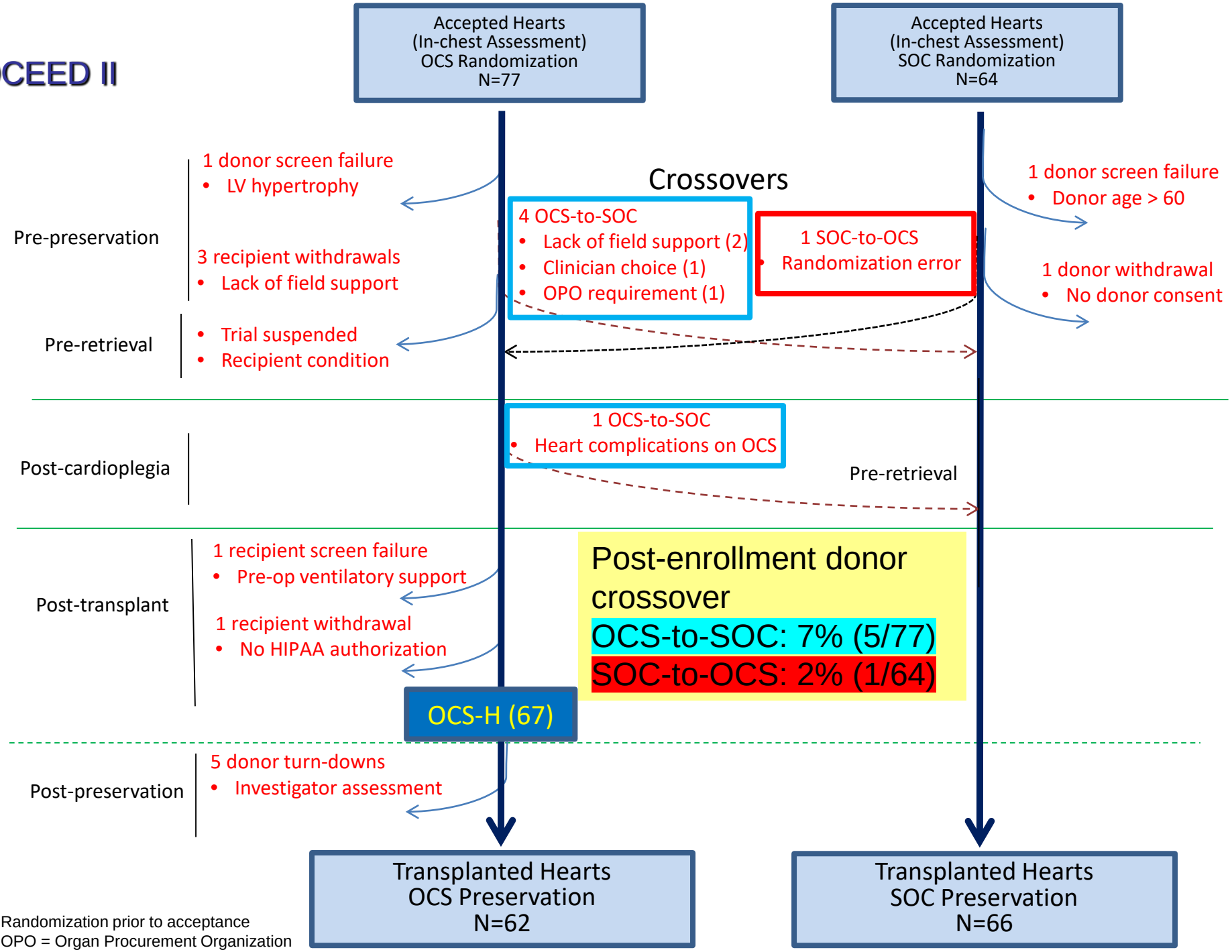


Randomization prior to acceptance
OPO = Organ Procurement Organization

PROCEED II



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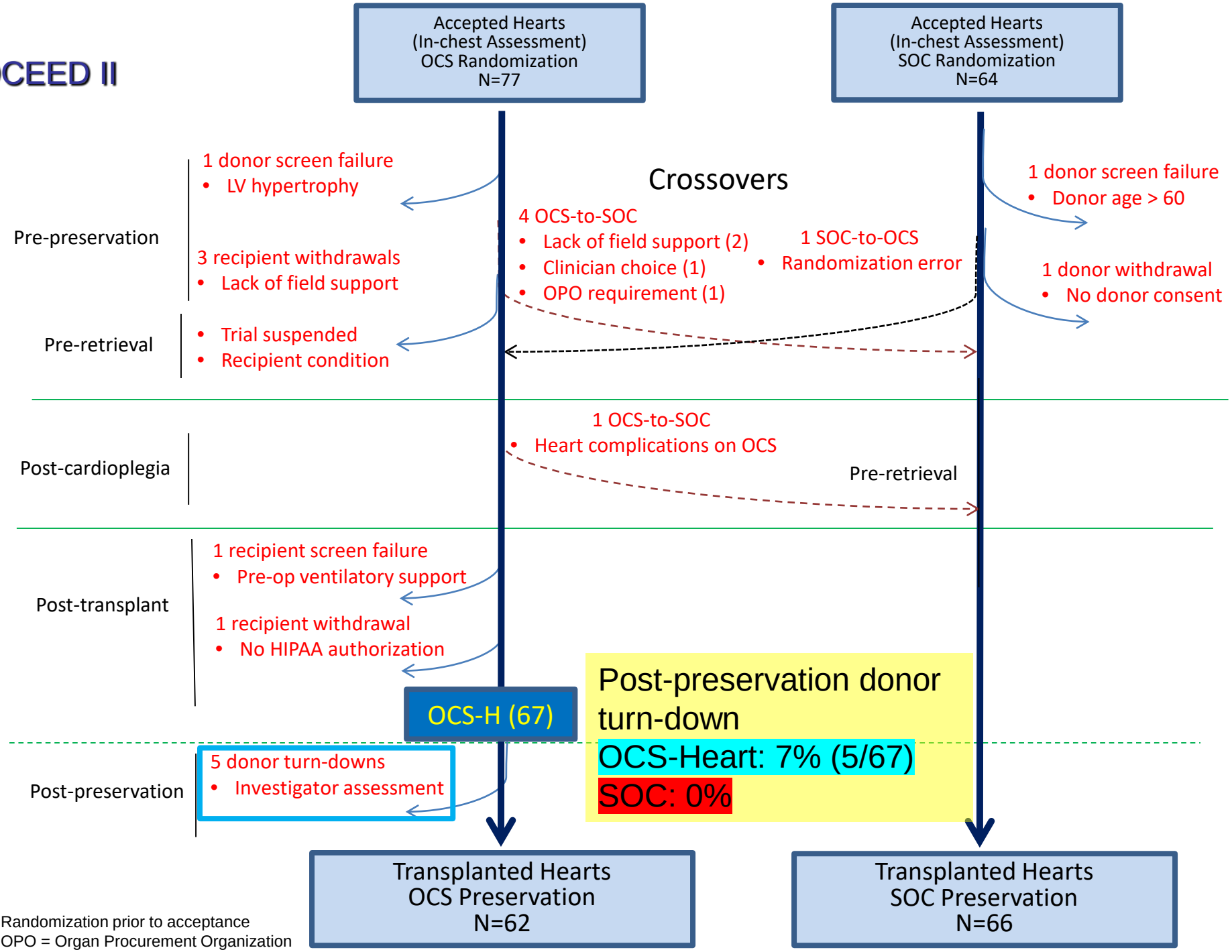

Randomization prior to acceptance
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Recipient Demographics and Characteristics PROCEED II (mITT)

Parameter	Statistic	OCS (N=67) n (%)	Control (N=63) n (%)	p-value [1]
Age (years)	N	67	63	
	Mean (SD)	53.09 (13.09)	54.46 (13.55)	0.5592
	Median	55.51	56.60	
	Min, Max	19.9, 74.9	20.4, 76.1	
Gender				0.0867
Male	n (%)	57 (85.1)	45 (71.4)	
Female	n (%)	10 (14.9)	18 (28.6)	
Blood Type				0.4965
O	n (%)	32 (47.8)	22 (34.9)	
A	n (%)	22 (32.8)	27 (42.9)	
B	n (%)	7 (10.4)	8 (12.7)	
AB	n (%)	6 (9.0)	6 (9.5)	
PRA%	N	64	61	
	Mean (SD)	2.1 (6.9)	3.2 (7.5)	0.3932
	Median	0.0	0.0	
	Min, Max	0, 40	0, 38	

*nominal p-values, not adjusted for multiple comparison

- Clinically similar overall
- SOC
  higher proportion female
- OCS
  higher proportion blood type O
- Prior sensitization low in both trial arms

Recipient Demographics and Characteristics PROCEED II (mITT)

Parameter	Statistic	OCS (N=67) n (%)	Control (N=63) n (%)	p-value [1]
Age (years)	N	67	63	
	Mean (SD)	53.09 (13.09)	54.46 (13.55)	0.5592
	Median	55.51	56.60	
	Min, Max	19.9, 74.9	20.4, 76.1	
Gender				0.0867
Male	n (%)	57 (85.1)	45 (71.4)	
Female	n (%)	10 (14.9)	18 (28.6)	
Blood Type				0.4965
O	n (%)	32 (47.8)	22 (34.9)	
A	n (%)	22 (32.8)	27 (42.9)	
B	n (%)	7 (10.4)	8 (12.7)	
AB	n (%)	6 (9.0)	6 (9.5)	
PRA%	N	64	61	
	Mean (SD)	2.1 (6.9)	3.2 (7.5)	0.3932
	Median	0.0	0.0	
	Min, Max	0, 40	0, 38	

*nominal p-values, not adjusted for multiple comparison

- Clinically similar overall
- SOC
  higher proportion female
- OCS
  higher proportion blood type O
- Prior sensitization low in both trial arms

Recipient Demographics and Characteristics PROCEED II (mITT)

Parameter	Statistic	OCS (N=67) n (%)	Control (N=63) n (%)	p-value [1]
Age (years)	N	67	63	
	Mean (SD)	53.09 (13.09)	54.46 (13.55)	0.5592
	Median	55.51	56.60	
	Min, Max	19.9, 74.9	20.4, 76.1	
Gender				0.0867
Male	n (%)	57 (85.1)	45 (71.4)	
Female	n (%)	10 (14.9)	18 (28.6)	
Blood Type				0.4965
O	n (%)	32 (47.8)	22 (34.9)	
A	n (%)	22 (32.8)	27 (42.9)	
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PRA%	N	64	61	
	Mean (SD)	2.1 (6.9)	3.2 (7.5)	0.3932
	Median	0.0	0.0	
	Min, Max	0, 40	0, 38	

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*nominal p-values, not adjusted for multiple comparison

- Clinically similar overall
- SOC
  higher proportion female
- OCS
  higher proportion blood type O
- Prior sensitization low in both trial arms

Recipient Preoperative MCS
PROCEED II mITT

ITT Population			
Support	OCS (N=67) n/N (%)	Control (N=65) n/N (%)	p-value (1)
IABP	0/66 (0.0)	6/63 (9.5)	0.0119
VAD	19/66 (28.8)	15/63 (23.8)	0.5541
ECMO	0/62 (0.0)	0/63 (0.0)	--
Treated Population*			
Support	OCS (N=62) n/N (%)	Control (N=66) n/N (%)	p-value
IABP	0/62 (0.0)	6/66 (9.1)	0.0281
VAD	18/62 (29.0)	15/66 (22.7)	0.4276
ECMO	0/58 (0.0)	0/66 (0.0)	--
VAD duration (Days)			
Mean	350	481	0.198
Std Dev	229	321	
Median	409	581	
Min	23	56	
Max	704	1052	

(1) P-value is based on Fisher's Exact Test
* Treated Population is the same as "As Treated"

*nominal p-values, not adjusted for multiple comparison

- 28% OCS
- 33% SOC

- Chronic MCS (VAD)
  Proportions similar

Recipient Preoperative MCS
PROCEED II mITT

ITT Population			
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* Treated Population is the same as "As Treated"

*nominal p-values, not adjusted for multiple comparison

- 28% OCS
- 33% SOC

- Chronic MCS (VAD)
  - Proportions similar
    - Longer support duration in SOC

Recipient Preoperative MCS
PROCEED II mITT

ITT Population			
Support	OCS (N=67) n/N (%)	Control (N=65) n/N (%)	p-value (1)
IABP	0/66 (0.0)	6/63 (9.5)	0.0119
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*nominal p-values, not adjusted for multiple comparison

- 28% OCS
- 33% SOC

- Chronic MCS (VAD)
  - Proportions similar
    - Longer support duration in SOC

- Acute MCS (IABP)
  - 0% OCS
  - 9% SOC

Recipient Preoperative MCS
PROCEED II mITT

ITT Population			
Support	OCS (N=67) n/N (%)	Control (N=65) n/N (%)	p-value (1)
IABP	0/66 (0.0)	6/63 (9.5)	0.0119
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* Treated Population is the same as "As Treated"

*nominal p-values, not adjusted for multiple comparison

- 28% OCS
- 33% SOC

- Chronic MCS (VAD)
  - Proportions similar
    - Longer support duration in SOC

- Acute MCS (IABP)
  - 0% OCS
  - 9% SOC

- Uncertain equivalence of hemodynamic status pre-transplantation

Donor Organ Demographics and Characteristics PROCEED II

Transplanted Donor Heart Population					OCS Heart Population
Parameter	Statistic	OCS (N=61) n (%)	Control (N=62) n (%)	p-value	OCS (N=67) n (%)
Age (years)	N	58	62	0.4509	64
	Mean (SD)	36.09 (12.81)	34.36 (12.20)		35.43 (12.65)
	Median	35.61	33.61		35.29
	Min, Max	18.0, 57.9	13.4, 59.6		18.0, 57.9
Gender				0.6992	
Male	n (%)	41 (67.2)	44 (71.0)		44 (65.7)
Female	n (%)	20 (32.8)	18 (29.0)		23 (34.3)
Blood Type					
O	n (%)	34 (55.7)	31 (50.0)	0.9328	36 (53.7)
A	n (%)	20 (32.8)	23 (37.1)		24 (35.8)
B	n (%)	5 (8.2)	6 (9.7)		5 (7.5)
AB	n (%)	2 (3.3)	2 (3.2)		2 (3.0)

*nominal p-values, not adjusted for multiple comparison

- 1 donor heart with EF < 50%
  SOC
- Similar and expected rates of cause of death
  - ~25% associated cardiac arrest
    - Downtime not collected

  In EXPAND, ≥ 20 minutes
  => extended criterion

Procurement, Transport, and Transplantation Characteristics PROCEED II (AT)

Parameter	Statistic	OCS (N=62)	Control (N=66)	p-value [1]
Pre-OCS Ischemic Time (mins)	N	61	n/a	
	Mean (SD)	30.0 (8.2)		
	Median	29		
	Min, Max	16 - 64		
OCS Perfusion Time (mins)	n	61	n/a	
	Mean (SD)	212.1 (74.6)		
	Median	200		
	Min - Max	56 - 420		
Post-OCS Ischemic Time (mins)	n	61	n/a	
	Mean (SD)	82.0 (22.7)		
	Median	84		
	Min - Max	36 - 142		
Total Cold Ischemia Time (mins)	N	61	66	
	Mean (SD)	112.0 (24.5)	196.2 (65.3)	<0.0001
	Median	118	189	
	Min, Max	62 - 169	72 - 461	
Out of Body Time (min)	N	61	66	
	Mean (SD)	324.1 (78.6)	196.2 (65.3)	<0.0001
	Median	315	189	
	Min, Max	149 - 543	72 - 461	

1 OCS times are excluded; 1 due to the [redacted] user error
(1) p-value is from the two-sample t-test, testing for a difference in means between treatments

*nominal p-values, not adjusted for multiple comparison

- Average cold ischemia time
  - OCS: 1.9 hours
  - SOC: 3.3 hour

Procurement, Transport, and Transplantation Characteristics PROCEED II (AT)

Parameter	Statistic	OCS (N=62)	Control (N=66)	p-value [1]
Pre-OCS Ischemic Time (mins)	N	61	n/a	
	Mean (SD)	30.0 (8.2)		
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	Min, Max	16 - 64		
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*nominal p-values, not adjusted for multiple comparison

- Average cold ischemia time
  - OCS: 1.9 hours
  - SOC: 3.3 hour
- "Out-of-body" time ≡ Cross-clamp time

  128 minutes longer for OCS Heart

  65% increase

Procurement, Transport, and Transplantation Characteristics PROCEED II (AT)

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Pre-OCS Ischemic Time (mins)	N	61	n/a	
	Mean (SD)	30.0 (8.2)		
	Median	29		
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  - SOC: 3.3 hour
- "Out-of-body" time ≡ Cross-clamp time

  128 minutes longer for OCS Heart

  65% increase
- Pre-perfusion ischemia = 30 minutes

Procurement, Transport, and Transplantation Characteristics PROCEED II (AT)

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Pre-OCS Ischemic Time (mins)	N	61	n/a	
	Mean (SD)	30.0 (8.2)		
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- Average cold ischemia time
  - OCS: 1.9 hours
  - SOC: 3.3 hour
- "Out-of-body" time ≡ Cross-clamp time
  128 minutes longer for OCS Heart
  65% increase
- Pre-perfusion ischemia = 30 minutes
- OCS perfusion ≈ SOC cross-clamp
  Despite randomization

Cardioplegia
PROCEED II (AT)

- OCS Heart System cardioplegia solution
  - Custodiol HTK (“extracellular”) crystalloid cardioplegia: 80%
    - FDA requirement: no non-approved solution in OCS Heart System
- Multiple cardioplegia solutions used in SOC
  - University of Wisconsin (“intracellular”) crystalloid solution: 40%
    - Custodiol HTK 6%
- *Post hoc* covariate adjustment of Primary Study Endpoint
  - More variance and heterogeneity to Primary Study Endpoint
    - Adjusted treatment difference (95% UCB): 23%
- Cardioplegia selection may affect OCS Heart System safety-effectiveness
  - EXPAND standardized OCS Heart System cardioplegia
    - del Nido solution (4:1 crystalloid:blood)

Primary Study Endpoint
PROCEED II

Patient and Graft Survival without MCS at Day 30 post-transplantation	SOC % (n/N)	OCS % (n/N)	SOC-OCS Difference % (95% UCB)	p-value ($\delta = 10\%$)
PP analysis	97 (59/61)	93 (56/60)	3.7 (9.9%)	0.047

Primary Study Endpoint
PROCEED II

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- Statistical non-inferiority of OCS

Primary Study Endpoint
PROCEED II

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PP analysis	97 (59/61)	93 (56/60)	3.7 (9.9%)	0.047

- Statistical non-inferiority of OCS
  - All endpoint failures on the basis of death
    - 4 OCS, 2 SOC
      2 OCS non-endpoint deaths at Days 33 and 38

Primary Study Endpoint
PROCEED II

Patient and Graft Survival without MCS at Day 30 post-transplantation	SOC % (n/N)	OCS % (n/N)	SOC-OCS Difference % (95% UCB)	p-value ($\delta = 10\%$)
PP analysis	97 (59/61)	93 (56/60)	3.7 (9.9%)	0.047

- Statistical non-inferiority of OCS
  - All endpoint failures on the basis of death
    - 4 OCS, 2 SOC
      2 OCS non-endpoint deaths at Days 33 and 38
  - 10% non-inferiority margin applied to 30-day mortality

Primary Study Endpoint
PROCEED II

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- Statistical non-inferiority of OCS
  - All endpoint failures on the basis of death
    - 4 OCS, 2 SOC
      2 OCS non-endpoint deaths at Days 33 and 38
  - 10% non-inferiority margin applied to 30-day mortality
- Point estimates favored SOC
  - Statistical superiority not demonstrated

Primary Study Endpoint
PROCEED II

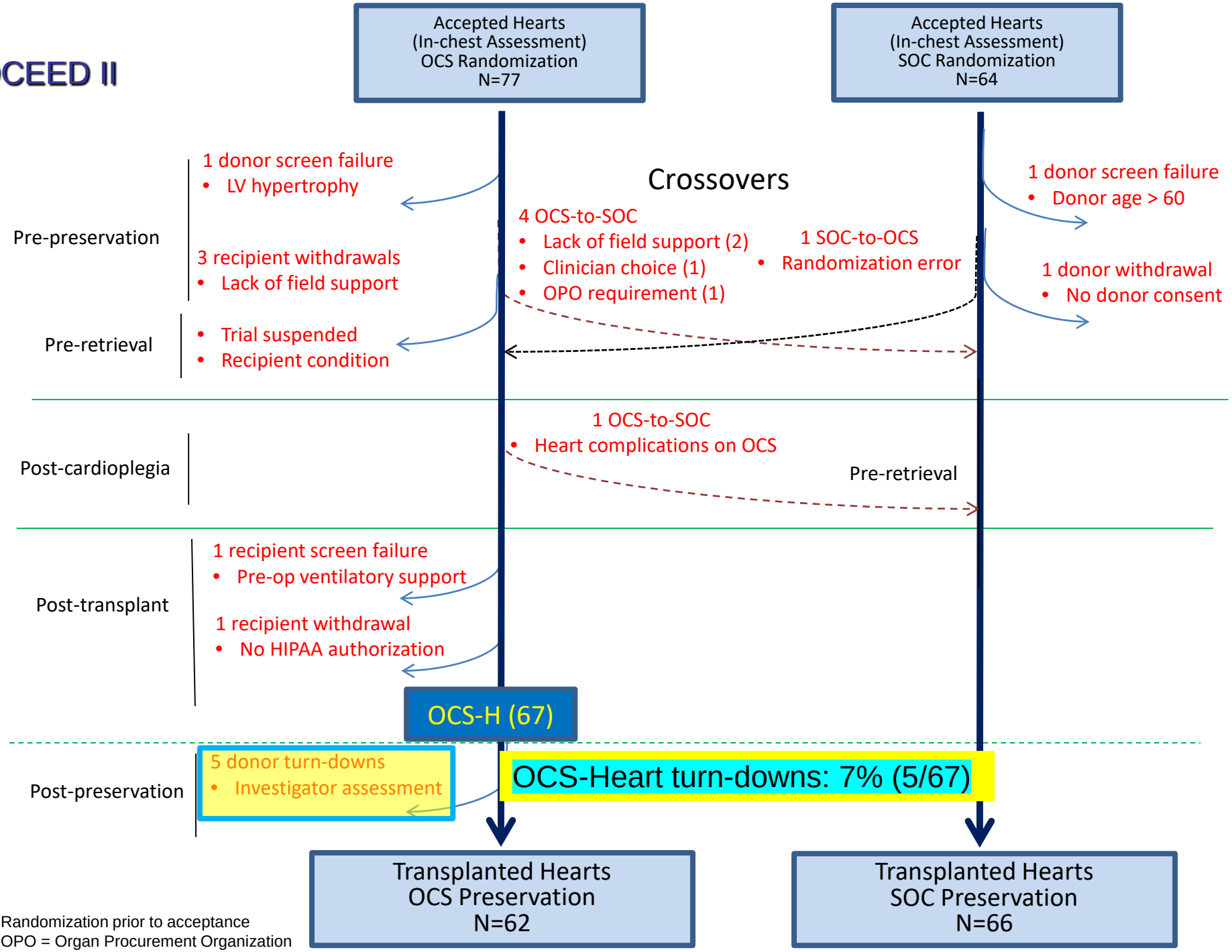
Patient and Graft Survival without MCS at Day 30 post-transplantation	SOC % (n/N)	OCS % (n/N)	SOC-OCS Difference % (95% UCB)	p-value ($\delta = 10\%$)
PP analysis	97 (59/61)	93 (56/60)	3.4 (9.9%)	0.047
mITT analysis*	97 (61/63)	94 (63/67)	2.8 (8.8%)	0.024

*2 turn-downs imputed

- Statistical non-inferiority of OCS in mITT population
  - Non-inferiority in AT population also
- Endpoints keyed to completed transplantation

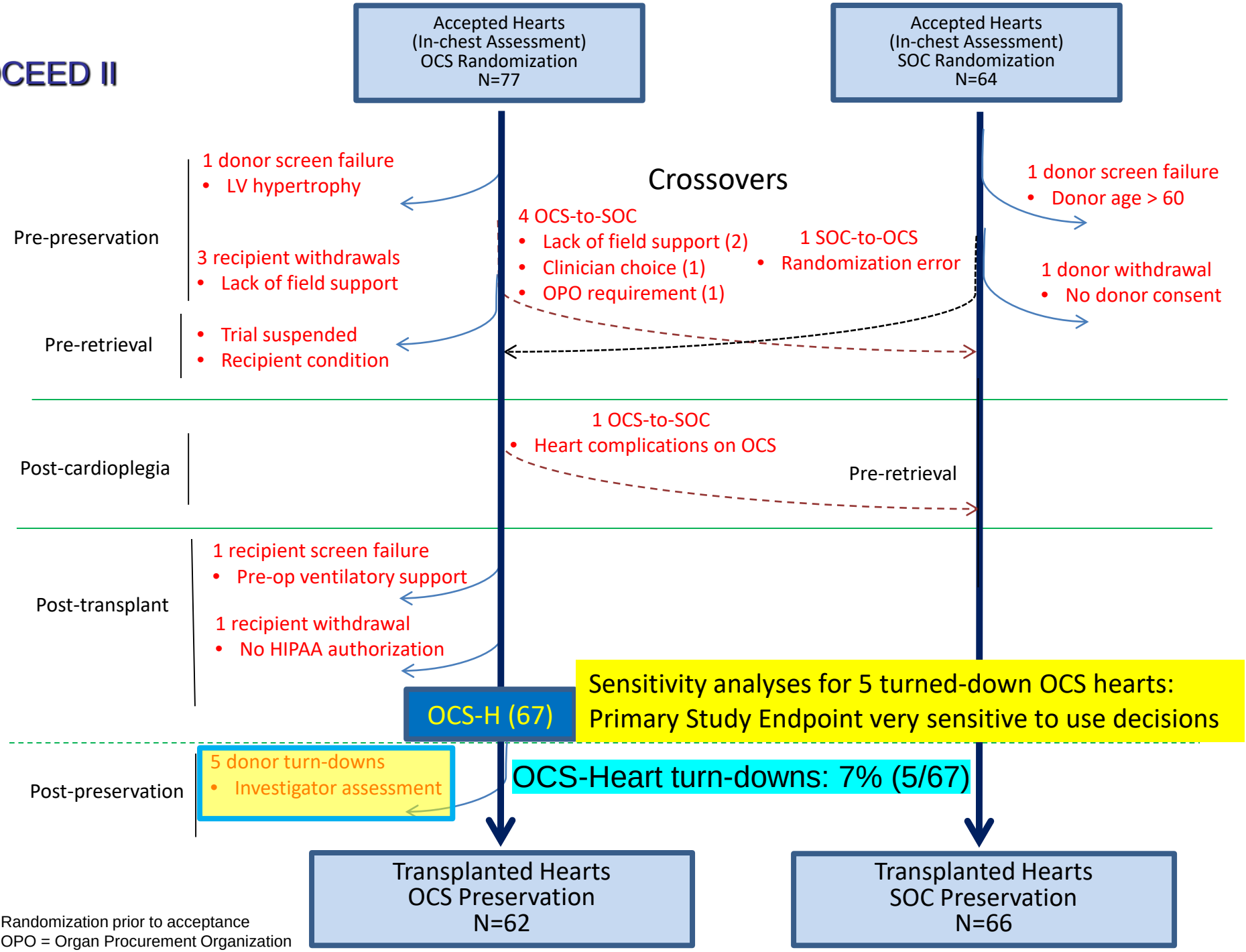
No pre-specified analysis fully accounted for effects of OCS-H turn-down

PROCEED II



Randomization prior to acceptance
OPO = Organ Procurement Organization

PROCEED II



Randomization prior to acceptance
OPO = Organ Procurement Organization

ICU and Hospital Stay
PROCEED II

Initial ICU Stay (Secondary Endpoint)

Hours	Treated Population		Completed Treatment Population	
	OCS	Control	OCS	Control
n	62	66	58	64
Mean (SD)	234.24 (349.02)	161.34 (92.10)	244.39 (358.72)	157.62 (90.84)
Median	147.05	137.09	150.67	128.23
95% Upper CL	37.68		46.92	
Min, Max	54.3, 2653.8	40.7, 447.7	54.3, 2653.8	40.7, 447.7
p-value	0.1157			

nominal p-value, not adjusted for multiple comparison

ICU and Hospital Stay
PROCEED II

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Min, Max	54.3, 2653.8	40.7, 447.7	54.3, 2653.8	40.7, 447.7
p-value	0.1157			

nominal p-value, not adjusted for multiple comparison

Non-inferiority not demonstrated (δ = 12 hours)

ICU and Hospital Stay
PROCEED II

Initial ICU Stay (Secondary Endpoint)

Hours	Treated Population		Completed Treatment Population	
	OCS	Control	OCS	Control
n	62	66	58	64
Mean (SD)	234.24 (349.02)	161.34 (92.10)	244.39 (358.72)	157.62 (90.84)
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p-value	0.1157			

nominal p-value, not adjusted for multiple comparison

Non-inferiority not demonstrated (δ = 12 hours)

Overall ICU Stay

Hours	Treated Population	
	OCS	Control
n	62	66
Mean (SD)	239.80 (348.13)	175.16 (130.30)
Median	150.67	144.94
Min, Max	54.3, 2653.8	40.7, 911.8
Number re-admitted	4/62	3/66

Clinically similar

ICU and Hospital Stay
PROCEED II

Initial ICU Stay (Secondary Endpoint)

Hours	Treated Population		Completed Treatment Population	
	OCS	Control	OCS	Control
n	62	66	58	64
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	OCS	Control
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Mean (SD)	239.80 (348.13)	175.16 (130.30)
Median	150.67	144.94
Min, Max	54.3, 2653.8	40.7, 911.8
Number re-admitted	4/62	3/66

Clinically similar

MCS after transplant

Type of MCS	Study arm	n	Mean ± SD (hours)	Median (hours)	Range (hours)
IABP	OCS	6	79.2±36.5	90.6	34-111
	SOC	5	53.7±48.5	32.3	13-134
VAD	OCS	3	225±173	135.6	115-425
	SOC	1	n/a	n/a	102
ECMO	OCS	4	67.8±29.0	54	52-111
	SOC	1	n/a	n/a	313

More frequent and longer MCS after OCS Heart

ICU and Hospital Stay
PROCEED II

Initial ICU Stay (Secondary Endpoint)

Hours	Treated Population		Completed Treatment Population	
	OCS	Control	OCS	Control
n	62	66	58	64
Mean (SD)	234.24 (349.02)	161.34 (92.10)	244.39 (358.72)	157.62 (90.84)
Median	147.05	137.09	150.67	128.23
95% Upper CL	37.68		46.92	
Min, Max	54.3, 2653.8	40.7, 447.7	54.3, 2653.8	40.7, 447.7
p-value	0.1157			

nominal p-value, not adjusted for multiple comparison

Non-inferiority not demonstrated (δ = 12 hours)

Overall ICU Stay

Hours	Treated Population	
	OCS	Control
n	62	66
Mean (SD)	239.80 (348.13)	175.16 (130.30)
Median	150.67	144.94
Min, Max	54.3, 2653.8	40.7, 911.8
Number re-admitted	4/62	3/66

Clinically similar

MCS after transplant

Type of MCS	Study arm	n	Mean ± SD (hours)	Median (hours)	Range (hours)
IABP	OCS	6	79.2±36.5	90.6	34-111
	SOC	5	53.7±48.5	32.3	13-134
VAD	OCS	3	225±173	135.6	115-425
	SOC	1	n/a	n/a	102
ECMO	OCS	4	67.8±29.0	54	52-111
	SOC	1	n/a	n/a	313

More frequent and longer MCS use after OCS Heart preservation

ICU and Hospital Stay
PROCEED II

Initial ICU Stay (Secondary Endpoint)

Hours	Treated Population		Completed Treatment Population	
	OCS	Control	OCS	Control
n	62	66	58	64
Mean (SD)	234.24 (349.02)	161.34 (92.10)	244.39 (358.72)	157.62 (90.84)
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	SOC	1	n/a	n/a	313

More frequent and longer MCS use after OCS Heart preservation

ICU and Hospital Stay
PROCEED II

Initial Hospital Stay

Days	Treated Population	
	OCS	Control
n	62	66
Mean (SD)	19.8 (23.6)	15.4 (8.1)
Median	14.3	12.8
Min, Max	3, 187	7, 46
Number re-admitted	5/62	6/66

Longer hospitalization after OCS Heart preservation

Clinically significant difference

Secondary Endpoints
PROCEED II

Acute Rejection

Grade 2R or 3R acute rejection at Day 30 post-transplantation	SOC % (n/N)	OCS % (n/N)	OCS-SOC Difference % (95% UCB)	p-value ($\delta = 10\%$)
AT analysis	14 (9/66)	18 (11/62)	4 (15%)	0.52*

Non-inferiority not demonstrated

All rejection episodes biopsy-proven 2R

Cardiac Graft-Related SAEs (Safety Endpoint)

CGRSAEs up to Day 30 post-transplantation	SOC % (n/N)	OCS % (n/N)	OCS-SOC Difference % (95% UCB)	p-value ($\delta = 10\%$)
AT analysis	14 (9/66)	13 (8/62)	-1 (9%)	0.04*

Non-inferiority demonstrated

* nominal p-values, not adjusted for multiple comparison

LONGER-TERM SURVIVAL as of 2020 PROCEED II

- US As-treated subjects only (N=118)
  - 91% of PROCEED II mITT population
    - Low censoring at 5 years (8.9% OCS Heart, 6.5% SOC)

Time Post-transplantation	OCS Heart Arm (N=56)				SOC Arm (N=62)			
	Subjects Left	Censored	Died	Survival Probability % (95% CI)	Subjects Left	Censored	Died	Survival Probability % (95% CI)
6 Months	49	1	6	89.3 (77.7, 95.0)	59	1	2	96.8 (87.7, 99.2)
1 Year	45	1	10	82.0 (69.1, 89.9)	58	1	3	95.1 (85.7, 98.4)
2 Years	41	1	14	74.7 (61.1, 84.2)	54	2	6	90.2 (79.5, 95.5)
3 Years	36	3	17	69.2 (55.3, 79.6)	52	2	8	86.9 (75.5, 93.2)
4 Years	33	5	18	67.3 (53.2, 78.0)	48	4	10	83.4 (71.3, 90.7)
5 Years	32	5	19	65.3 (51.1, 76.3)	48	4	10	83.4 (71.3, 90.7)

LONGER-TERM SURVIVAL as of 2020 PROCEED II

- US As-treated subjects only (N=118)
  - 91% of PROCEED II mITT population
    - Low censoring at 5 years (8.9% OCS Heart, 6.5% SOC)
- SOC survival point estimates greater than OCS Heart at all time points
  - Cox proportional hazard ratio for mortality: 1.927 (95% CI: 0.987, 3.876)

Time Post-transplantation	OCS Heart Arm (N=56)				SOC Arm (N=62)			
	Subjects Left	Censored	Died	Survival Probability % (95% CI)	Subjects Left	Censored	Died	Survival Probability % (95% CI)
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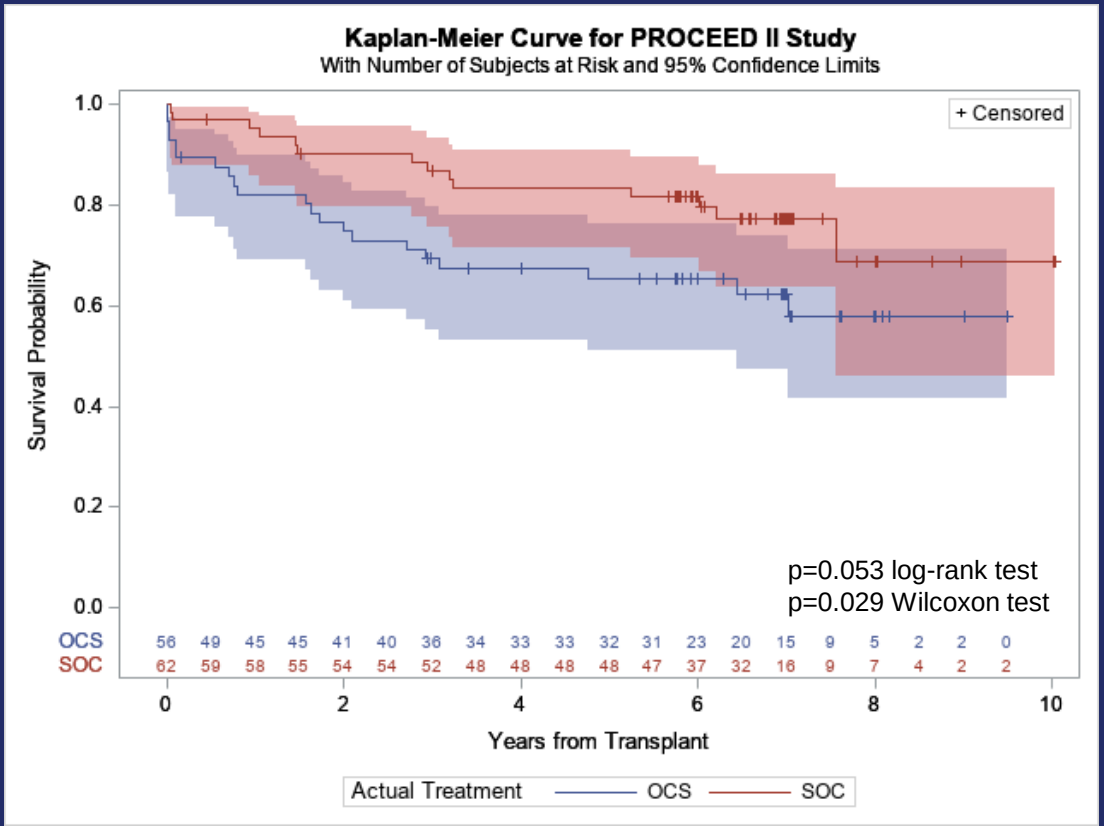
LONGER-TERM SURVIVAL as of 2020
PROCEED II

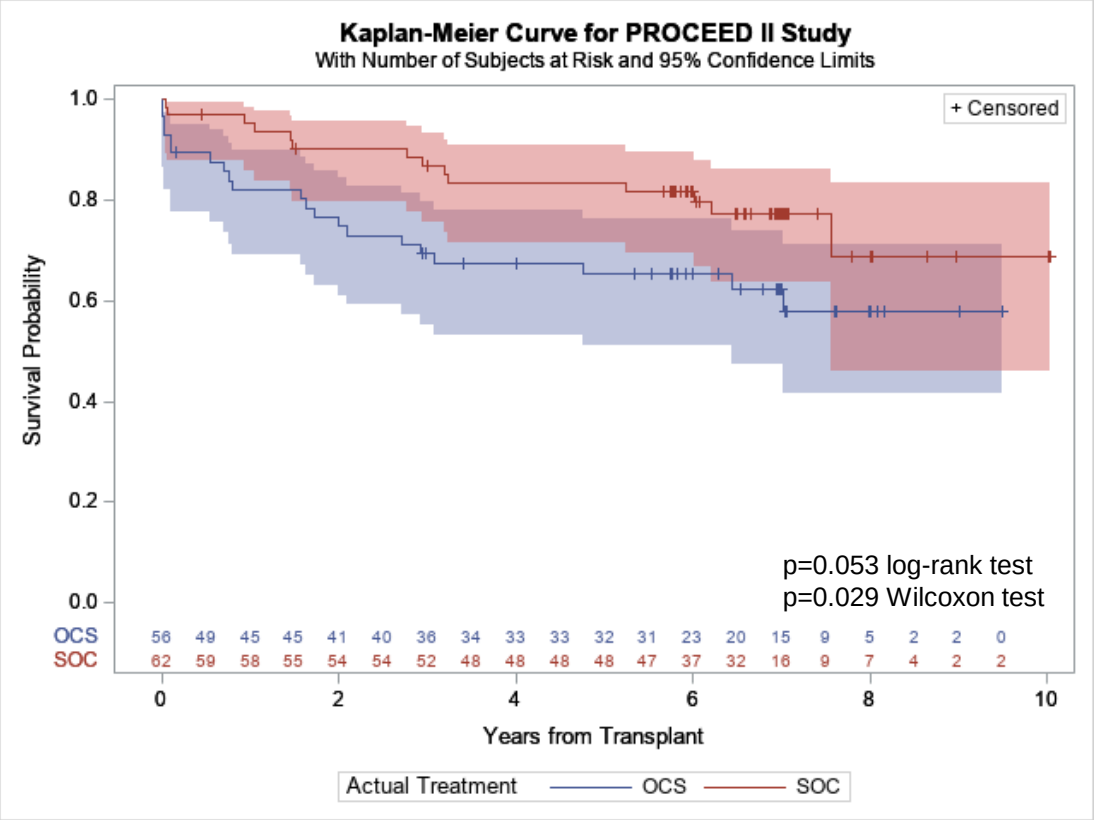
PROCEED II



p-value calculated from post-hoc analysis

LONGER-TERM SURVIVAL as of 2020
PROCEED II

PROCEED II



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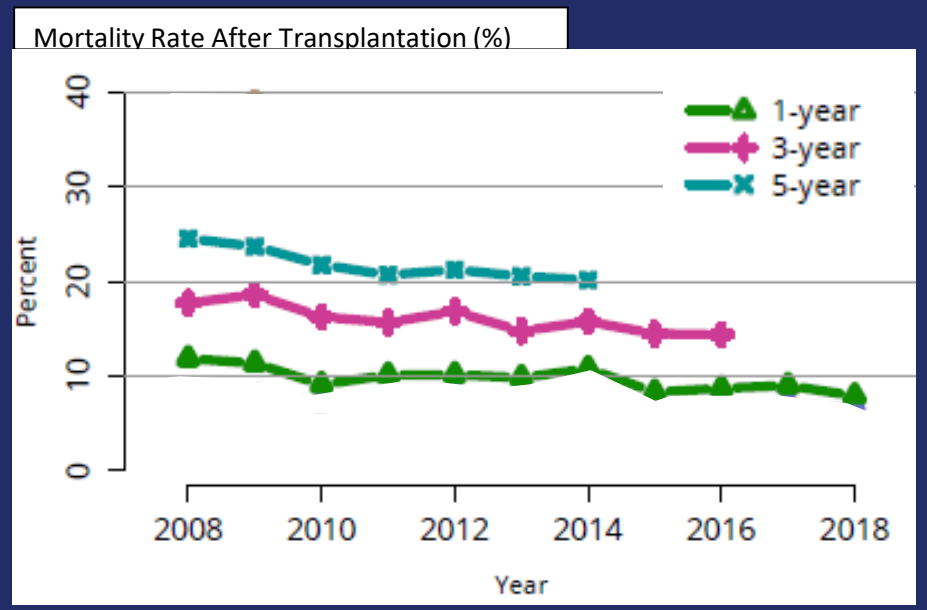
SRTR Annual Report (2019)



LONGER-TERM SURVIVAL as of 2020
PROCEED II

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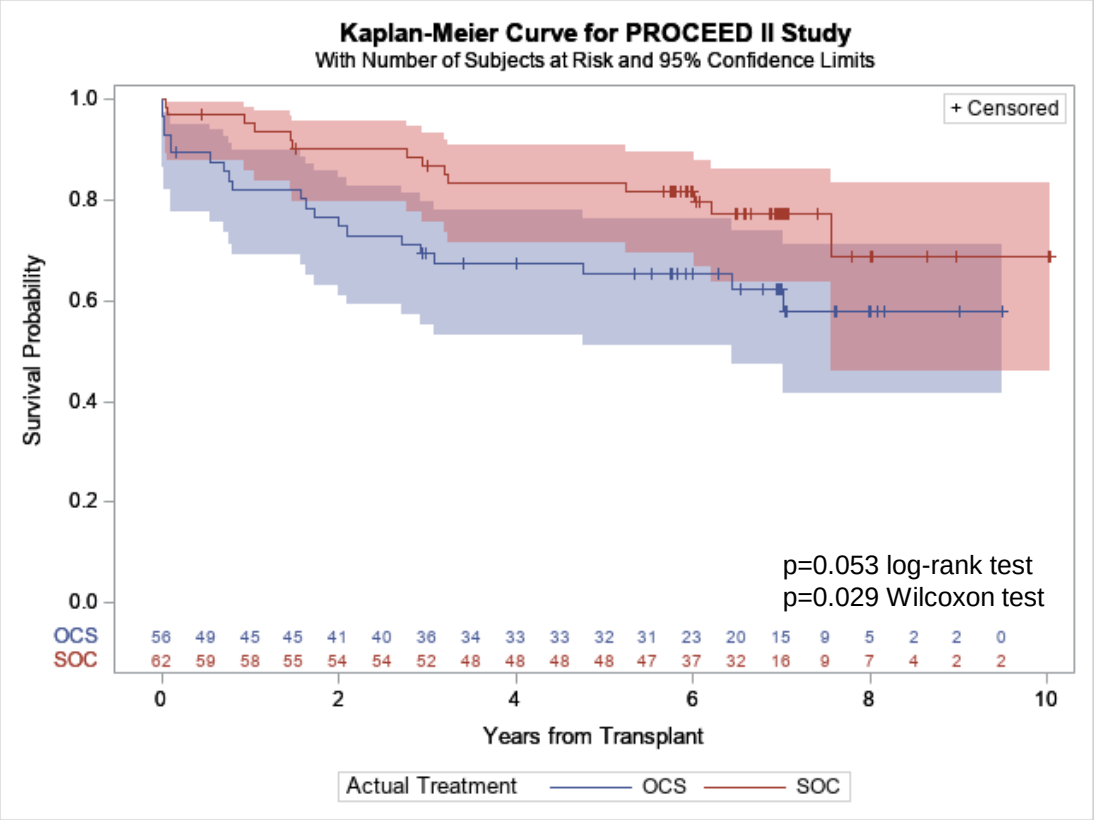

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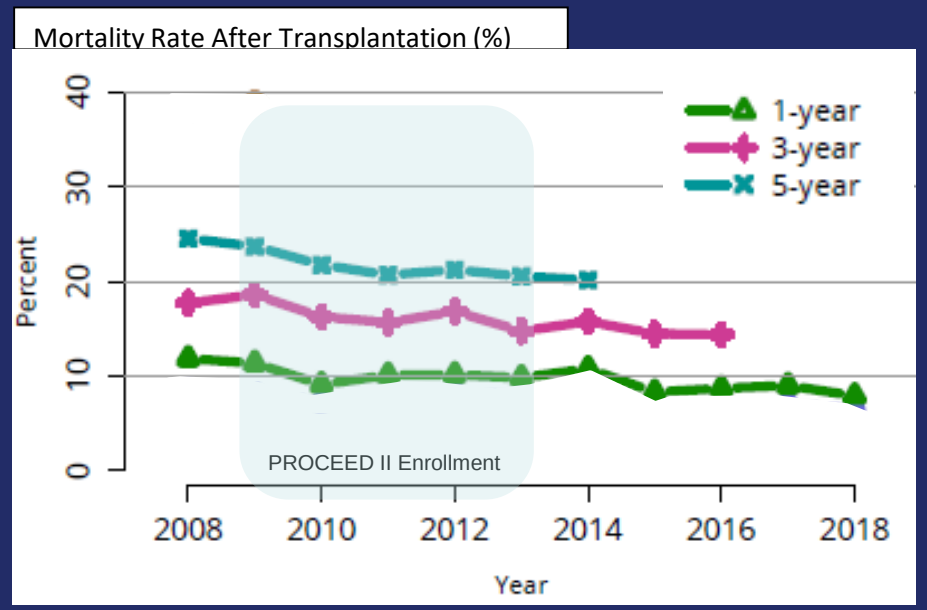

LONGER-TERM SURVIVAL as of 2020
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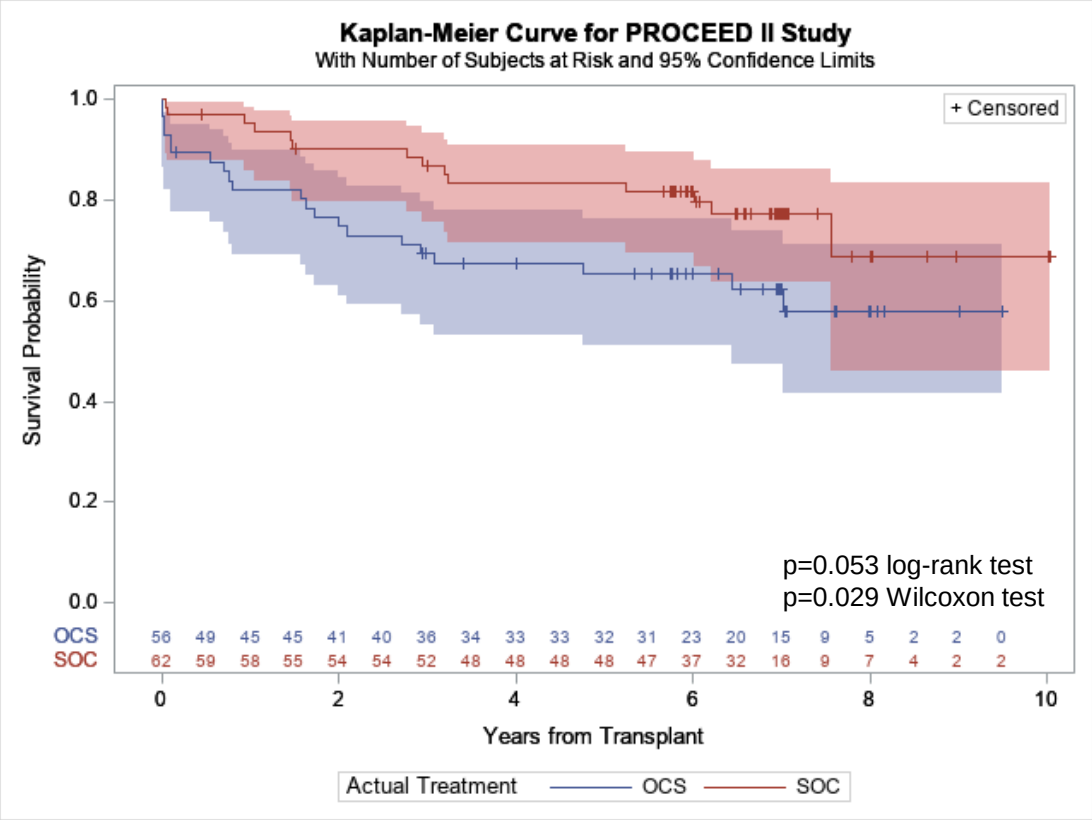

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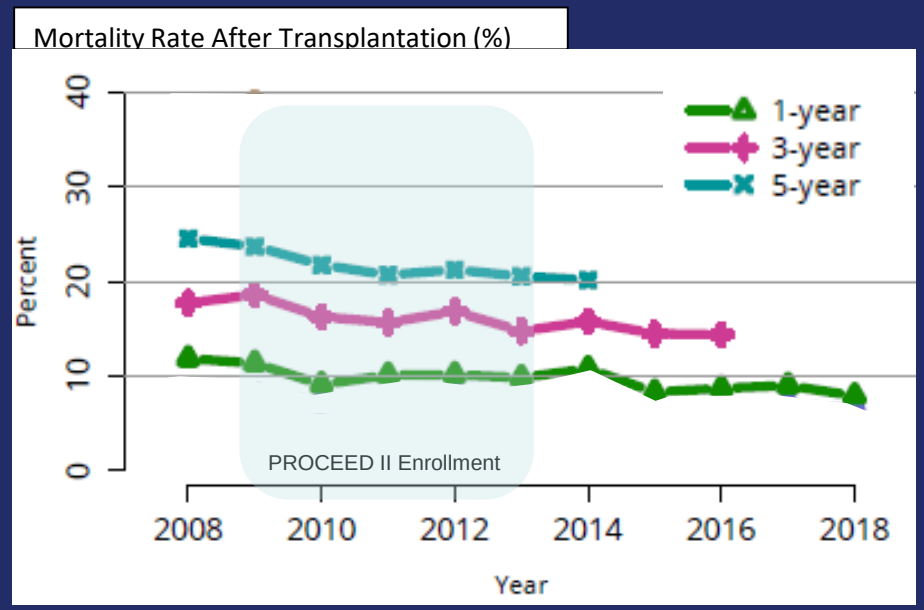
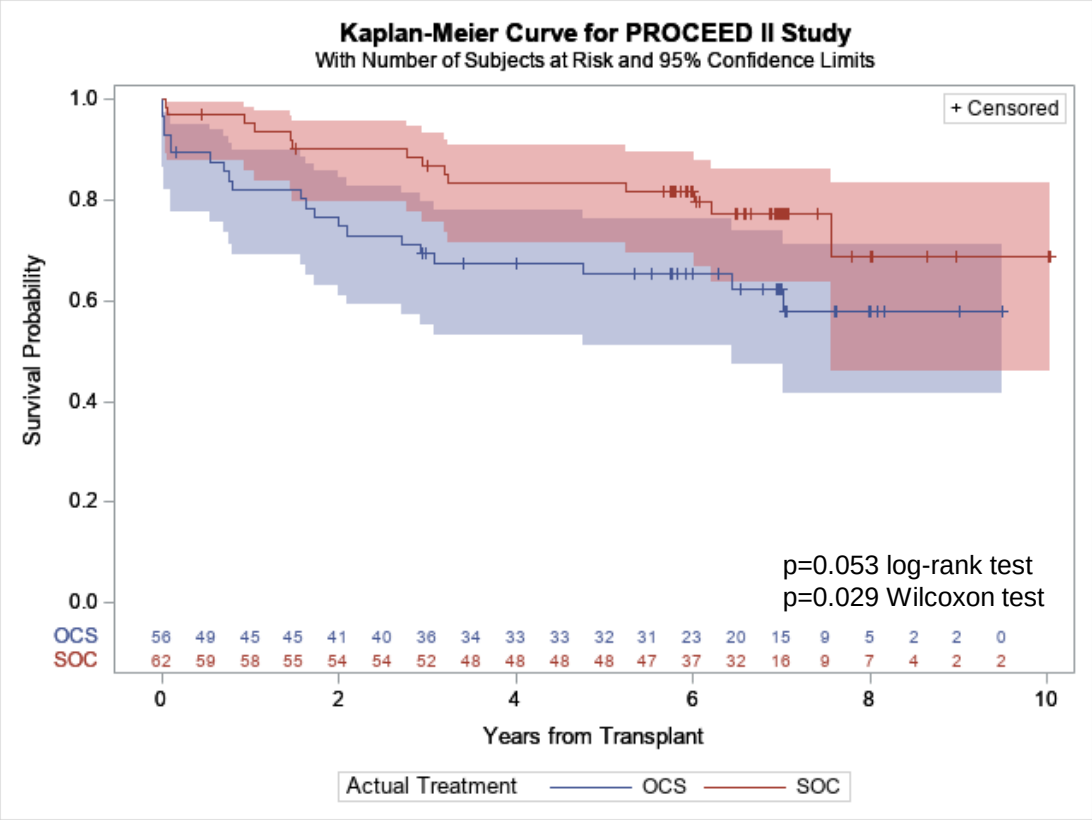


Compared to contemporaneous SRTR recipients

- OCS Heart recipient mortality higher
  - 1 year: 18%
  - 3 year: 31%
  - 5 year: 35%
- SOC recipient mortality lower
  - 1 year: 5%
  - 3 year: 13%
  - 5 year: 17%

LONGER-TERM SURVIVAL as of 2020
PROCEED II

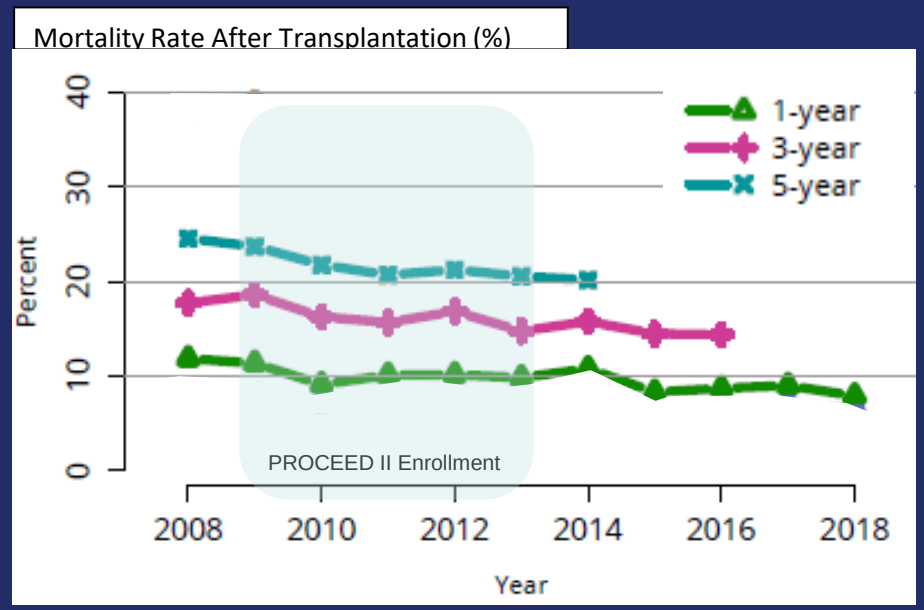
PROCEED II



p-value calculated from post-hoc analysis

Based on 2 comparators, clinically meaningful survival benefit for SOC cold static preservation

SRTR Annual Report (2019)



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LONGER-TERM SURVIVAL as of 2020
PROCEED II

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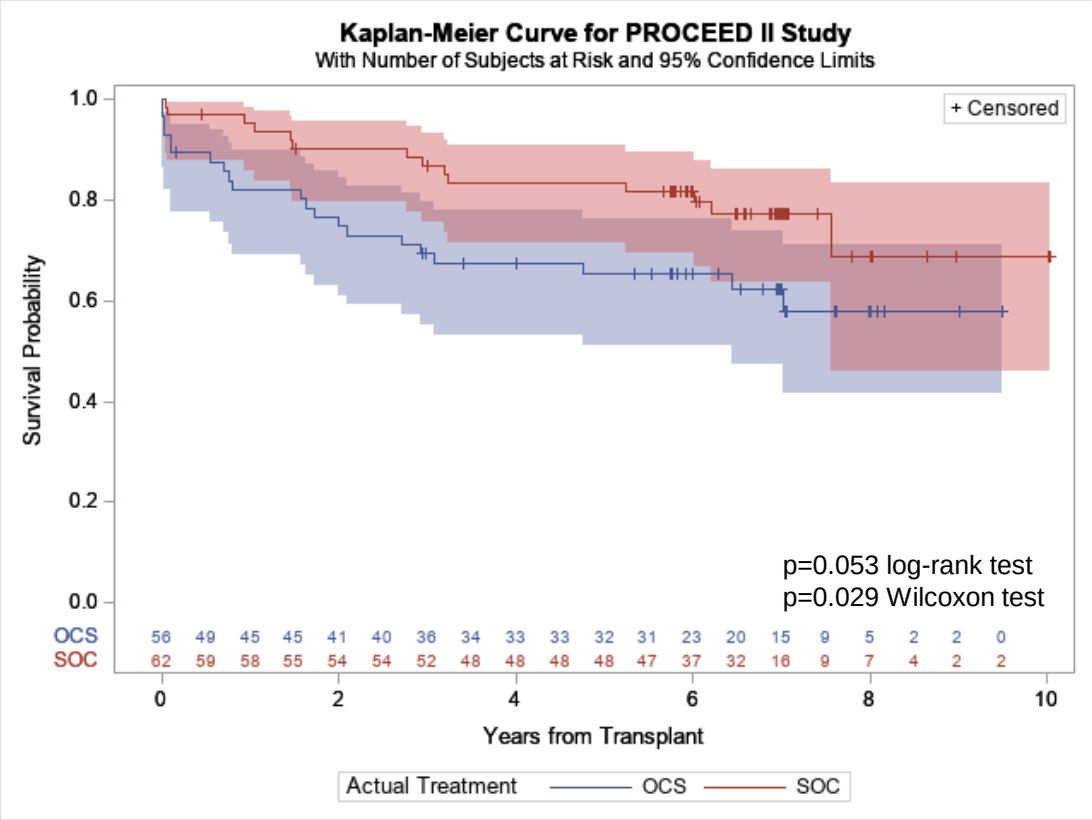
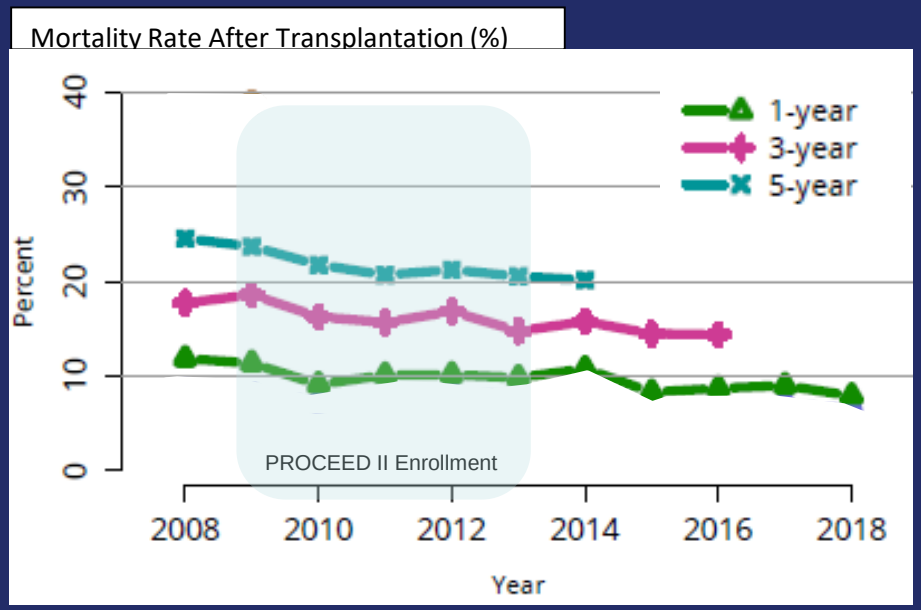


p-value calculated from post-hoc analysis

This finding should inform the benefit-risk assessment of the current PMA (EXPAND)

SRTR Annual Report (2019)



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Summary
PROCEED II

- PROCEED II had complex trial design
  - Necessary because of organ transplantation logistics
  - Important selection bias cannot be excluded
- Longer preservation times with OCS Heart System as compared to cold static preservation (SOC)
  - System decreases, but does not eliminate, cold ischemia
- PROCEED II demonstrated non-inferiority of 30-day effectiveness to SOC
  - Clinical value of non-inferiority uncertain
- Need for mechanical circulatory support, post-transplantation ICU time, and hospital length of stay more favorable after SOC than after OCS Heart
- 30-day mortality higher in subjects transplanted with OCS Heart donor organs compared to SOC donor organs and to SRTR data
  - SOC survival benefit has persisted over long-term follow-up

EXPAND

- Single-armed multicenter trial
  - Unblinded
  - Enrollment after in-chest acceptance (before procurement)
  - Testing against performance goal (PG)
    - Sponsor justification: randomized comparator not available
    - FDA recommendation: non-randomized concurrent comparator (SOC)
      - Safety and effectiveness of OCS Heart not yet demonstrated

        PROCEED II not available to FDA

EXPAND--Primary Effectiveness Endpoint
Choice of Performance Goal

- FDA accepted performance goal metric

  Patient survival at Day 30 post-transplantation in the absence of severe PGD-LV or PGD-RV ISHLT Primary Graft Dysfunction (PGD)

- FDA concerns regarding performance goal value (65%)

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  - Cited literature had heterogenous definitions of PGD for endpoint

    “Each of these studies utilized a slightly different definition, but what is clear is that the incidence of PGD is high…”

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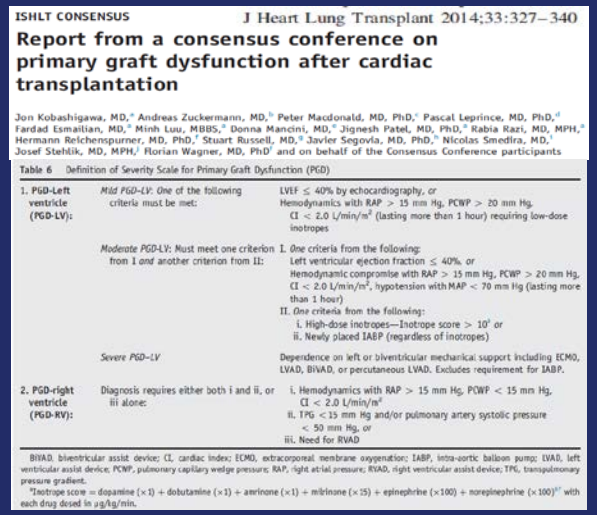

ISHLT CONSENSUS J Heart Lung Transplant 2014;33:327–340

Report from a consensus conference on primary graft dysfunction after cardiac transplantation

Jon Kobashigawa, MD,[a] Andreas Zuckermann, MD,[b] Peter Macdonald, MD, PhD,[c] Pascal Leprince, MD, PhD,[d] Fardad Esmailian, MD,[e] Minh Luu, MBBS,[a] Donna Mancini, MD,[a] Jignesh Patel, MD, PhD,[a] Rabia Razi, MD, MPH,[a] Hermann Reichenspurner, MD, PhD,[f] Stuart Russell, MD,[g] Javier Segovia, MD, PhD,[h] Nicolas Smedira, MD,[i] Josef Stehlik, MD, MPH,[j] Florian Wagner, MD, PhD[k] and on behalf of the Consensus Conference participants

Table 6 Definition of Severity Scale for Primary Graft Dysfunction (PGD)

1. PGD-Left ventricle (PGD-LV):	*Mild PGD-LV*: One of the following criteria must be met:	LVEF ≤ 40% by echocardiography, *or* Hemodynamics with RAP > 15 mm Hg, PCWP > 20 mm Hg, CI < 2.0 L/min/m² (lasting more then 1 hour) requiring low-dose inotropes
	Moderate PGD-LV: Must meet one criterion from I *and* another criterion from II:	I. *One* criteria from the following: Left ventricular ejection fraction ≤ 40%, *or* Hemodynamic compromise with RAP > 15 mm Hg, PCWP > 20 mm Hg, CI < 2.0 L/min/m², hypotension with MAP < 70 mm Hg (lasting more than 1 hour) II. *One* criteria from the following: i. High-dose inotropes—Inotrope score > 10[*] or ii. Newly placed IABP (regardless of inotropes)
	Severe PGD-LV	Dependence on left or biventricular mechanical support including ECMO, LVAD, BiVAD, or percutaneous LVAD. Excludes requirement for IABP.
2. PGD-right ventricle (PGD-RV):	Diagnosis requires either both i and ii, or iii alone:	i. Hemodynamics with RAP > 15 mm Hg, PCWP < 15 mm Hg, CI < 2.0 L/min/m² ii. TPG < 15 mm Hg and/or pulmonary artery systolic pressure < 50 mm Hg, *or* iii. Need for RVAD

BiVAD, biventricular assist device; CI, cardiac index; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RVAD, right ventricular assist device; TPG, transpulmonary pressure gradient.

[*]Inotrope score = dopamine (×1) + dobutamine (×1) + amrinone (×1) + milrinone (×15) + epinephrine (×100) + norepinephrine (×100)[47] with each drug dosed in μg/kg/min.

- Importantly, the diagnosis of PGD is to be made within 24 hours after completion of the cardiac transplant surgery.
- Because RV failure can often be more difficult to quantify, there are no grades for the severity of PGD-RV.
- Graft dysfunction is to be classified into PGD or secondary graft dysfunction where there is a discernible cause

EXPAND
Secondary Endpoints

FDA

Effectiveness

1. Patient survival at Day 30

   No hypothesis, component of Primary Endpoint

2. Incidence of severe PGD-LV / PGD-RV (in 24°)

   No hypothesis, component of Primary Endpoint

3. Utilization (transplantation) rate among OCS Heart-preserved donor organs

   No hypothesis

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   No hypothesis

Safety

Incidence of Medical Monitor (MM)-adjudicated heart graft-related serious adverse events (HGRSAEs) up to 30 days

HGRSAEs*

- Graft failure leading to re-transplantation
- Moderate or severe PGD-LV / PGD-RV (ISHLT, within 24°)

* Differed from PROCEED II CGRSAEs

No hypothesis
FDA recommended hypothesis-testing

EXPAND
Secondary Endpoints

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- Moderate or severe PGD-LV / PGD-RV (ISHLT, within 24°)

* Differed from PROCEED II CGRSAEs

No hypothesis
FDA recommended hypothesis-testing

Other Effectiveness Measures

- 12-month survival (Kaplan-Meier analysis)
- *Post hoc* analyses
  - Stratification
    - Preservation time
    - Donor heart inclusion criteria
    - Study site
  - Turned-down donor organ
    - Tipping point analysis for Primary Effectiveness Endpoint
    - Pathology review
  - Pooling of EXPAND + EXPAND CAP datasets

EXPAND
Recipient Inclusion/Exclusion Criteria

Recipient	
	EXPAND
Inclusion Criteria	
Heart transplant	Primary
Age	≥ 18 years
Informed consent	≠ enrollment
Exclusion Criteria	
Prior transplant	Excluded
Concurrent transplant	Excluded
Prior sternotomy	Not excluded
Ventilator	Not excluded
VAD > 30 days (+ sepsis/hemorrhage/HITT)	Not excluded
PRA	Not excluded
Renal dysfunction	• Chronic insufficiency • Chronic hemodialysis

Recipient Inclusion/Exclusion Criteria EXPAND versus PROCEED II

Recipient		
	EXPAND	PROCEED II
Inclusion Criteria		
Heart transplant	Primary	Primary
Age	≥ 18 years	≥ 18 years
Informed consent	≠ enrollment	≠ enrollment
Exclusion Criteria		
Prior transplant	Excluded	Not excluded
Concurrent transplant	Excluded	Excluded → Renal Tx allowed
Prior sternotomy	Not excluded	> 4 → > 2
Ventilator	Not excluded	Excluded
VAD > 30 days (+ sepsis/hemorrhage/HITT)	Not excluded	Excluded
PRA	Not excluded	> 40%
Renal dysfunction	• Chronic insufficiency • Chronic hemodialysis	• Chronic serum creatinine >3.0 mg/dl • Hemodialysis

Recipient Inclusion/Exclusion Criteria EXPAND versus PROCEED II

Recipient		
	EXPAND	PROCEED II
Inclusion Criteria		
Heart transplant	Primary	Primary
Age	≥ 18 years	≥ 18 years
Informed consent	≠ enrollment	≠ enrollment
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Recipient Inclusion/Exclusion Criteria EXPAND versus PROCEED II

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	EXPAND	PROCEED II
Inclusion Criteria		
Heart transplant	Primary	Primary
Age	≥ 18 years	≥ 18 years
Informed consent	≠ enrollment	≠ enrollment
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Prior transplant	Excluded	Not excluded
Concurrent transplant	Excluded	Excluded → Renal Tx allowed
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Ventilator	Not excluded	Excluded
VAD > 30 days (+ sepsis/hemorrhage/HITT)	Not excluded	Excluded
PRA	Not excluded	> 40%
Renal dysfunction	• Chronic insufficiency • Chronic hemodialysis	• Chronic serum creatinine >3.0 mg/dl • Hemodialysis

EXPAND
Donor Inclusion/Exclusion Criteria

Inclusion

- Expected total cross-clamp time of ≥ 4 hours

--or--

- Expected total cross-clamp time of ≥ 2 hours and ≥ 1 of:
  - ≥ 55 years old
  - 45-55 years old, no coronary catheterization
  - LVH: IVS or PW thickness > 12 mm but ≤ 16 mm
  - EF ≥ 40% and ≤ 50%
  - Reported down time ≥ 20 min, stable hemodynamics
  - Angiographic luminal irregularities, no significant CAD
  - Carbon monoxide poisoning
  - Social history of alcoholism
  - Diabetes, no angiographic CAD

Exclusion

- Abnormal angiography (> 50% stenosis, needing CABG)
- Donor-to-recipient body weight ratio of < 0.6
- Vasoactive support at final in-chest assessment
- Any criterion based on site standard practice

Donor Inclusion/Exclusion Criteria
EXPAND versus PROCEED II

PROCEED II

Inclusion

- < 60 years old
- MAP > 60 mmHg at final assessment
- Satisfactory echocardiography:
  - Ejection fraction > 40%
  - Absence of severe segmental wall motion Δ
  - Absence of LVH: IVS and PW thickness < 13 mm)
  - Absence of valve abnormalities ($\bar{x}$ regurg. > mod)

Exclusion

- Abnormal angiography (> 50% stenosis, needing CABG)
- Donor-to-recipient body weight ratio of < 0.6
- Vasoactive support at final assessment
- Any criterion based on site standard practice

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  - Social history of alcoholism
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Exclusion

- Angiographic CAD (> 50% stenosis)
- Sustained EF < 40% at final inspection
- MI or cardiogenic shock
- Significant valve disease ($\bar{x}$ bicuspid AV)

Inclusion/Exclusion Criteria
Donor

PROCEED II

Inclusion

- < 60 years old
- MAP > 60 mmHg at final assessment
- Satisfactory echocardiography:
  - Ejection fraction > 40%
  - Absence of severe segmental wall motion Δ
  - Absence of LVH: IVS and PW thickness < 13 mm)
  - Absence of valve abnormalities ($\bar{x}$ regurg. > mod)

Exclusion

- Abnormal angiography (> 50% stenosis, needing CABG)
- Donor-to-recipient body weight ratio of < 0.6
- Vasoactive support at final assessment
- Any criterion based on site standard practice

EXPAND

Inclusion

- Expected total cross-clamp time of ≥ 4 hours

--or--

- Expected total cross-clamp time of ≥ 2 hours and ≥ 1 of:
  - ≥ 55 years old
  - 45-55 years old, no coronary catheterization
  - LVH: IVS or PW thickness > 12 mm but ≤ 16 mm
  - EF ≥ 40% and ≤ 50%
  - Reported down time ≥ 20 min, stable hemodynamics
  - Angiographic luminal irregularities, no significant CAD
  - Carbon monoxide poisoning
  - Social history of alcoholism
  - Diabetes, no angiographic CAD

Exclusion

- Angiographic CAD (> 50% stenosis)
- Sustained EF < 40% at final inspection
- MI or cardiogenic shock
- Significant valve disease ($\bar{x}$ bicuspid AV)

Inclusion/Exclusion Criteria
Donor

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- < 60 years old
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- Satisfactory echocardiography:
  - Ejection fraction > 40%
  - Absence of severe segmental wall motion Δ
  - Absence of LVH: IVS and PW thickness < 13 mm)
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Exclusion

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- Donor-to-recipient body weight ratio of < 0.6
- Vasoactive support at final assessment
- Any criterion based on site standard practice

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- Any criterion based on site standard practice

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- Significant valve disease ($\bar{x}$ bicuspid AV)

EXPAND
Pre-specified Analysis Populations

Donor Hearts

OCS Heart (OCS-H)

All donor hearts instrumented onto and transported with OCS Heart System

Recipients

Transplanted Recipient (TR)

All subjects transplanted with an OCS Heart-preserved donor organ, in the absence of:

- recipient/donor enrollment criteria violation
- failure to follow IFU
- failure to follow protocol

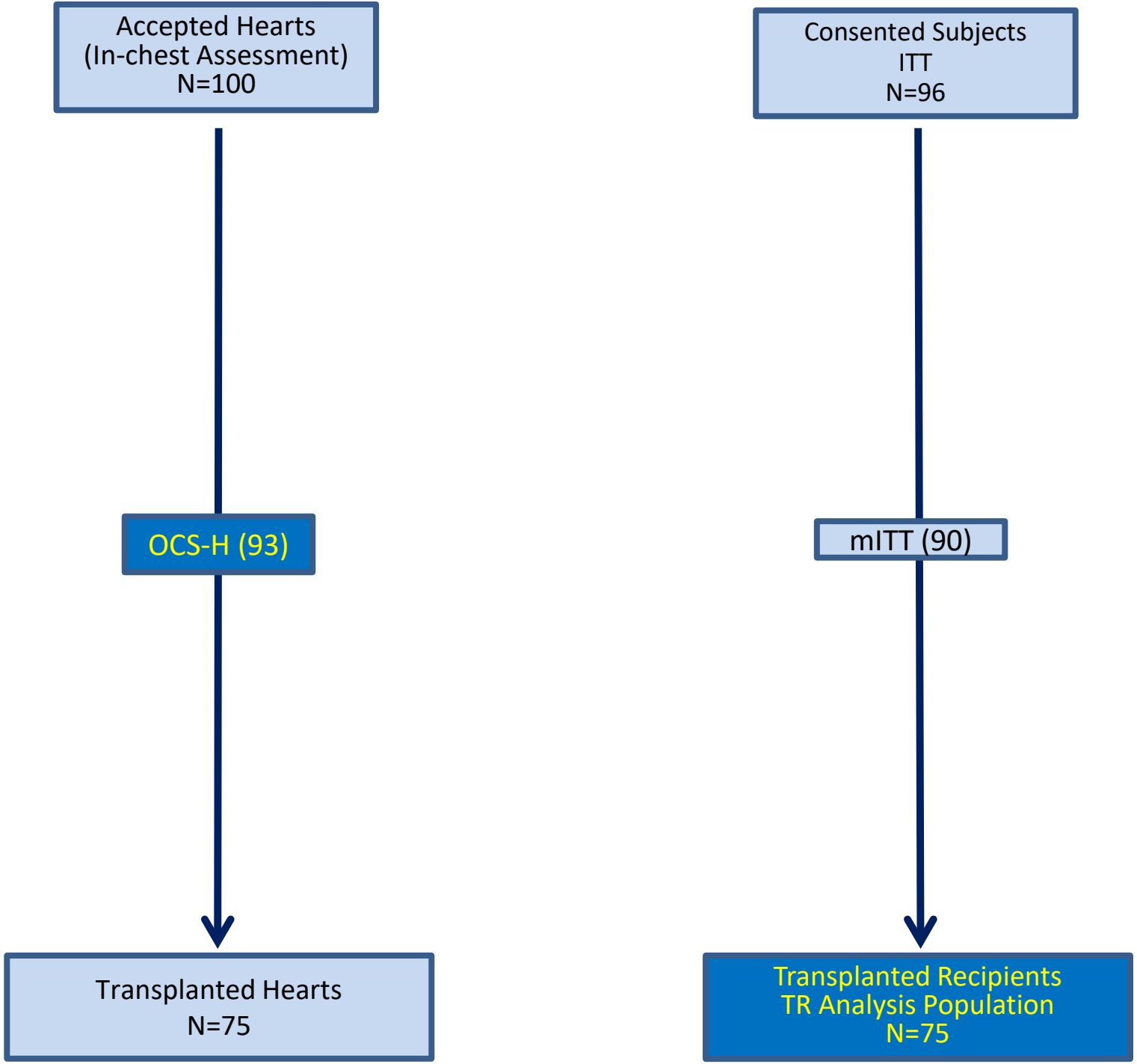
Equivalent to a “PP” analysis population

EXPAND
Recipient Enrollment

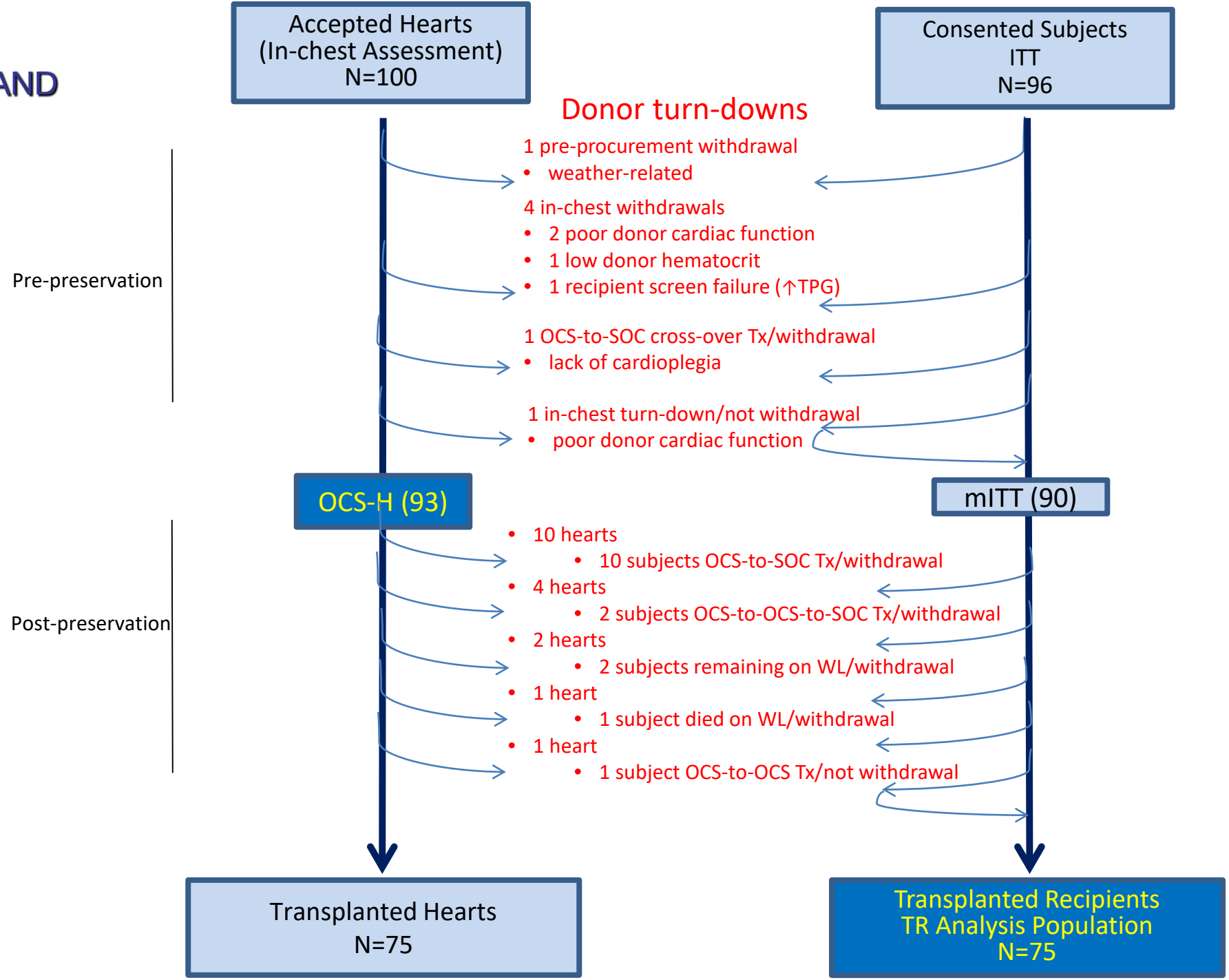
#	Site Name	Transplanted Recipients (TR) n=75
1		0
2		7
3		13
4		1
5		2
6		29
7		0
8		1
9		7
10		12
11		3
12		0

- 9 US enrolling sites
  - September, 2015 – March, 2018
    1 IRB approval withdrawal (#2)
- Highest enrolling site (#6)
  - 39% of EXPAND TR subjects
- No outcome data for ~1/4 of consented subjects:
  - Withdrawn pre-preservation: 6%
    - 1% crossover to SOC
  - Withdrawn after preservation: 16%
    - OCS-H turn-down

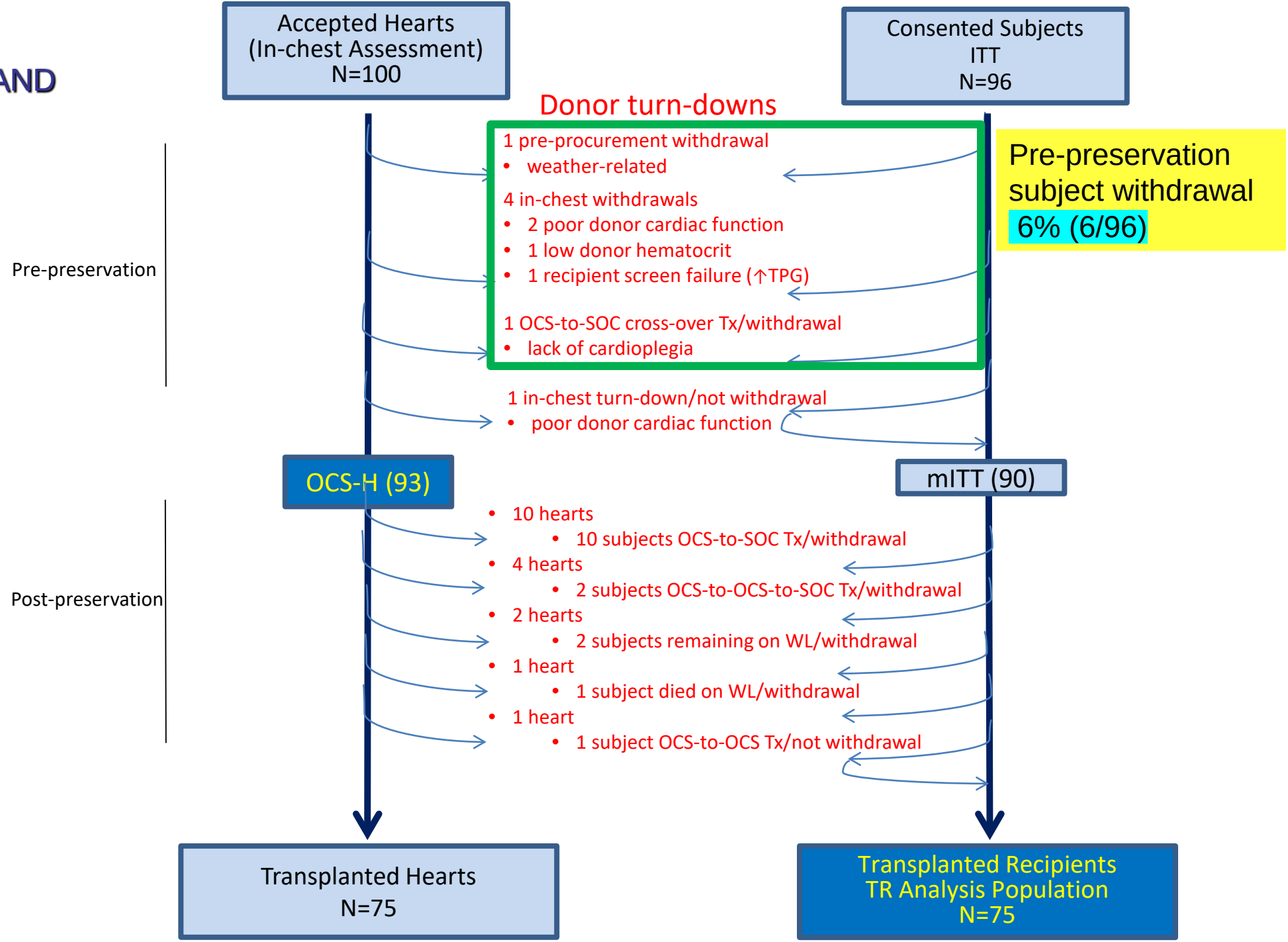
EXPAND


Accepted Hearts
(In-chest Assessment)
N=100
OCS-H (93)
Transplanted Hearts
N=75
Consented Subjects
ITT
N=96
mITT (90)
Transplanted Recipients
TR Analysis Population
N=75

EXPAND


Accepted Hearts
(In-chest Assessment)
N=100
Consented Subjects
ITT
N=96
Donor turn-downs
1 pre-procurement withdrawal
• weather-related
4 in-chest withdrawals
• 2 poor donor cardiac function
• 1 low donor hematocrit
• 1 recipient screen failure (↑TPG)
1 OCS-to-SOC cross-over Tx/withdrawal
• lack of cardioplegia
1 in-chest turn-down/not withdrawal
• poor donor cardiac function
Pre-preservation
OCS-H (93)
mITT (90)
• 10 hearts
• 10 subjects OCS-to-SOC Tx/withdrawal
• 4 hearts
• 2 subjects OCS-to-OCS-to-SOC Tx/withdrawal
• 2 hearts
• 2 subjects remaining on WL/withdrawal
• 1 heart
• 1 subject died on WL/withdrawal
• 1 heart
• 1 subject OCS-to-OCS Tx/not withdrawal
Post-preservation
Transplanted Hearts
N=75
Transplanted Recipients
TR Analysis Population
N=75

EXPAND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Consented Subjects
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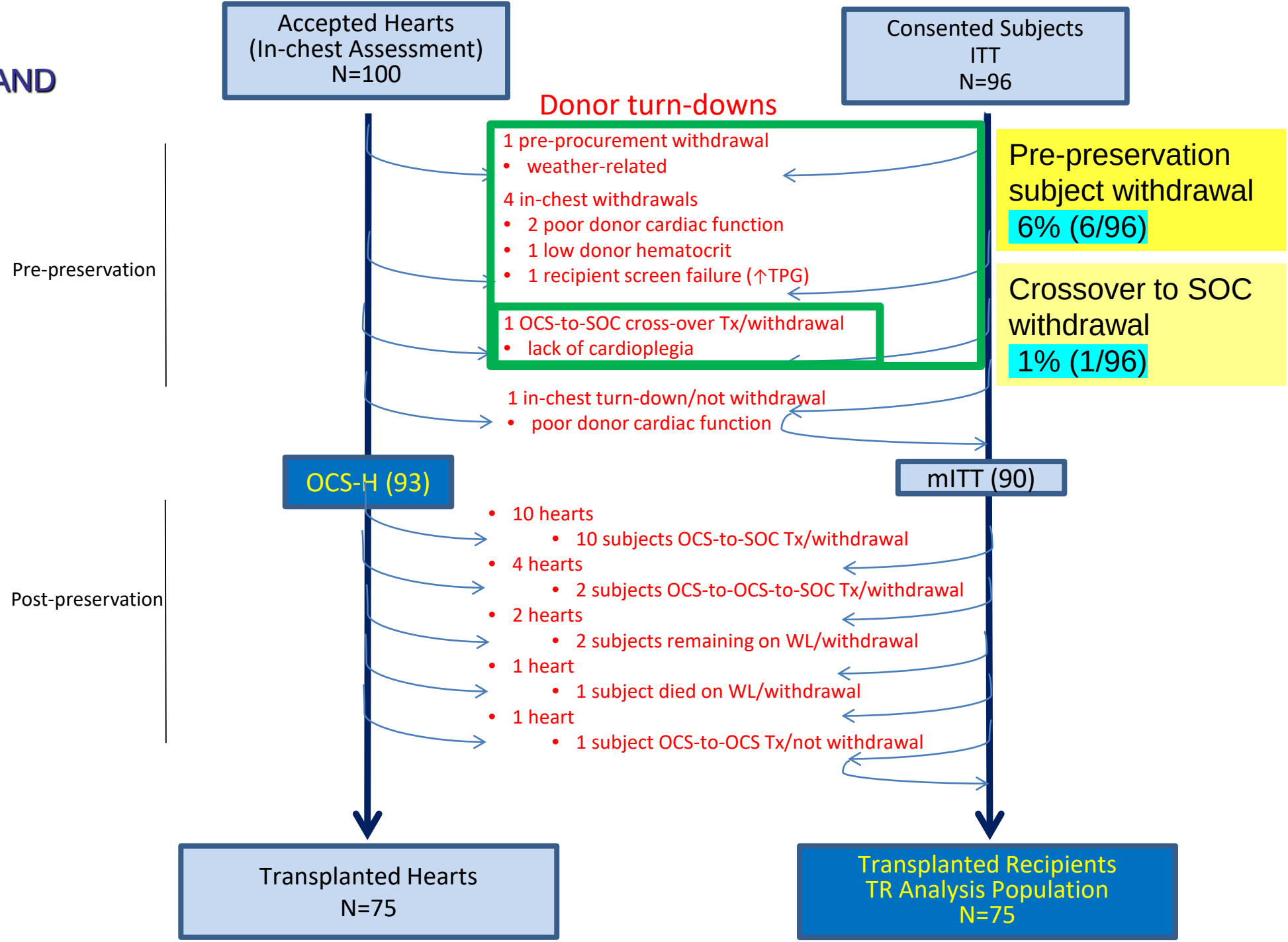
Donor turn-downs
1 pre-procurement withdrawal
• weather-related
4 in-chest withdrawals
• 2 poor donor cardiac function
• 1 low donor hematocrit
• 1 recipient screen failure (↑TPG)
1 OCS-to-SOC cross-over Tx/withdrawal
• lack of cardioplegia
Pre-preservation subject withdrawal
6% (6/96)
Pre-preservation
1 in-chest turn-down/not withdrawal
• poor donor cardiac function
OCS-H (93)
mITT (90)
Post-preservation
• 10 hearts
• 10 subjects OCS-to-SOC Tx/withdrawal
• 4 hearts
• 2 subjects OCS-to-OCS-to-SOC Tx/withdrawal
• 2 hearts
• 2 subjects remaining on WL/withdrawal
• 1 heart
• 1 subject died on WL/withdrawal
• 1 heart
• 1 subject OCS-to-OCS Tx/not withdrawal
Transplanted Hearts
N=75
Transplanted Recipients
TR Analysis Population
N=75

EXPAND


Accepted Hearts
(In-chest Assessment)
N=100
Consented Subjects
ITT
N=96
Donor turn-downs
1 pre-procurement withdrawal
• weather-related
4 in-chest withdrawals
• 2 poor donor cardiac function
• 1 low donor hematocrit
• 1 recipient screen failure (↑TPG)
1 OCS-to-SOC cross-over Tx/withdrawal
• lack of cardioplegia
Pre-preservation subject withdrawal
6% (6/96)
Crossover to SOC withdrawal
1% (1/96)
Pre-preservation
1 in-chest turn-down/not withdrawal
• poor donor cardiac function
OCS-H (93)
mITT (90)
Post-preservation
• 10 hearts
• 10 subjects OCS-to-SOC Tx/withdrawal
• 4 hearts
• 2 subjects OCS-to-OCS-to-SOC Tx/withdrawal
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• 2 subjects remaining on WL/withdrawal
• 1 heart
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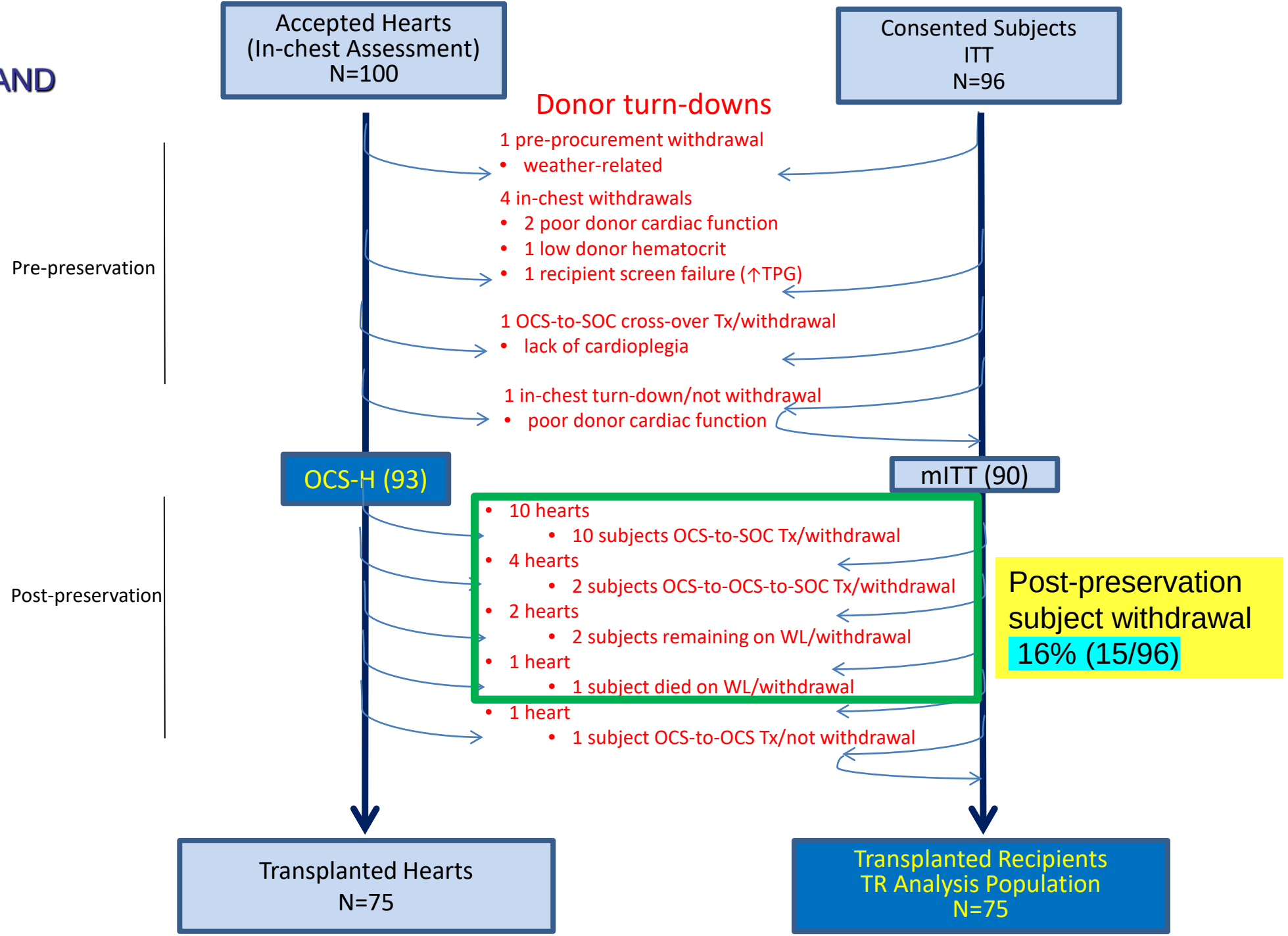
Transplanted Hearts
N=75
Transplanted Recipients
TR Analysis Population
N=75

EXPAND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ITT
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Pre-preservation
Post-preservation
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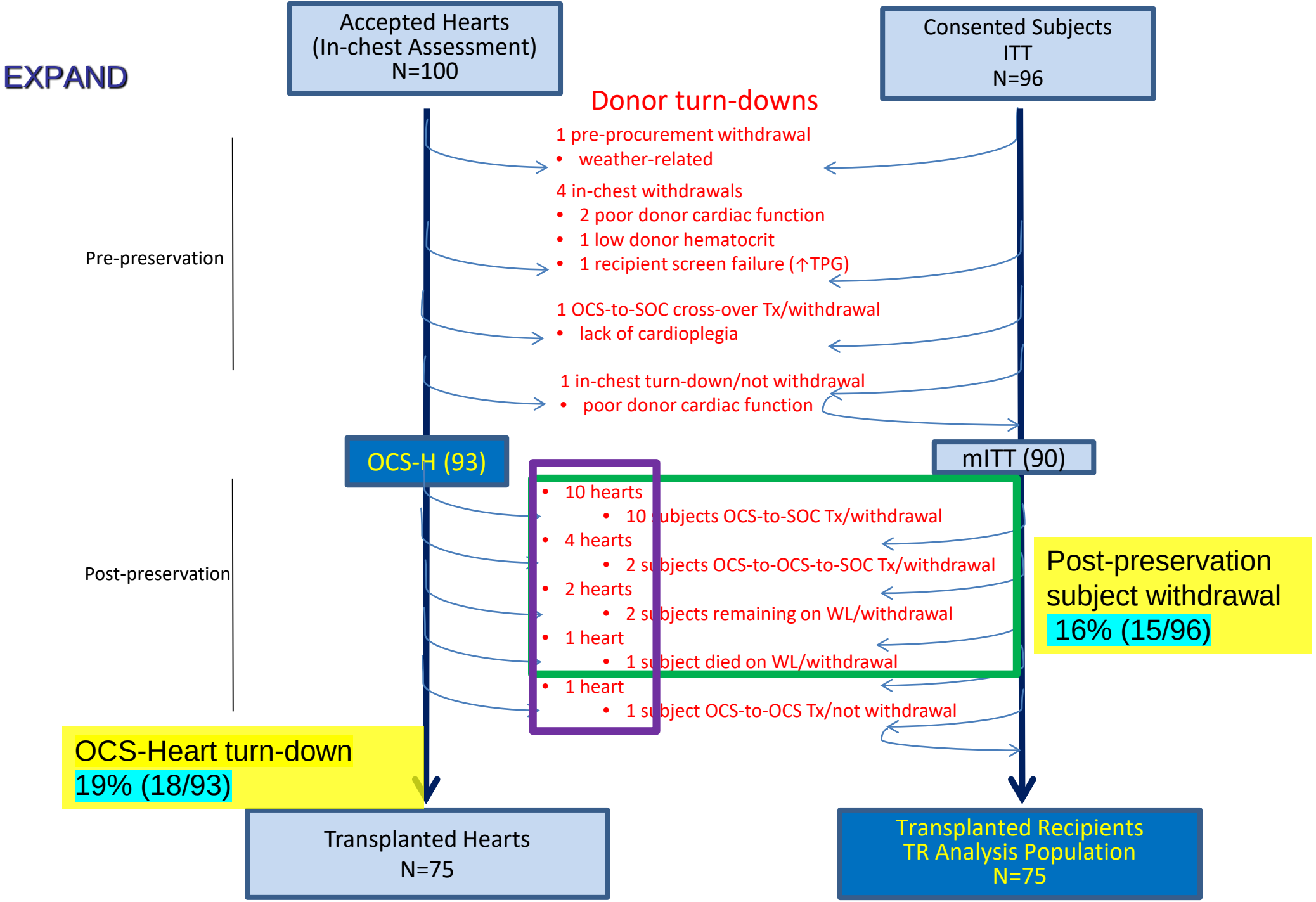
mITT (90)
• 10 hearts
• 10 subjects OCS-to-SOC Tx/withdrawal
• 4 hearts
• 2 subjects OCS-to-OCS-to-SOC Tx/withdrawal
• 2 hearts
• 2 subjects remaining on WL/withdrawal
• 1 heart
• 1 subject died on WL/withdrawal
• 1 heart
• 1 subject OCS-to-OCS Tx/not withdrawal
Post-preservation subject withdrawal
16% (15/96)
Transplanted Hearts
N=75
Transplanted Recipients
TR Analysis Population
N=75


EXPAND
Accepted Hearts
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N=100
Consented Subjects
ITT
N=96
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• weather-related
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• lack of cardioplegia
1 in-chest turn-down/not withdrawal
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Pre-preservation
Post-preservation
OCS-H (93)
mITT (90)
• 10 hearts
• 10 subjects OCS-to-SOC Tx/withdrawal
• 4 hearts
• 2 subjects OCS-to-OCS-to-SOC Tx/withdrawal
• 2 hearts
• 2 subjects remaining on WL/withdrawal
• 1 heart
• 1 subject died on WL/withdrawal
• 1 heart
• 1 subject OCS-to-OCS Tx/not withdrawal
Post-preservation subject withdrawal
16% (15/96)
OCS-Heart turn-down
19% (18/93)
Transplanted Hearts
N=75
Transplanted Recipients
TR Analysis Population
N=75

Recipient and Donor Demographics / Characteristics
EXPAND

Transplant Recipient population				
		Recipients (n=75)		Donors (n=75)
Age				
	Mean (SD)	55.46 (12.56)		37.34 (12.58)
	Median	59.22		35.99
	Min - Max	18.8 - 73.2		14.3 - 57.6
Gender				
Male	n (%)	61 (81.3)		54 (72.0)
Female	n (%)	14 (18.7)		21 (28.0)
Donor Final Ejection Fraction	N	-		74
	Mean (SD)	-		57.4 (8.70)
	Median	-		60.0
	Min - Max	-		40 - 79
Recipient PRA (%)	N	74		-
	Mean (SD)	7.9 (18.12)		-
	Median	0.0		-
	Min - Max	0 - 81		-
Recipient Diabetes	N	74		-
Yes	n (%)	29 (38.7%)		-
No	n (%)	45 (60.0%)		-
Recipient MCS	N	75		-
IABP	n (%)	11 (14.7%)		-
LVAD	n (%)	47 (62.7%)		-
BiVAD	n (%)	1 (1.3%)		-

Recipient and Donor Demographics / Characteristics EXPAND

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- Majority of donors met PROCEED II cardiac function criterion

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- Majority of donors met PROCEED II cardiac function criterion

- Compared to PROCEED II recipients
  - Higher average PRA
    - Most not sensitized
  - Higher prevalence of diabetes

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- Majority of donors met PROCEED II cardiac function criterion
- Compared to PROCEED II recipients
  - Higher average PRA
    - Most not sensitized
  - Higher prevalence of diabetes
  - Higher rate of preoperative MCS

OCS-H Donor Inclusion Criteria EXPAND

Donor inclusion criteria OCS-H hearts (n=93)	TR hearts (n=75)	Turned-down hearts (n=18)
ECCT ≥ 4	18	3
EF ≥ 40% ≤ 50%	10	1
Downtime ≥ 20 min + EF	5	1
Downtime ≥ 20 min	4	-
Downtime ≥ 20 min + LVH	4	1
Downtime ≥ 20 min + ECCT ≥ 4	4	5
LVH (> 12 and ≤ 16 mm)	3	
Luminal irregularities, no CAD	2	1
≥ 55 y/o	2	-
ECCT ≥ 4 + EF	2	-
EtOH + ≥ 55 y/o	2	-
≥ 55 y/o + other criteria	4	-
EtOH + LVH	2	-
LVH + other criteria	5	-
ECCT ≥ 4 + ≥ 55 y/o	1	-
ECCT ≥ 4 + ≥ 55 y/o + EtOH	1	-
ECCT ≥ 4 + luminal irregularities	1	1
ECCT ≥ 4 + 45-55 y/o, no cardiac cath	1	-
Downtime ≥ 20 min + luminal irregularities	-	1
Age > 55 + downtime + luminal irregularities	-	1
Downtime ≥ 20 min + diabetes	-	1
Downtime ≥ 20 min + carbon monoxide	1	-
45-55 y/o, no cardiac cath	-	1
EtOH	1	-
EF + diabetes or EtOH	2	1

OCS-H Donor Inclusion Criteria EXPAND

Donor inclusion criteria OCS-H hearts (n=93)	TR hearts (n=75)	Turned-down hearts (n=18)
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EF ≥ 40% ≤ 50%	10	1
Downtime ≥ 20 min + EF	5	1
Downtime ≥ 20 min	4	-
Downtime ≥ 20 min + LVH	4	1
Downtime ≥ 20 min + ECCT ≥ 4	4	5
LVH (> 12 and ≤ 16 mm)	3	
Luminal irregularities, no CAD	2	1
≥ 55 y/o	2	-
ECCT ≥ 4 + EF	2	-
EtOH + ≥ 55 y/o	2	-
≥ 55 y/o + other criteria	4	-
EtOH + LVH	2	-
LVH + other criteria	5	-
ECCT ≥ 4 + ≥ 55 y/o	1	-
ECCT ≥ 4 + ≥ 55 y/o + EtOH	1	-
ECCT ≥ 4 + luminal irregularities	1	1
ECCT ≥ 4 + 45-55 y/o, no cardiac cath	1	-
Downtime ≥ 20 min + luminal irregularities	-	1
Age > 55 + downtime + luminal irregularities	-	1
Downtime ≥ 20 min + diabetes	-	1
Downtime ≥ 20 min + carbon monoxide	1	-
45-55 y/o, no cardiac cath	-	1
EtOH	1	-
EF + diabetes or EtOH	2	1

- Sponsor modifications to inclusion criteria assignments after FDA review of PMA (2019)
  - 20 OCS-H donor hearts modified
    Added additional criteria
    17/20: single-criterion → multiple criteria

OCS-H Donor Inclusion Criteria EXPAND

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Downtime ≥ 20 min + EF	5	1
Downtime ≥ 20 min	4	-
Downtime ≥ 20 min + LVH	4	1
Downtime ≥ 20 min + ECCT ≥ 4	4	5
LVH (> 12 and ≤ 16 mm)	3	
Luminal irregularities, no CAD	2	1
≥ 55 y/o	2	-
ECCT ≥ 4 + EF	2	-
EtOH + ≥ 55 y/o	2	-
≥ 55 y/o + other criteria	4	-
EtOH + LVH	2	-
LVH + other criteria	5	-
ECCT ≥ 4 + ≥ 55 y/o	1	-
ECCT ≥ 4 + ≥ 55 y/o + EtOH	1	-
ECCT ≥ 4 + luminal irregularities	1	1
ECCT ≥ 4 + 45-55 y/o, no cardiac cath	1	-
Downtime ≥ 20 min + luminal irregularities	-	1
Age > 55 + downtime + luminal irregularities	-	1
Downtime ≥ 20 min + diabetes	-	1
Downtime ≥ 20 min + carbon monoxide	1	-
45-55 y/o, no cardiac cath	-	1
EtOH	1	-
EF + diabetes or EtOH	2	1

- Sponsor modifications to inclusion criteria assignments after FDA review of PMA (2019)
  - 20 OCS-H donor hearts modified
    Added additional criteria
    17/20: single-criterion → multiple criteria
  - Acceptance as “extended-criteria” to have been based upon investigators’ knowledge <u>at time of procurement decision-making</u>

    Unknown if criteria identified through *post hoc* data audits informed investigators’ determinations

OCS-H Donor Inclusion Criteria EXPAND

Donor inclusion criteria OCS-H hearts (n=93)	TR hearts (n=75)	Turned-down hearts (n=18)
ECCT ≥ 4	18	3
EF ≥ 40% ≤ 50%	10	1
Downtime ≥ 20 min + EF	5	1
Downtime ≥ 20 min	4	-
Downtime ≥ 20 min + LVH	4	1
Downtime ≥ 20 min + ECCT ≥ 4	4	5
LVH (> 12 and ≤ 16 mm)	3	
Luminal irregularities, no CAD	2	1
≥ 55 y/o	2	-
ECCT ≥ 4 + EF	2	-
EtOH + ≥ 55 y/o	2	-
≥ 55 y/o + other criteria	4	-
EtOH + LVH	2	-
LVH + other criteria	5	-
ECCT ≥ 4 + ≥ 55 y/o	1	-
ECCT ≥ 4 + ≥ 55 y/o + EtOH	1	-
ECCT ≥ 4 + luminal irregularities	1	1
ECCT ≥ 4 + 45-55 y/o, no cardiac cath	1	-
Downtime ≥ 20 min + luminal irregularities	-	1
Age > 55 + downtime + luminal irregularities	-	1
Downtime ≥ 20 min + diabetes	-	1
Downtime ≥ 20 min + carbon monoxide	1	-
45-55 y/o, no cardiac cath	-	1
EtOH	1	-
EF + diabetes or EtOH	2	1

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    Unknown if criteria identified through *post hoc* data audits informed investigators' determinations
- Key criteria prone to intra- and inter-observer variability
  - Expected total cross-clamp time ≥ 4° (ECCT ≥ 4)
  - LV ejection fraction (EF) ≥ 40 and ≤ 50%
  - Reported down time ≥ 20 minutes

OCS-H Donor Inclusion Criteria EXPAND

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Downtime ≥ 20 min	4	-
Downtime ≥ 20 min + LVH	4	1
Downtime ≥ 20 min + ECCT ≥ 4	4	5
LVH (> 12 and ≤ 16 mm)	3	
Luminal irregularities, no CAD	2	1
≥ 55 y/o	2	-
ECCT ≥ 4 + EF	2	-
EtOH + ≥ 55 y/o	2	-
≥ 55 y/o + other criteria	4	-
EtOH + LVH	2	-
LVH + other criteria	5	-
ECCT ≥ 4 + ≥ 55 y/o	1	-
ECCT ≥ 4 + ≥ 55 y/o + EtOH	1	-
ECCT ≥ 4 + luminal irregularities	1	1
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45-55 y/o, no cardiac cath	-	1
EtOH	1	-
EF + diabetes or EtOH	2	1

Uncertain degree of overlap of OCS-H populations in EXPAND and PROCEED II

Perfusion Characteristics
EXPAND (OCS-H)

OCS-H Population Preservation Parameters		TR hearts (N=75)	Turned-down hearts (N=18)
Arterial Lactate—Pre-OCS	n	73	16
	Mean (SD)	1.3 (0.58)	1.6 (1.02)
	Median	1.1	1.2
	Min - Max	0.39 - 3.49	0.34 - 3.90
Arterial Lactate—Final OCS	n	75	18
	Mean (SD)	3.1 (0.95)	5.1 (0.84)
	Median	3.0	4.9
	Min - Max	0.55 - 4.97	3.50 - 7.17
AoP Mean (mmHg)	n	75	18
	Mean (SD)	81.2 (7.8)	83.2 (7.0)
	Median	81.4	83.4
	Min - Max	48 - 102	68 - 97
Coronary Flow (L/min)	n	75	18
	Mean (SD)	0.760 (0.136)	0.751 (0.166)
	Median	0.785	0.785
	Min - Max	0.06 – 0.99	0.15 - 0.92

- Total cold ischemic time: ~1.7 hours
  - Similar to PROCEED II
- Perfusion time (mean/median): 4.6 hours
  - ~1 hour (15%) longer than PROCEED II
    - TR and turned-down times similar

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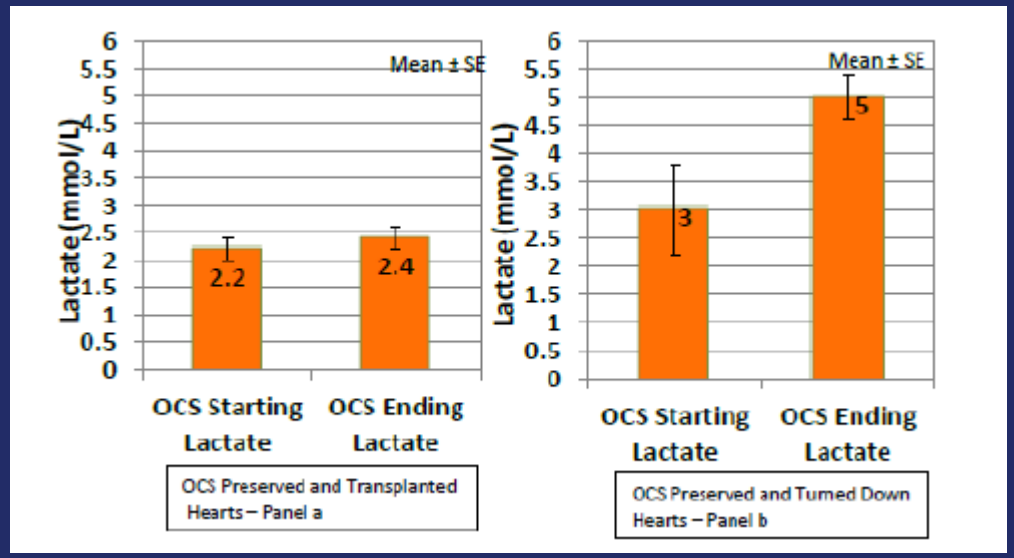
    - TR and turned-down similar
- Transplanted and turned-down donor hearts in EXPAND had similar starting lactate and device flow parameters
- Turned-down donor hearts manifested greater lactate rise

OCS Heart Lactate Measurements

- Lactate level a key OCS Heart System parameter
  - In PROCEED II
    - Rising perfusate lactate cited in 3/5 OCS Heart turned-down organs
    - Elevated *in vivo* lactate cited in 1/5 OCS→SOC crossovers

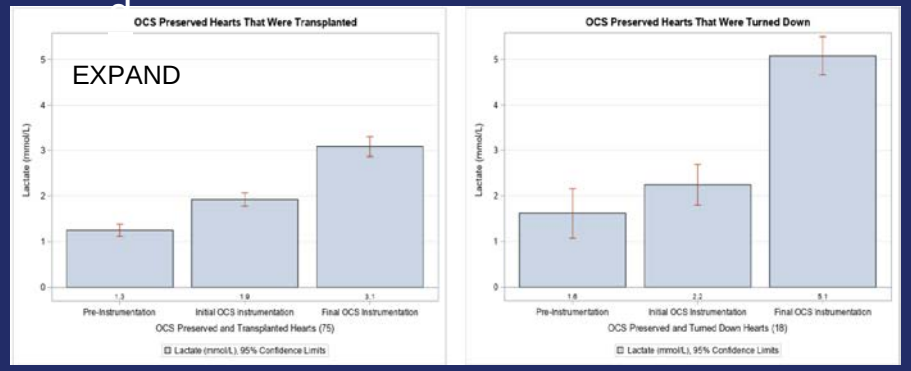


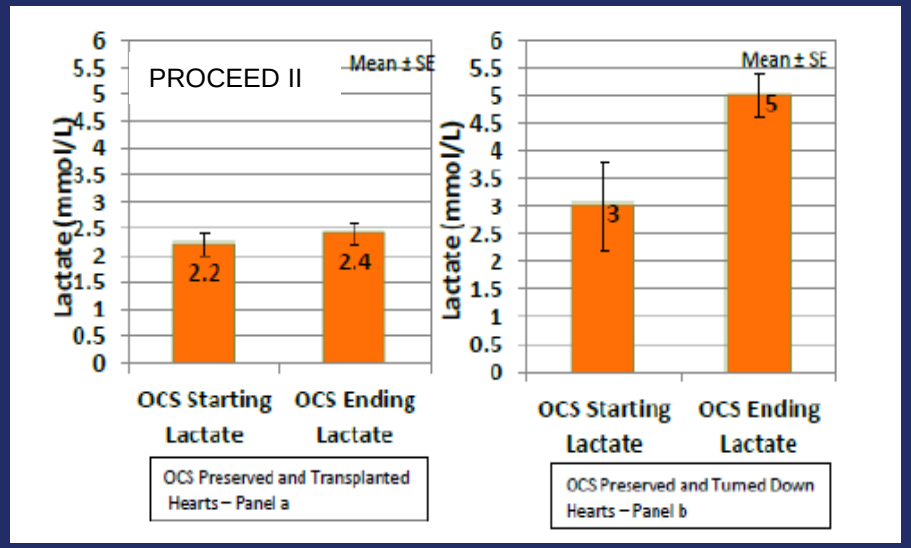
- Sponsor's threshold perfusate lactate: 5mmol/L

OCS Heart System and Lactate Biomarker for Donor Organ Turn-down

Transplanted

Turned-down





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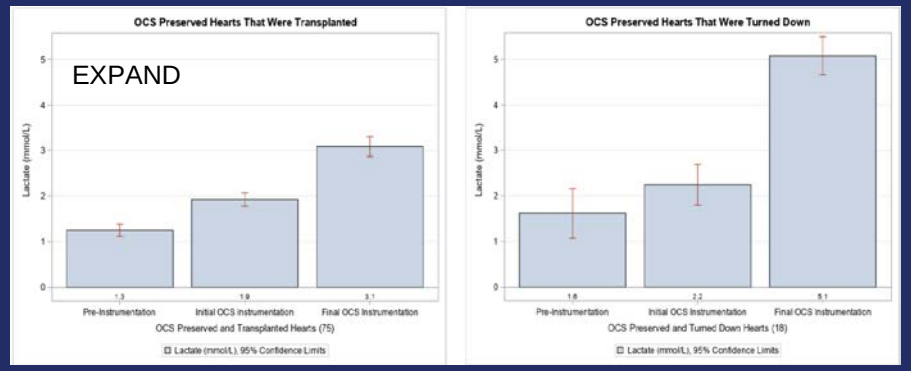

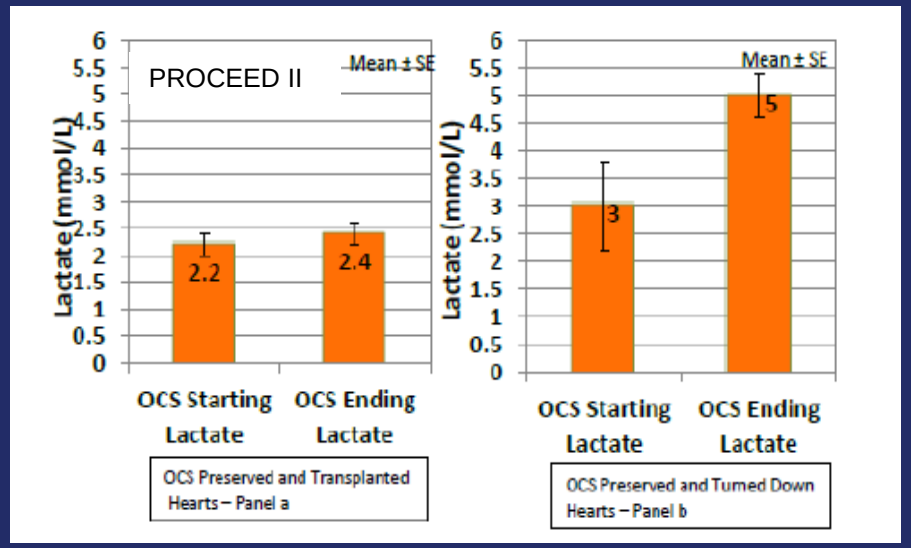

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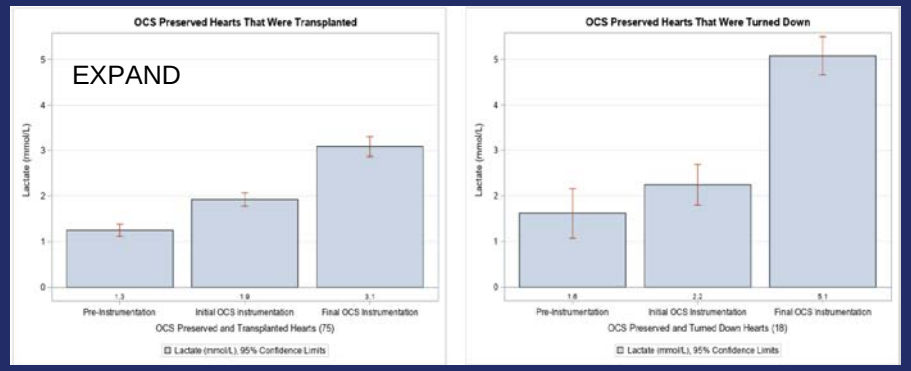

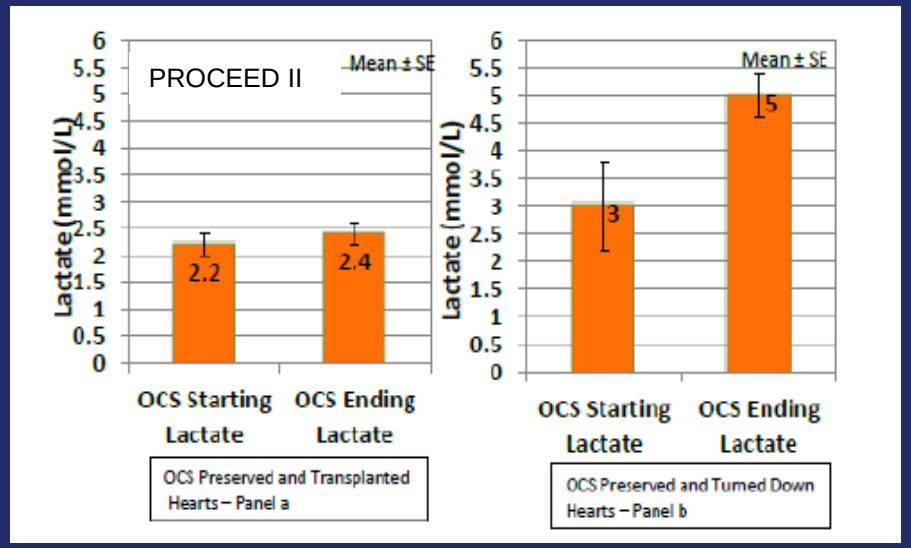

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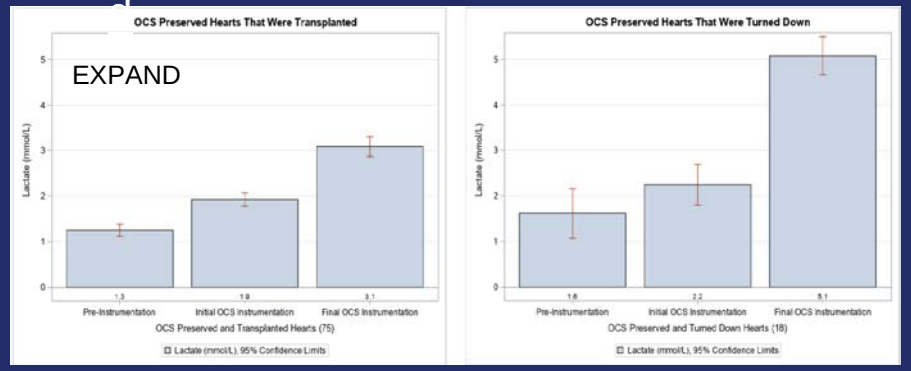
ECCT ≥ 4 sole criterion subgroup

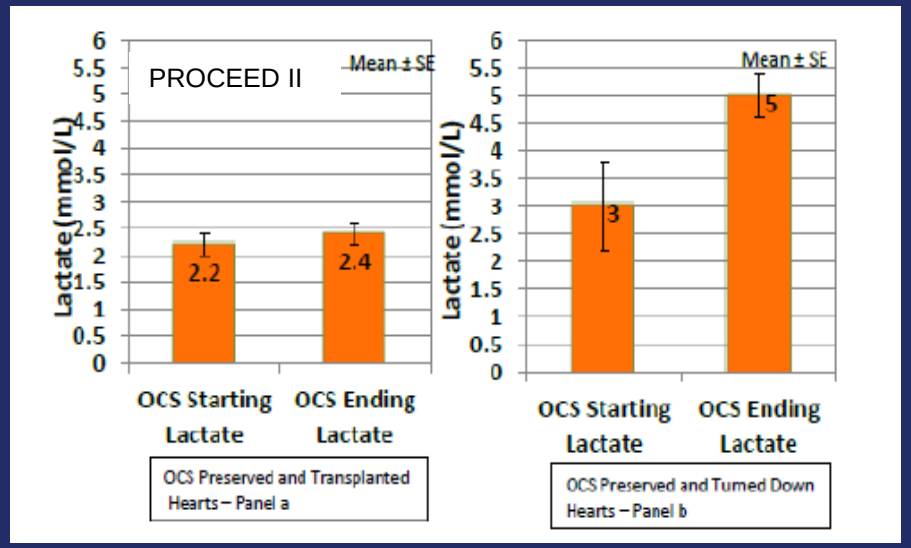
- 40 (29%) of pooled EXPAND+CAP OCS-H
  - No *a priori* donor-specific concerns
  - Only time-dependent ischemia concern
- Functionally "standard-criteria" organs
  ~100% utilization rate if procured SOC
  OCS-to-SOC crossover
- 18% (7/40) turned down → lactate

OCS Heart System and Lactate Biomarker for Donor Organ Turn-down

Transplanted

Turned-down





- Sponsor inference:

  Device unmasks hearts' pre-existing pathology and tolerance for preservation

- FDA inference:

  Etiology/significance of lactate elevation uncertain

  Device could also be:

  - Failing to prevent warm ischemia as intended
  - Contributing to other *de novo* injury
  - Identifying pathology incidental to post-transplantation function if preserved with SOC

Primary Effectiveness Endpoint
EXPAND

Patient survival at Day 30 post-transplantation, without severe PGD-LV or PGD-RV	TR population (N=75)	95% CI of Proportion	Performance Goal	p-value ($\delta = 10\%$)
Proportion (n/N)	88% (66/75)	78.4 - 94.4	65%	<0.0001*

*p-value from a one-sided exact binomial test (α=0.05)

- Performance goal was met
  - 9 Primary Effectiveness Endpoint failures
    - 3 severe PGD and death secondary to PGD within 30 days
    - 1 severe PGD and death not secondary to PGD within 30 days
    - 1 severe PGD and graft loss secondary to PGD within 30 days
    - 4 severe PGD and alive through 30 days
  - 33% mortality rate after PGD consistent with published reports

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Secondary Endpoints
EXPAND

FDA

Safety Endpoint

Safety Endpoint Mean number of HGRSAEs	TR population (N=75)	95% CI of Proportion
Number of HGRSAEs	12	-
Subjects with a HGRSAE (n/N)	14.7% (11/75)	-
Mean number of HGRSAEs/subject (Safety Endpoint)	0.16 (12/75)	(0.1 – 0.2)

- 6 severe PGD-LV
- 2 PGD-RV
- 3 moderate PGD
- 1 Re-transplantation within 30 days

Utilization Rate

80.6% (19.4% turn-down rate)

- Primary Effectiveness Endpoint tipping point:
  not sensitive to turn-down rate

Severe PGD-LV or PGD-RV

TR population (N=75)	95% CI of Proportion
10.7% (8/75)	4.7 - 19.9

Survival at Day 30

TR population (N=75)	95% CI of Proportion
94.7% (71/75)	86.9 - 98.5

Initial ICU and Hospital Stays EXPAND

Length of Initial Post-Transplant ICU Stay (Hours)	OCS (N=75)
Mean ± SD	316.8 ± 420.38
Median	199.9
Min.- Max.	55.4 – 2679.5
Length of Initial Post-Transplant Hospital Stay (Hours)	**OCS (N=74)**
Mean ± SD	666.68 ± 554.36
Median	515.09
Min.- Max.	211.42 – 3043.05

Mechanical Circulatory Support Post-Transplant	Percentage of Subjects (n/N)	Duration of Support (hours) Mean ± SD
Mechanical Circulatory Support	26.7% (20/75)	
RVAD	2.7% (2/75)	219.12 ± 31.35
LVAD	2.7% (2/75)	139.0 ± 93.34
IABP	18.7% (14/75)	80.0 ± 63.20
ECMO	12.0% (9/75)	132.04 ± 97.09
BiVAD	0% (0/75)	--

- Compared to PROCEED II OCS-H
  - Longer ICU and hospitalization
    - Initial ICU
      - Mean:: ~3.5 days
      - Median: ~2 days
    - Initial hospitalization
      - Mean:: ~8 days
      - Median: ~7 days
  - Post-operative ECMO/IABP rates
    - 2x PROCEED II

Waiting List Times
EXPAND versus SRTR

Waiting List Times	EXPAND TR (n=75)	SRTR 2017-2018 (n=2967)
Days on WL prior to transplant (median)		
All	138 (100%)	207 (100%)
Blood type		
O	151 (45%)	405 (40%)
A	126 (44%)	150 (39%)
B	146 (9%)	132 (16%)
AB	122 (1%)	45 (5%)
Urgency		
Status 1A	138 (69%)	59 (66%)
Status 1B	117 (29%)	216 (31%)
Status 2	186 (1%)	507 (3%)
Days on WL after EXPAND consent (median)		
All	35	
O	41	
A	22	
B	30	
AB	1	
Urgency		
Status 1A	35	
Status 1B	33	
Status 2	1	

- OCS Heart System associated with clinically significant decreases in waiting list times

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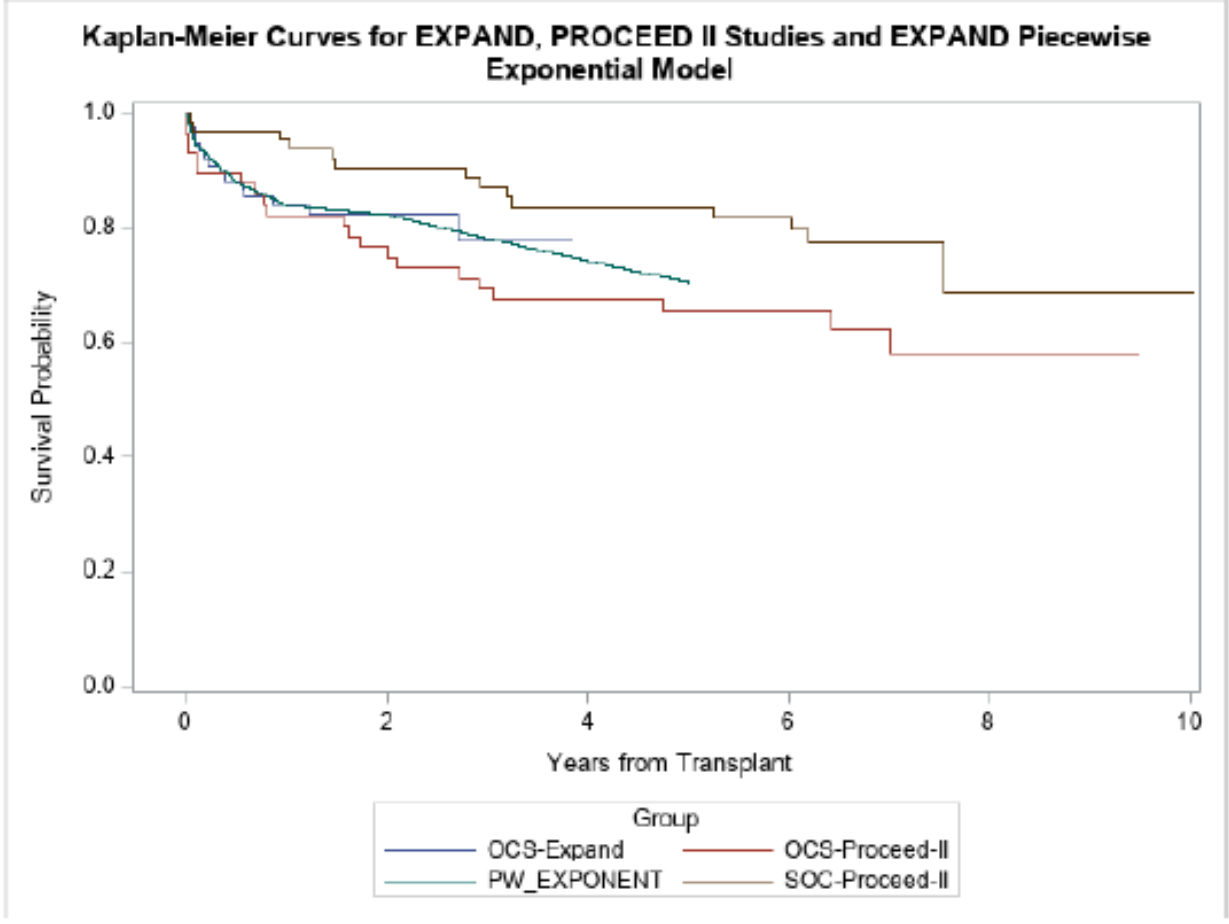
SRTR 2019

- Waiting list outcomes
  - Remained on waiting list: 45%
  - Died: 3%
  - Removed (too sick): 4%
  - Removed (not needed): 2%
  - Other: 6%
  - Transplanted: 41%
- Waiting list time before transplant
  - < 31 days: 46%
  - 31-60 days: 11%
  - 61-90 days: 7%
  - 3-12 months: 22%

SURVIVAL Estimates
EXPAND



- EXPAND 1-year survival equivalent to PROCEED II treatment-arm

Time Post-transplantation	Survival Probability % (95% CI)	
	Piecewise Model*	Kaplan-Meier
1 Year	83.8 (74.7, 91.2)	83.8 (73.2, 90.5)
2 Years	82.1 (72.8, 90.0)	82.2 (71.4, 89.3)
3 Years	78.0 (65.5, 87.8)	77.7 (62.7, 87.2)
4 Years	74.1 (55.4, 86.8)	-
5 Years	70.4 (46.1, 86.1)	-

Post hoc Analysis
Primary Effectiveness Endpoint and Donor Eligibility Criteria

Single criterion donor hearts exhibited lower point estimates of endpoint success

Survival at POD 30 without severe PGD	Single or Multiple Criteria	Single Criterion	Multiple Criteria
All	66/75 (88.0%)	34/40 (85.0%)	32/35 (91.4%)
ECCT ≥ 4	25/28 (89.3%)	15/18 (83.3%)	10/10 (100.0%)
EF ≥ 40% ≤ 50%	20/21 (95.2%)	9/10 (90.0%)	11/11 (100.0%)
Downtime ≥ 20 minutes	20/23 (87.0%)	4/4 (100.0%)	16/19 (84.2%)
LVH	14/17 (82.4%)	2/3 (66.7%)	12/14 (85.7%)
Luminal irregularities / no CAD	7/7 (100.0%)	2/2 (100.0%)	n/a
≥ 55 y/o	9/10 (90.0%)	1/2 (50.0%)	8/8 (100.0%)
EtOH	8/9 (88.9%)	1/1 (100%)	7/8 (87.5%)

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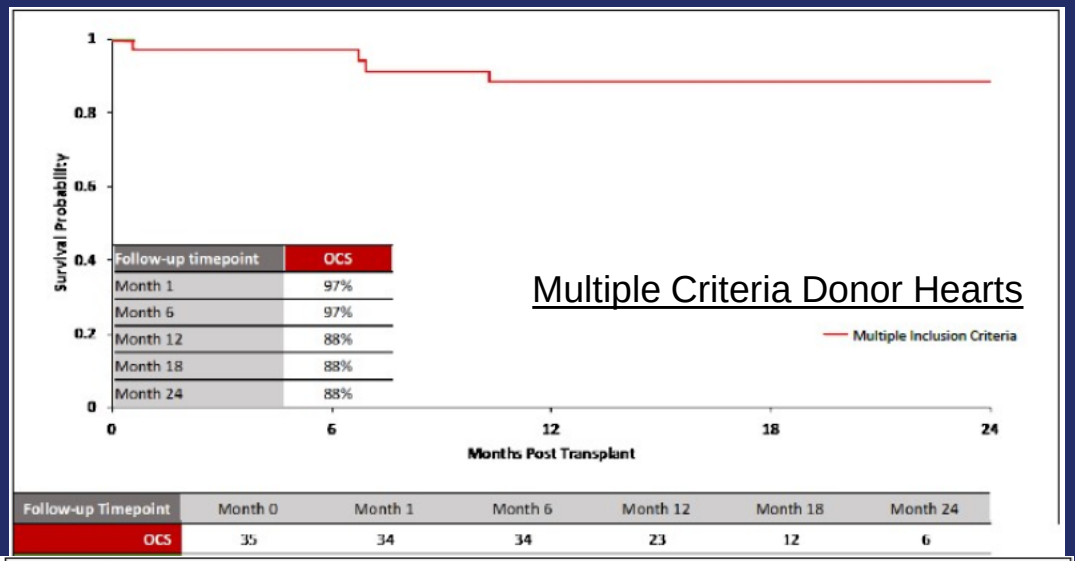
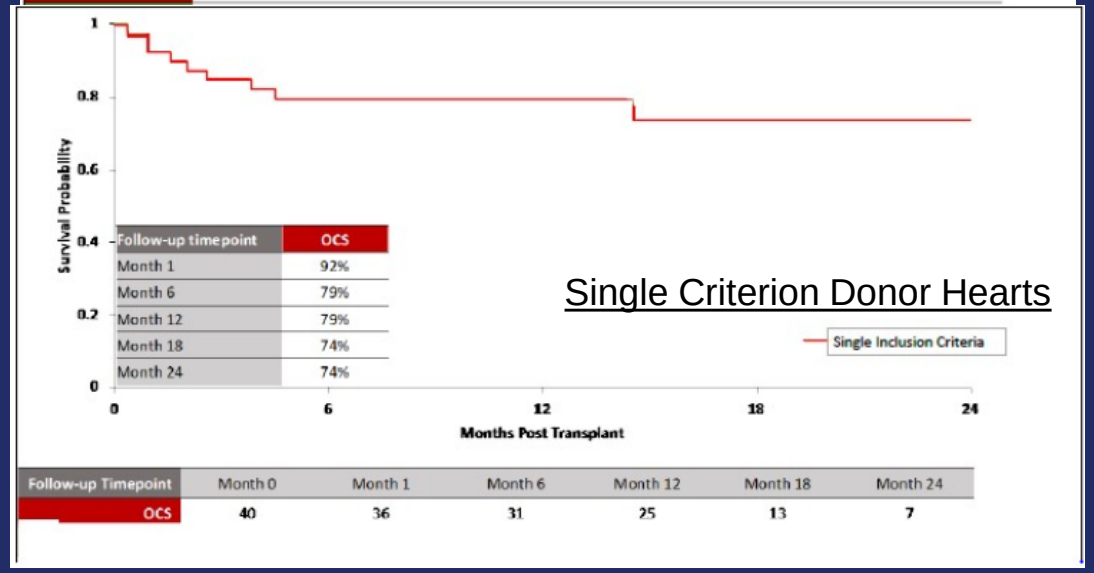
Two Year Survival Estimates
Post hoc Stratification



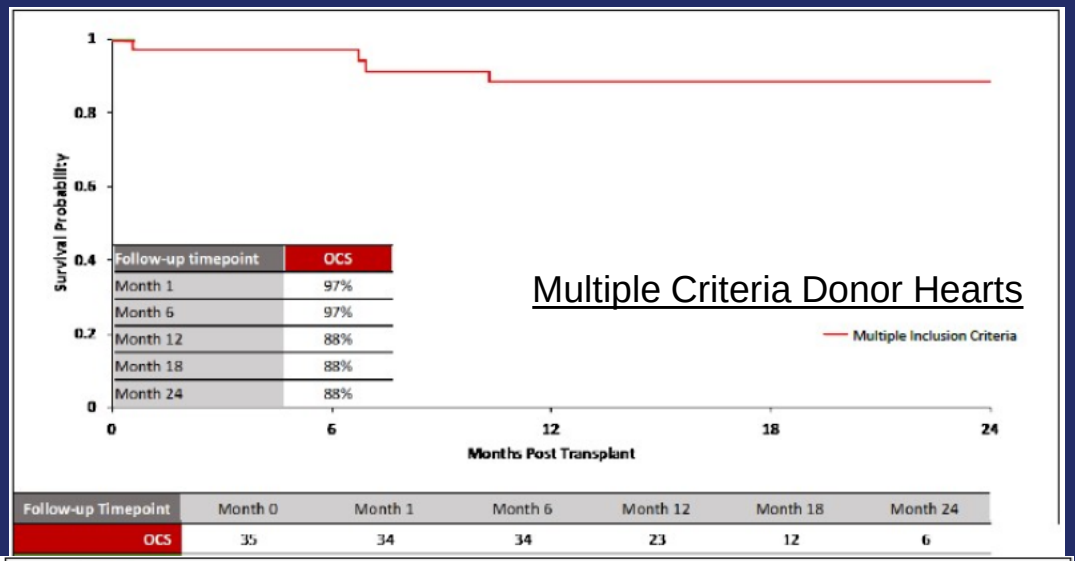


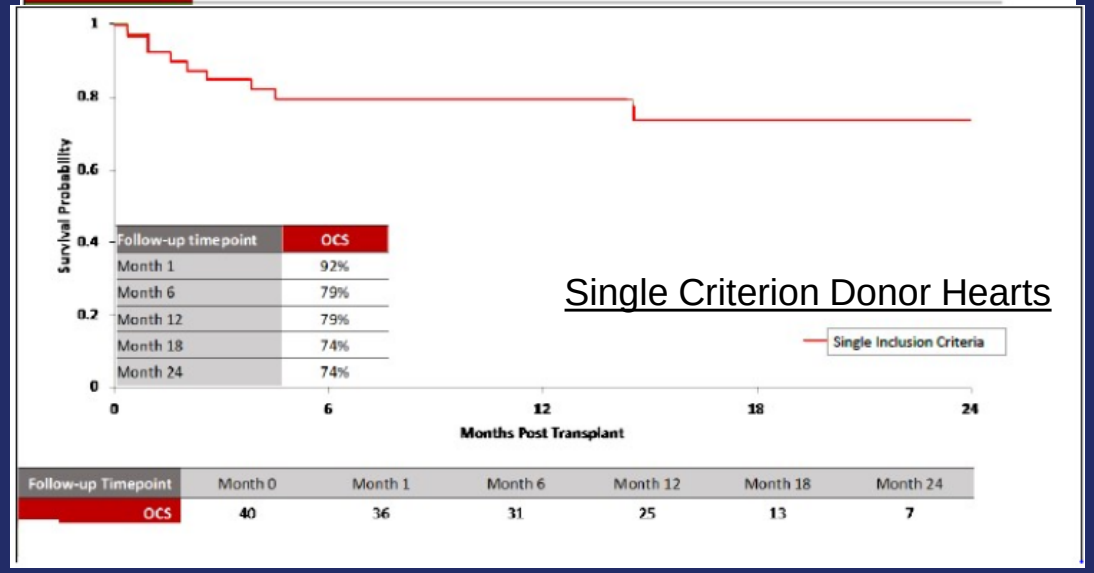
Number of donor inclusion criteria

- Multiple (n=35): 88%
- Single (n=40): 74%

Point estimates of survival trend lower with donor organs having only 1 criterion

Two Year Survival Estimates
Post hoc Stratification





Number of donor inclusion criteria

- Multiple (n=35): 88%
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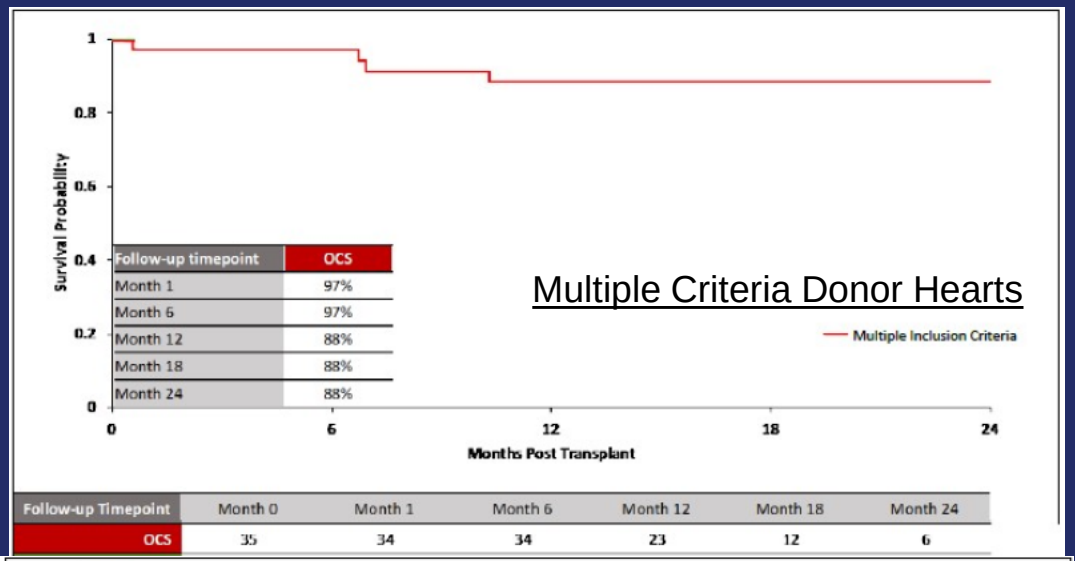
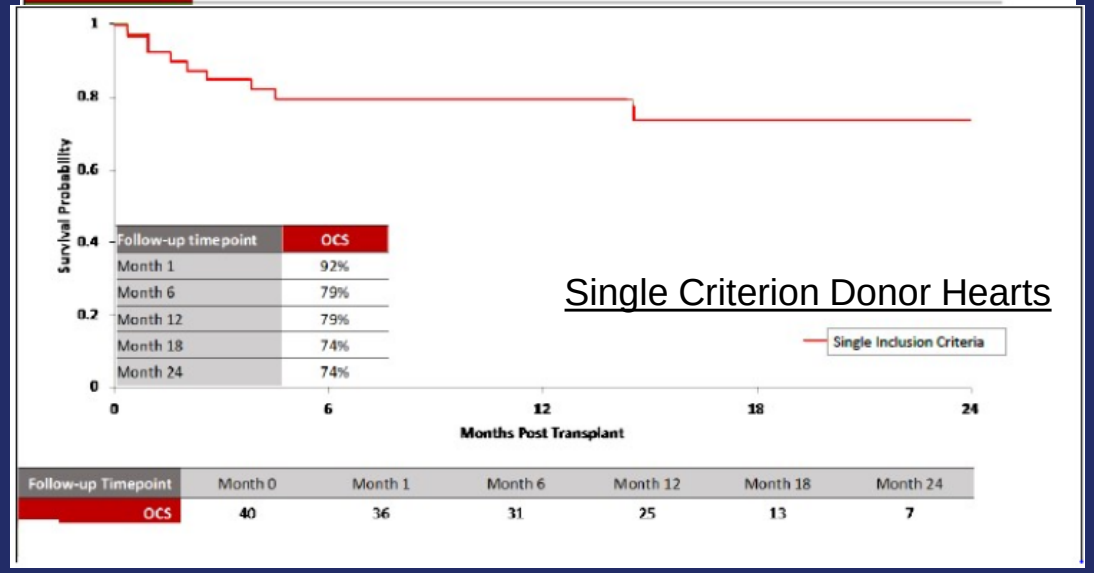
Expected cross-clamp time ≥ 4

- Within multiple criteria (n=10): 100%
- As sole criterion (n=18): 74%

Two Year Survival Estimates
Post hoc Stratification





Number of donor inclusion criteria

- Multiple (n=35): 88%
- Single (n=40): 74%

Point estimates of survival trend lower with donor organs having only 1 criterion

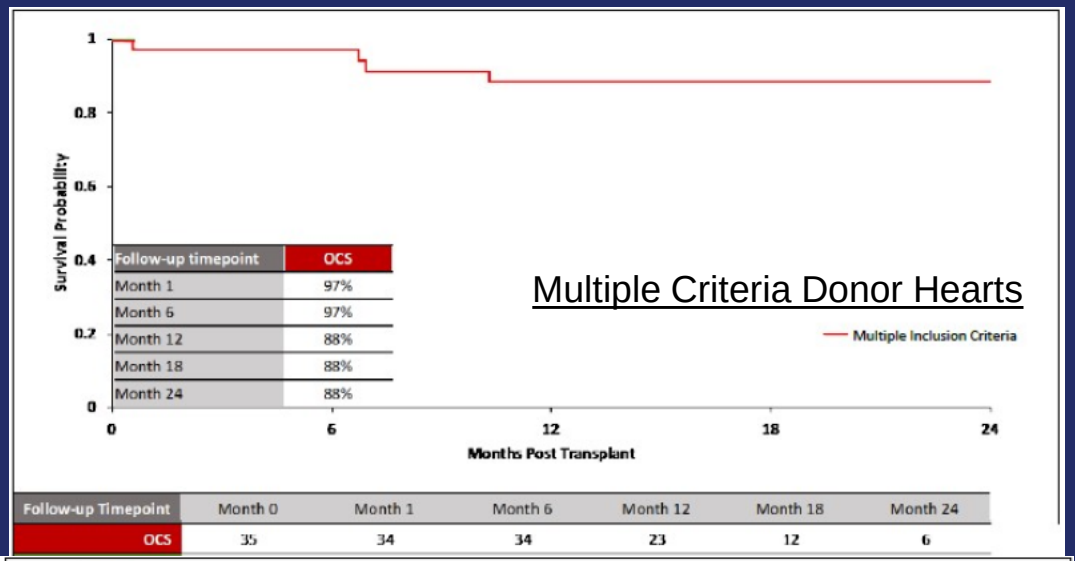
Expected cross-clamp time ≥ 4

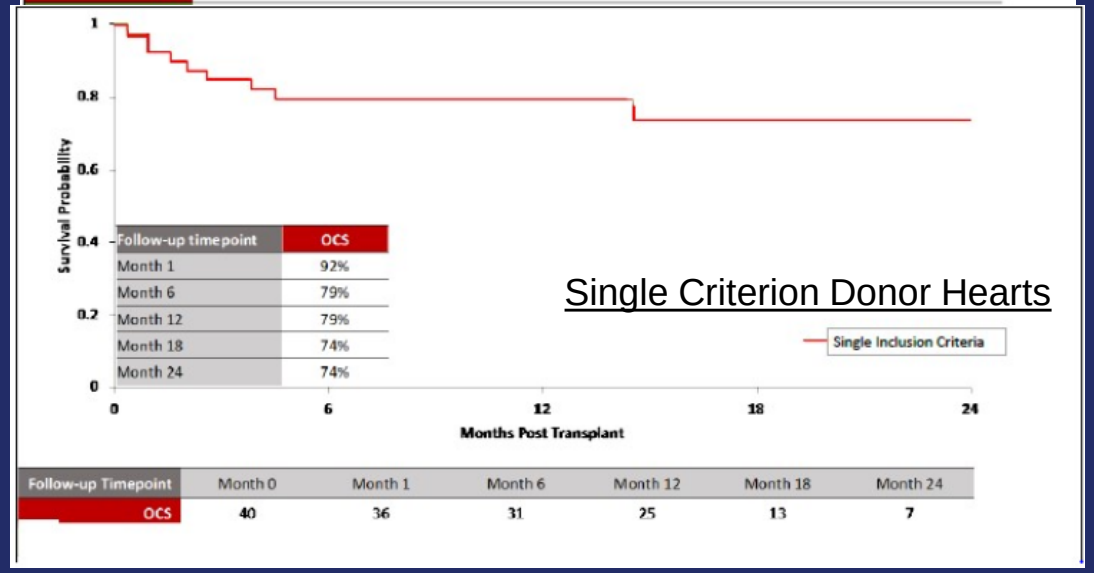
- Within multiple criteria (n=10): 100%
- As sole criterion (n=18): 74%

Actual cross-clamp time

- > 6 hours (n=43): 85%
- ≤ 6 hours (n=18): 75%

Two Year Survival Estimates
Post hoc Stratification





Number of donor inclusion criteria

- Multiple (n=35): 88%
- Single (n=40): 74%

Point estimates of survival trend lower with donor organs having fewer extended criteria

Expected cross-clamp time ≥ 4

- Within multiple criteria (n=10): 100%
- As sole criterion (n=18): 74%

Actual cross-clamp time

- > 6 hours (n=43): 85%
- ≤ 6 hours (n=18): 75%

PROCEED II 2-year survival probability: 75%

Adjunctive Dataset
EXPAND CAP

Enrollment

- 45 subjects enrolled
  - 41 reached Primary Effectiveness Endpoint time point (TR population)
- 49 donor organs transported (OCS-H population)
  - 4/49 (8%) turned down after preservation
- 24/41 (59%) at EXPAND's highest-enrolling site (Site A)

Protocol

- Minor modifications from EXPAND

Recipient and donor demographics

- Consistent with EXPAND, except:
  - Proportionately fewer female donors in CAP
  - More female-donor-to-male-recipient transplants in EXPAND
  - CAP recipients were younger and included more Blacks
  - Substantially less pre-operative VAD / more pre-operative IABP use in CAP

Preservation parameters

- Similar to EXPAND's dataset

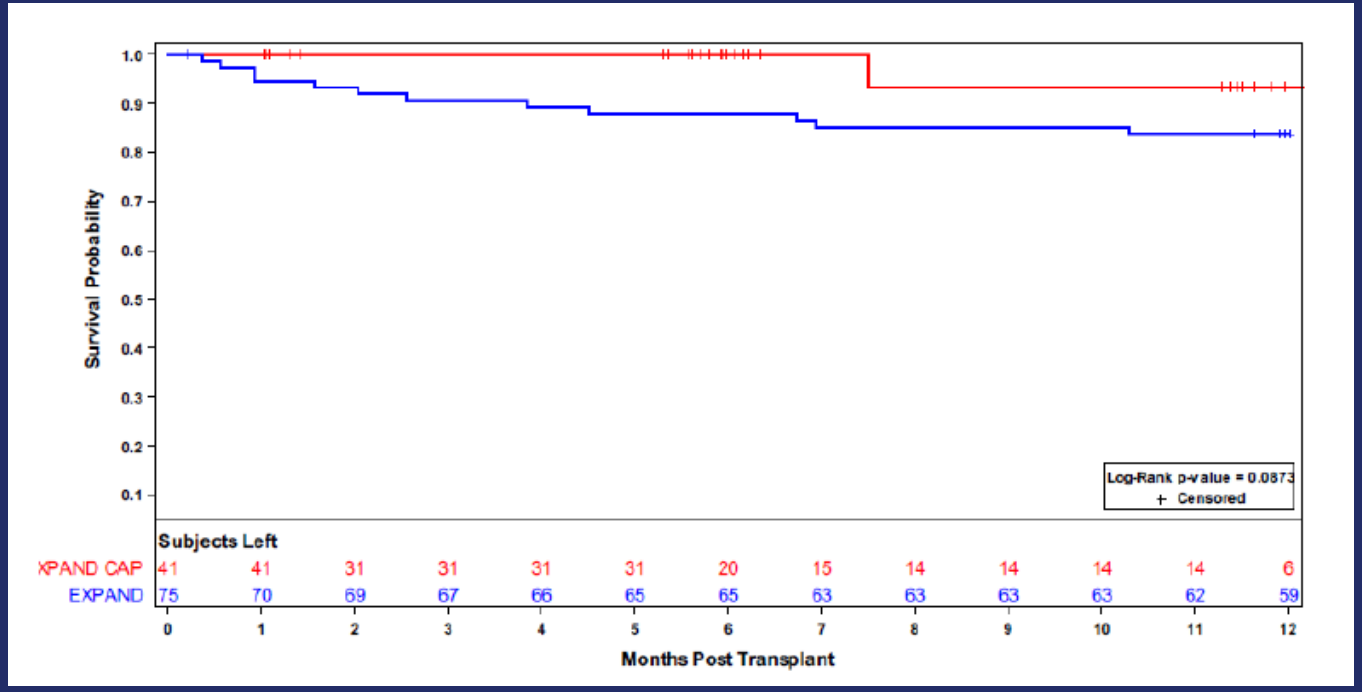
Adjunctive Dataset
EXPAND CAP

Primary and secondary endpoint results

- Consistent with EXPAND's

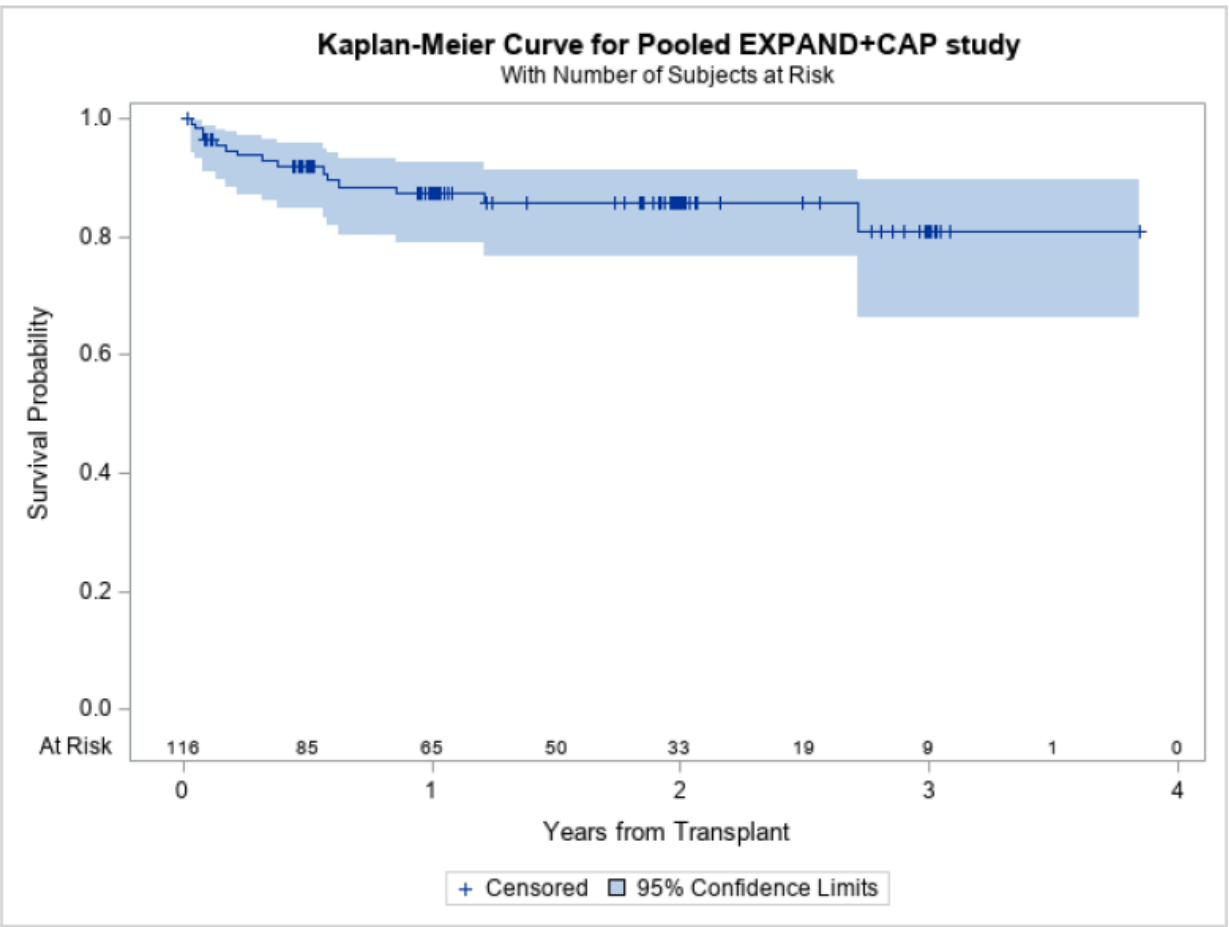
CAP 1 year survival

- Reported CAP 6- and 12-month survival estimates (100% and 93%) higher than EXPAND (93% and 84%)
  - Substantial censoring (> 50%) at 6 months and beyond



p-value calculated from post-hoc analysis

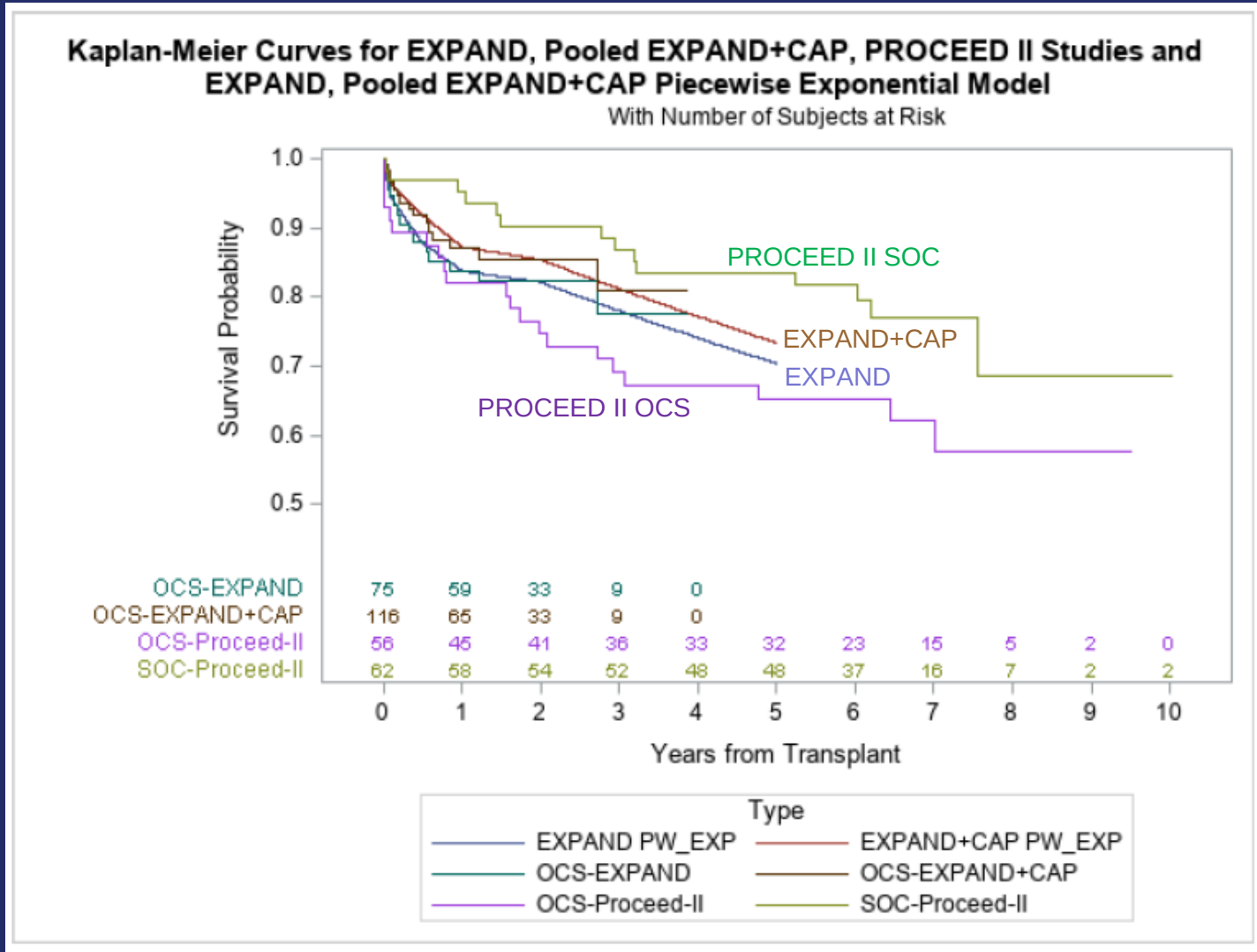
Adjunctive Analysis
Pooled EXPAND+CAP Survival



Time Post-transplantation	Survival Probability % (95% CI)	
	Piecewise Model*	Kaplan-Meier
1 Year	87.1 (79.9, 92.9)	87.2 (78.8, 92.4)
2 Years	85.4 (77.6, 91.7)	85.5 (76.5, 91.3)
3 Years	81.1 (69.4, 89.7)	80.8 (66.3, 89.5)
4 Years	77.1 (58.3, 88.8)	-
5 Years	73.2 (48.8, 88.2)	-

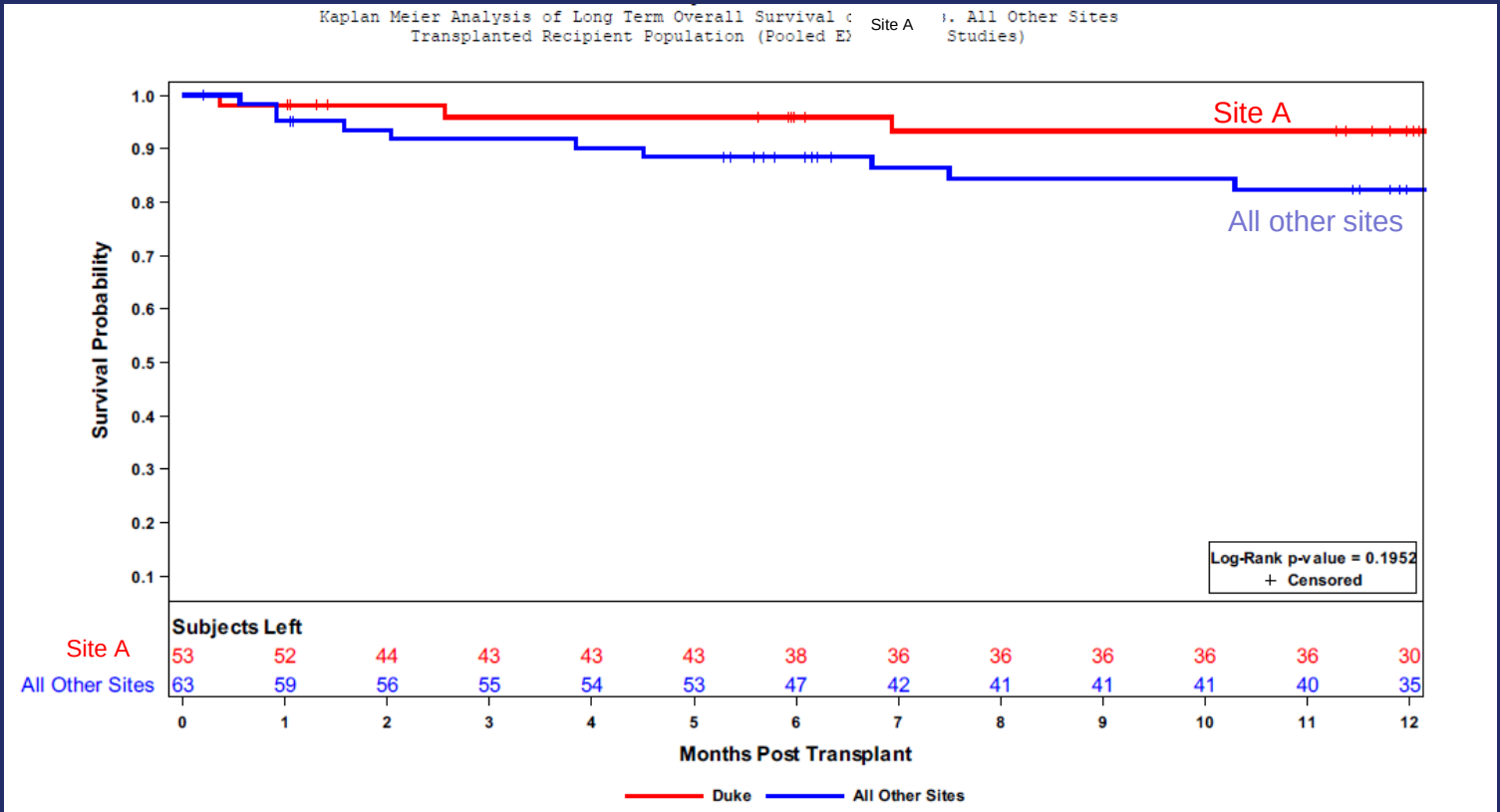
- Increasing uncertainty with model at later time points

Adjunctive Analysis
Pooled EXPAND+CAP Survival



- EXPAND+CAP shifts modeled survival curve upward
- Finding may be clinically meaningful
  - Data pooling *post hoc*
  - Increasing uncertainty with model at later time points
  - Substantial site effect

Adjunctive Analysis
Pooled EXPAND+CAP Survival — Site Effect



- Single site contributed 46% of EXPAND+CAP
- 12-month survival
  Site A: 93% (80-98)
  Others: 82% (69-90)
- May affect generalizability of results

p-value calculated from post-hoc analysis

Summary

- OCS Heart System is a first-of-a-kind organ preservation device
  - Intuitive appeal to heart transplantation physicians
    - Presumed reduction in ischemia-reperfusion injury
    - Presumed increase in procurement flexibility and frequency
- PROCEED II and EXPAND conducted in series over 10 years
  - PROCEED II and EXPAND had complex trial designs
    - Necessary because of organ transplantation logistics

Summary

- EXPAND to evaluate “extended criteria” donor hearts not in PROCEED II
  - Most common reason to use the device in EXPAND was expectation of prolonged cross-clamp time (≥ 4 hours)
  - Overlap present in studies’ donor characteristics
- EXPAND met a performance goal of 30-day effectiveness
  - Appropriateness of pre-specified performance goal uncertain
- Mid-term survival of EXPAND’s extended criteria donor organs is higher than PROCEED II’s OCS Heart experience
  - Survival in hearts selected for ECCT ≥ 4 similar to PROCEED II

Summary

- OCS Heart System was associated with
  - Shorter waiting list times compared to US averages
  - Longer preservation times compared to cold static preservation (SOC)
    - System decreases, but does not eliminate, cold ischemia
- 13% of accepted donor organs were subsequently turned down after OCS Heart preservation
  - System–reported lactate level principal reason for turn-down
    - Validity of lactate as a determinant of transplantability is unclear
  - Ischemic injury observed in turned-down organs
    - Correlation of ischemia with device preservation is uncertain

OCS Heart Turned Down Hearts Clinicopathologic Analysis

Andrew Farb, MD
Chief Medical Officer
FDA, Office of Cardiovascular Devices (OHT-2)

Methods (1)

- EXPAND, EXPAND CAP, and PROCEED II donor hearts perfused on the OCS Heart device but subsequently turned down for transplantation were identified
- Pathology reports, gross cardiac specimen photos, and photomicrographs from 2 core pathology labs reviewed

Methods (2)

Data extracted from submitted medical records and case report forms reviewed for:

- Demographics
- Medical history leading to brain death
- Hospital course information including:
  - Vital signs
  - Labs
  - Cardiac assessment reports
    - Echocardiograms
    - Cardiac catheterizations

Methods (3)

- Study enrollment criteria
- Brain death to cross-clamp time
- OCS Heart System evaluation
  - Perfusion time
  - Mean aortic pressure
  - Mean coronary flow
  - Lactate level assessment
- Reason for donor heart turn down for transplantation

EXPAND Cardiac Pathology Review

Path reports for 17 of 18 OCS Heart perfused hearts turned down for transplant provided (1 report not available)

- 16 of 17 hearts had acute diffuse or multifocal ventricular myocardial damage
  - Contraction band necrosis
  - Coagulation necrosis
  - Myocyte wavy fiber change
  - Interstitial edema
- None had other significant cardiac findings except for one heart with LVH and severe 3-vessel CAD
- One heart with healing subendocardial infarcts, consistent with myocardial injury prior to OCS Heart perfusion

EXPAND CAP Cardiac Pathology Review

Path reports for 4 OCS Heart perfused hearts turned down for transplant provided

- 4 of 4 hearts had acute diffuse or multifocal ventricular myocardial damage
- No heart had other significant cardiac findings

PROCEED II Cardiac Pathology Review

Path reports for 5 OCS Heart perfused hearts turned down for transplant provided

- Acute diffuse myocardial damage in 3 cases
- Focal myocardial damage in one case

OCS Heart Device Turned Down Hearts

Addressing the effectiveness of organ preservation and/or potential myocardial damage associated with donor heart perfusion using the OCS Heart System

Insights into the Potential Limitations of the OCS Heart to Provide Effective Organ Preservation

- Pathology review of turned-down donor hearts (n=20) that had normal left ventricular function in the immediate antemortem period (echo-documented LV ejection fraction ≥55% within 1 to 2 days pre-cardiectomy)
  - N = 12 EXPAND hearts
  - N = 4 EXPAND CAP hearts
  - N = 4 PROCEED II hearts
- During this period, available vital signs flowsheets showed no prolonged episodes of hemodynamic instability

Cardiac Path Findings in Turned Down Hearts with LVEF ≥55% within 1 to 2 days and Stable Vital Signs Antemortem

18 of 20 turned down EXPAND, EXPAND CAP, and PROCEED II hearts showed

- Acute diffuse ventricular myocardial damage in 12 individual hearts
  - EXPAND, n=6; EXPAND CAP, n=3; PROCEED II, N=3
- Acute multifocal ventricular myocardial damage in 6 hearts
  - EXPAND, n=5; EXPAND CAP n=1

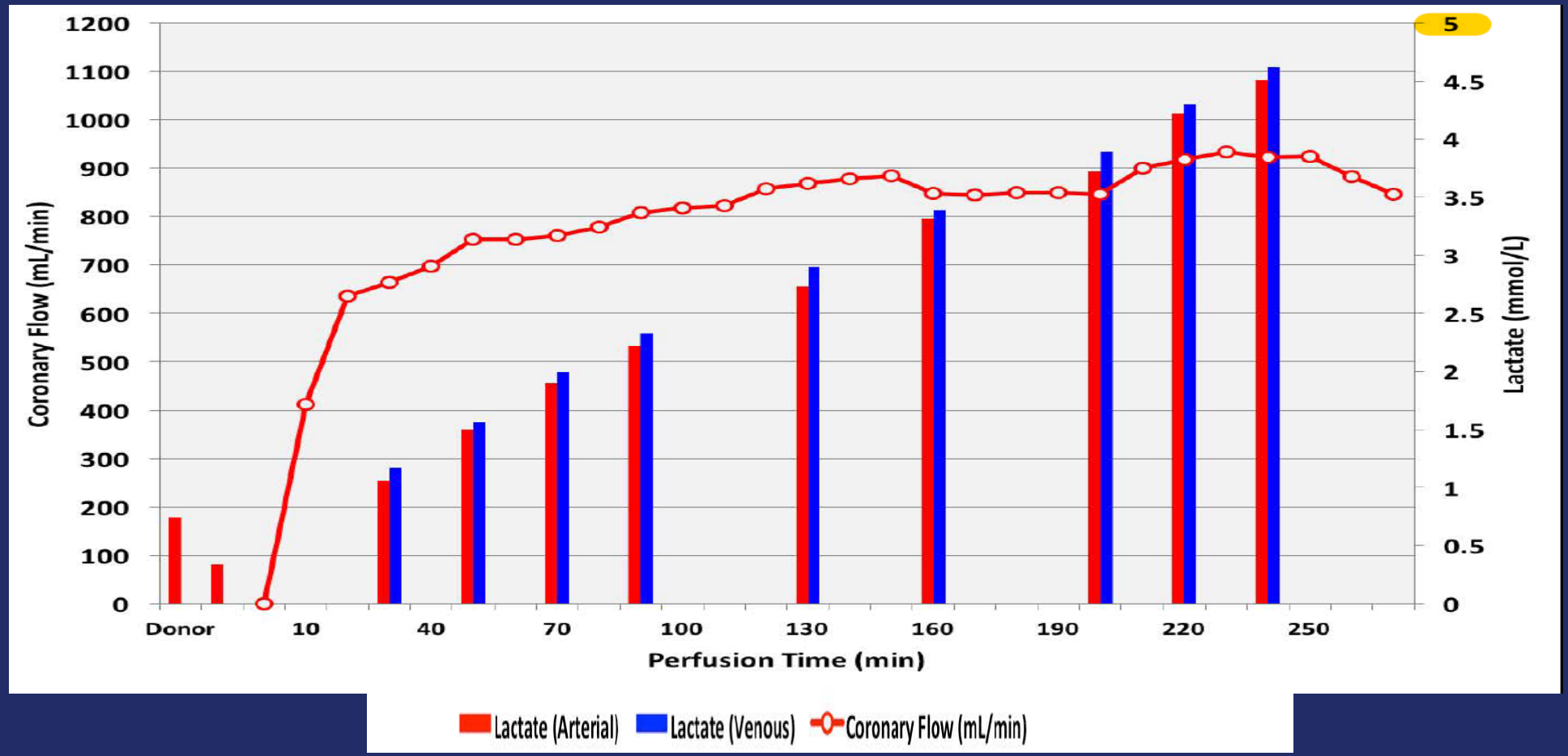
Example 1: EXPAND Turned Down Heart

Donor: 52-year old man with hemorrhagic stroke approximately 3.5 days pre-cardiectomy

- No cardiac arrest; troponin not elevated
- Cardiac cath showed coronary luminal irregularities
- Echo within 48 hours prior to cardiectomy showed an LVEF = 60%
- Stable vital signs prior to cardiectomy
- Inclusion criteria met: Estimated cross-clamp time ≥4 hours and coronary luminal irregularities

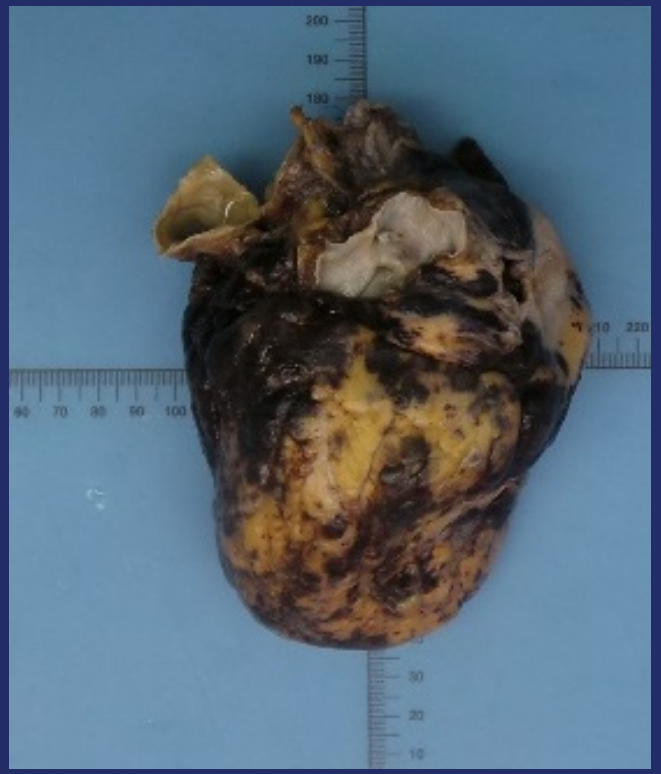
Example 1: EXPAND Turned Down Heart

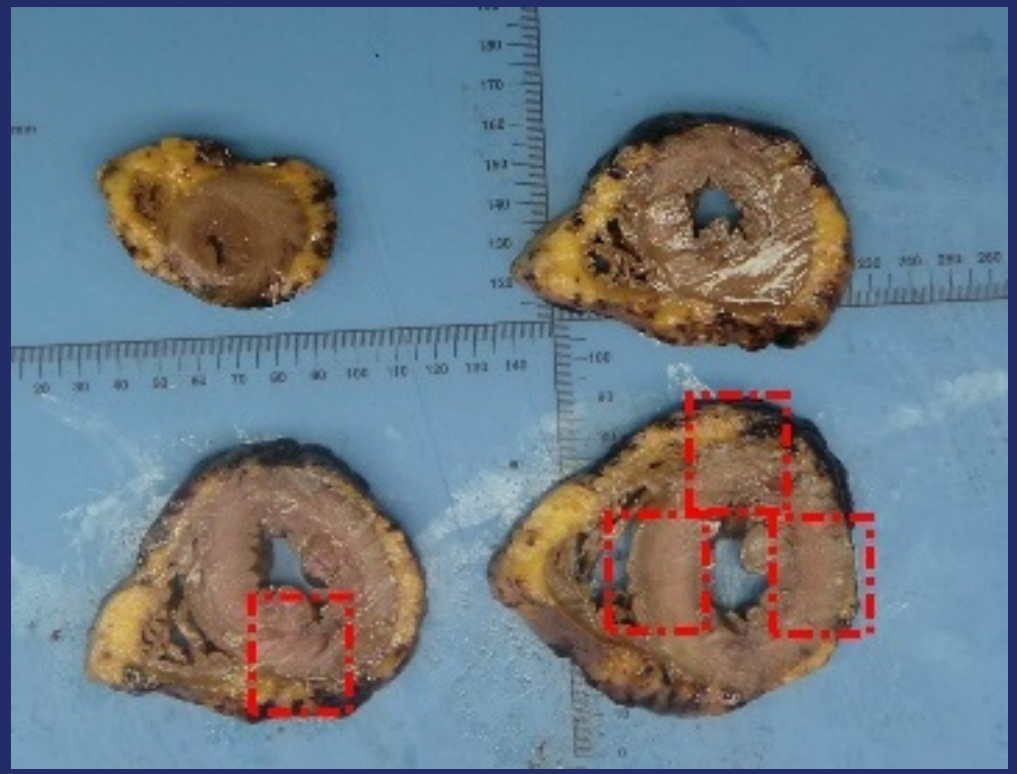
OCS Heart perfusion time, coronary flow, and lactate levels



Gross Cardiac Pathology
Example 1: EXPAND Turned Down Heart

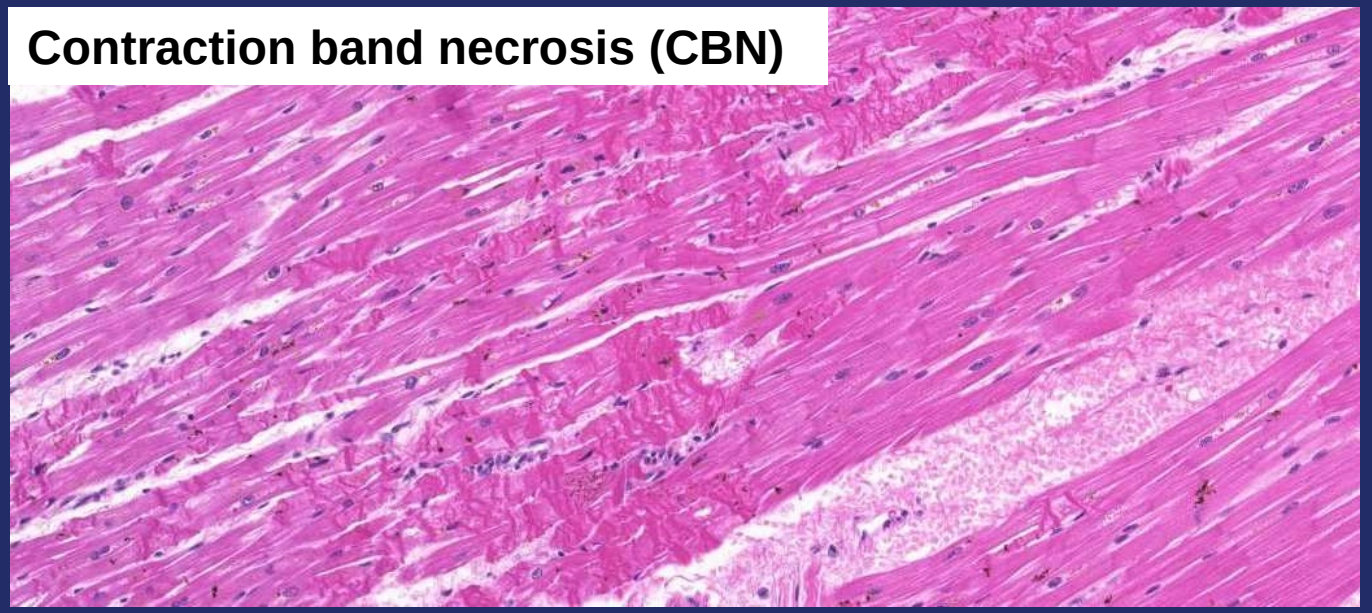
Right Atrial and left ventricular subendocardial hemorrhage



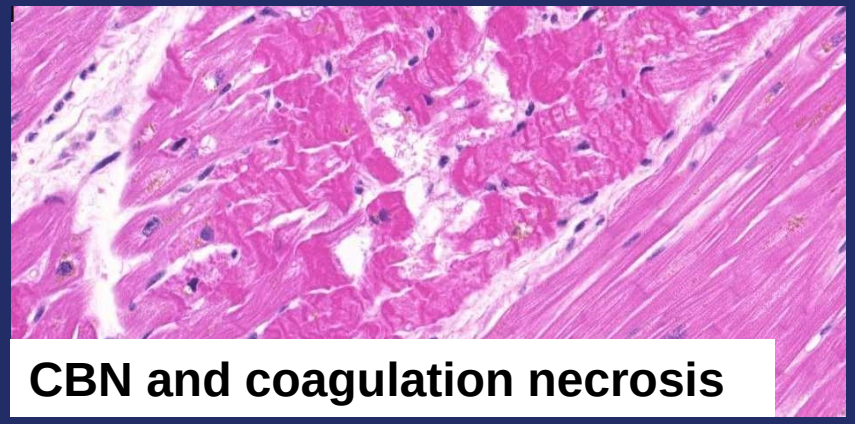


Myocardial Histology Example 1: EXPAND Turned Down Heart

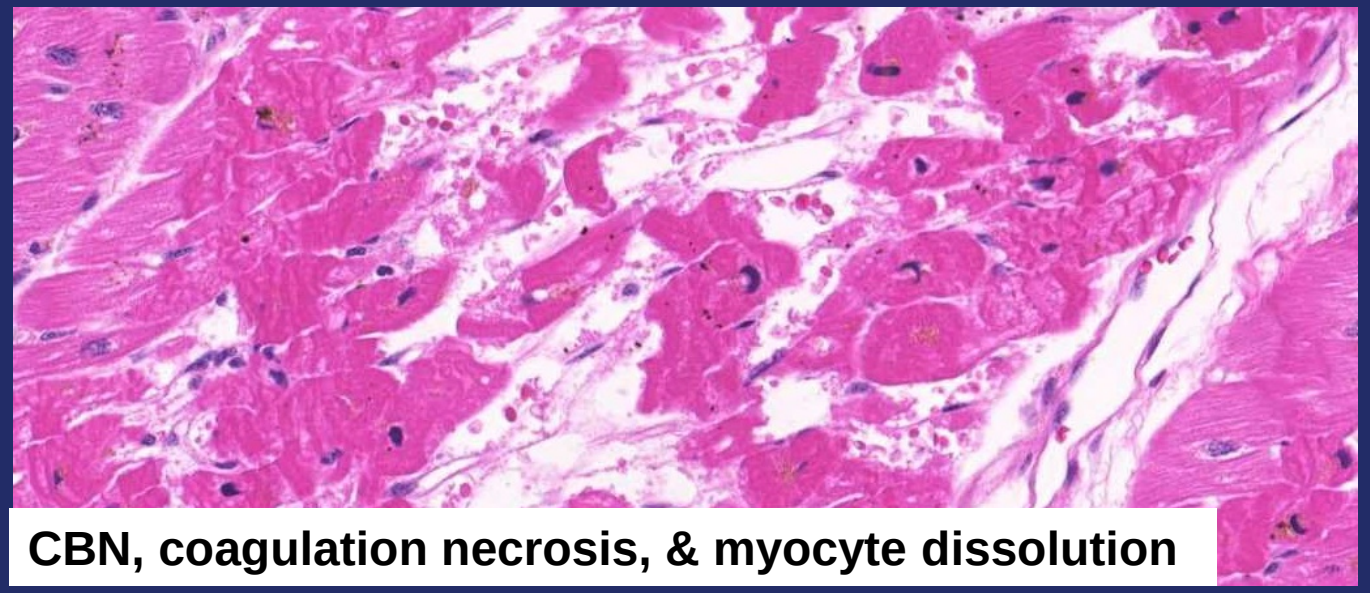
- Sections of all gross myocardial lesions showed severe and extensive (~25% of myocyte area) ischemic injury
  - Contraction band necrosis
  - Coagulation necrosis
  - Focal tissue dissolution in center of damaged areas
- Myocardial damage seen in nearly all gross lesion and non-gross lesion sections



Contraction band necrosis (CBN)



CBN and coagulation necrosis



CBN, coagulation necrosis, & myocyte dissolution

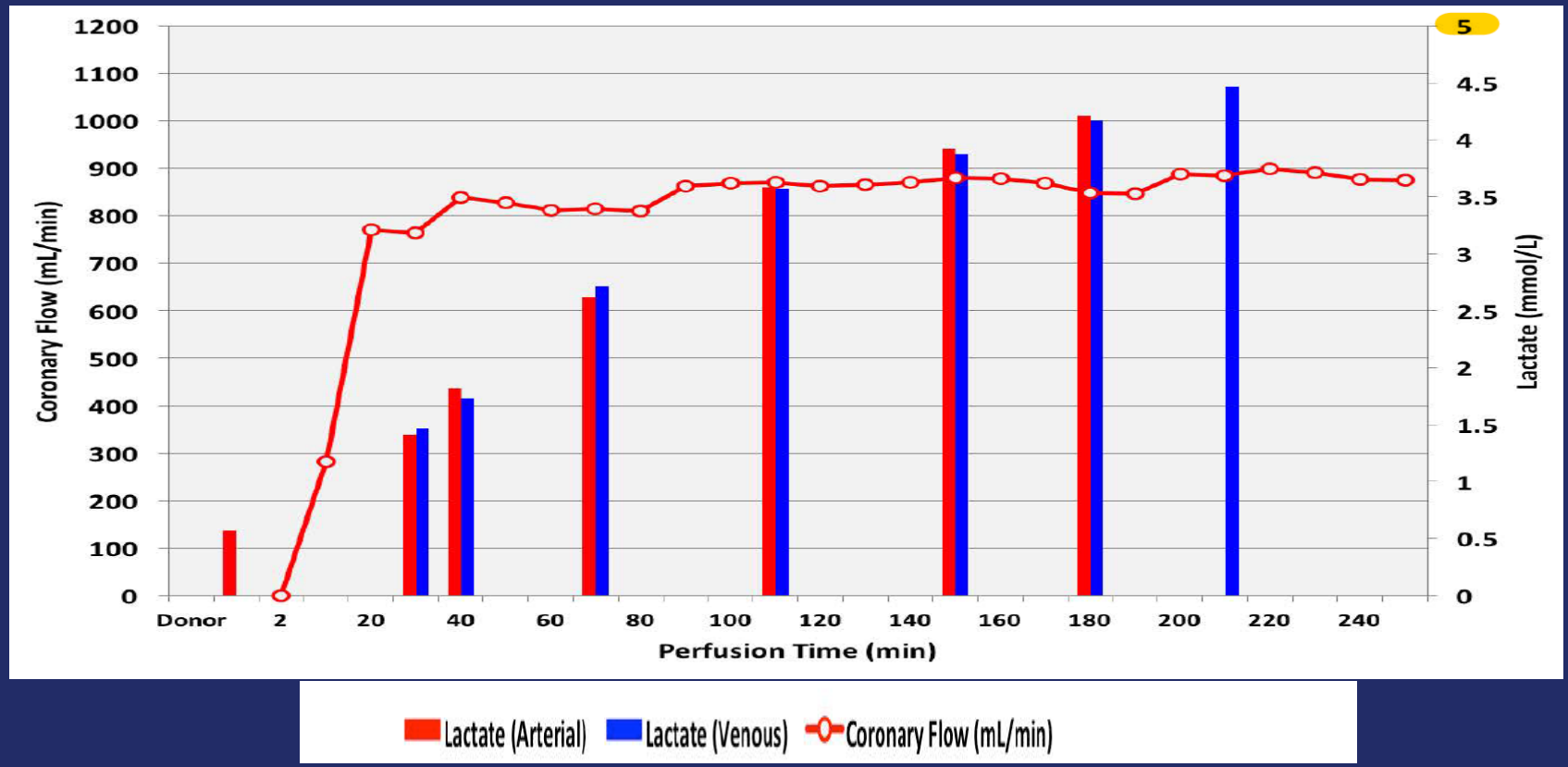
Example 2: EXPAND Turned Down Heart

Donor: 31-year old man with anoxia secondary to drug intoxication approximately 7.5 days pre-cardiectomy

- Cardiac arrest lasting 18 minutes at presentation
- Cardiac biomarkers not elevated
- Echo within 48 hours prior to cardiectomy showed LVEF 60% with trace to mild MR and TR
- Stable vital signs prior to cardiectomy
- Inclusion criteria met: Estimated cross-clamp time ≥4 hours and downtime

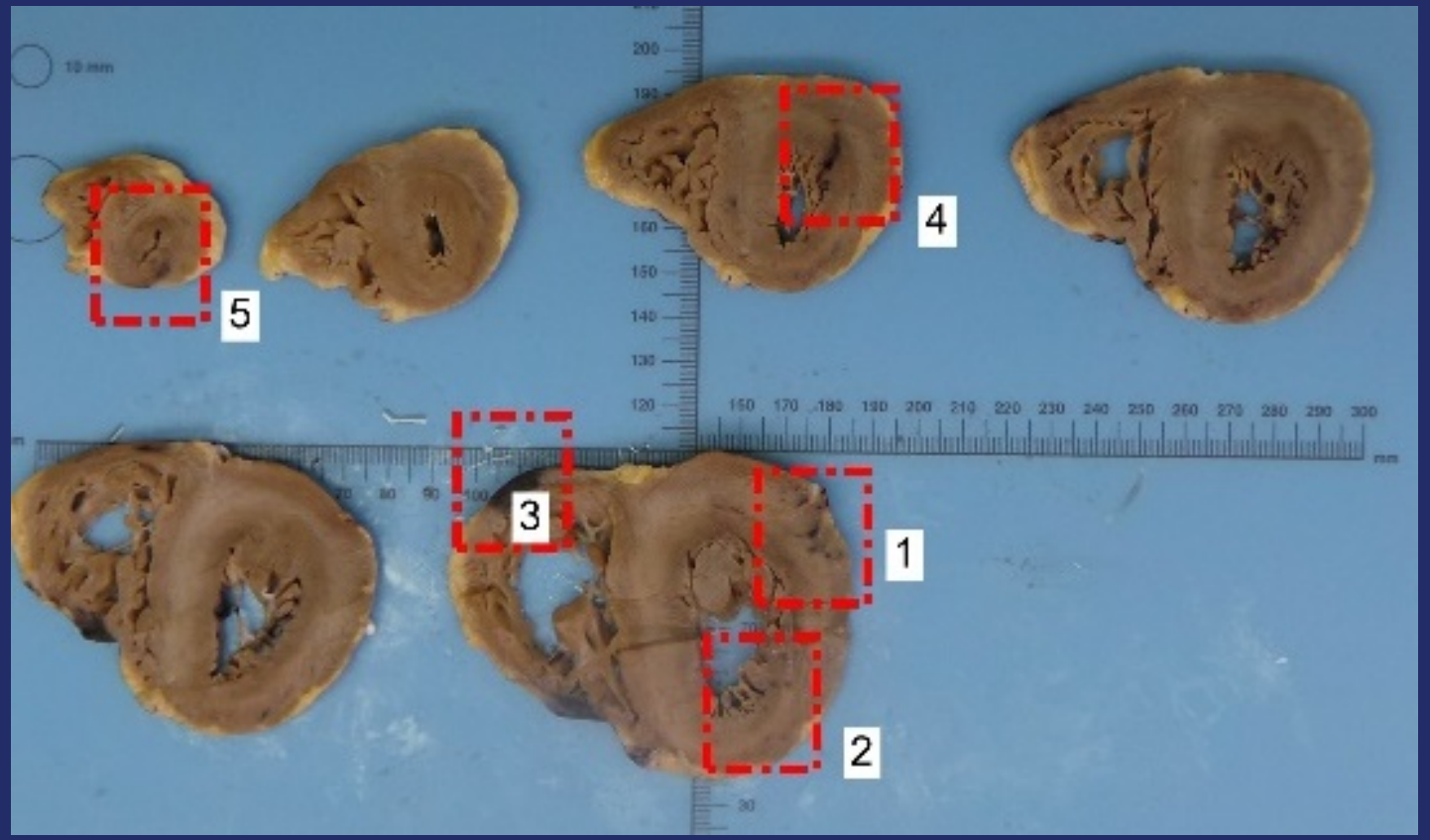
Example 2: EXPAND Turned Down Heart

OCS Heart perfusion time, coronary flow, and lactate levels



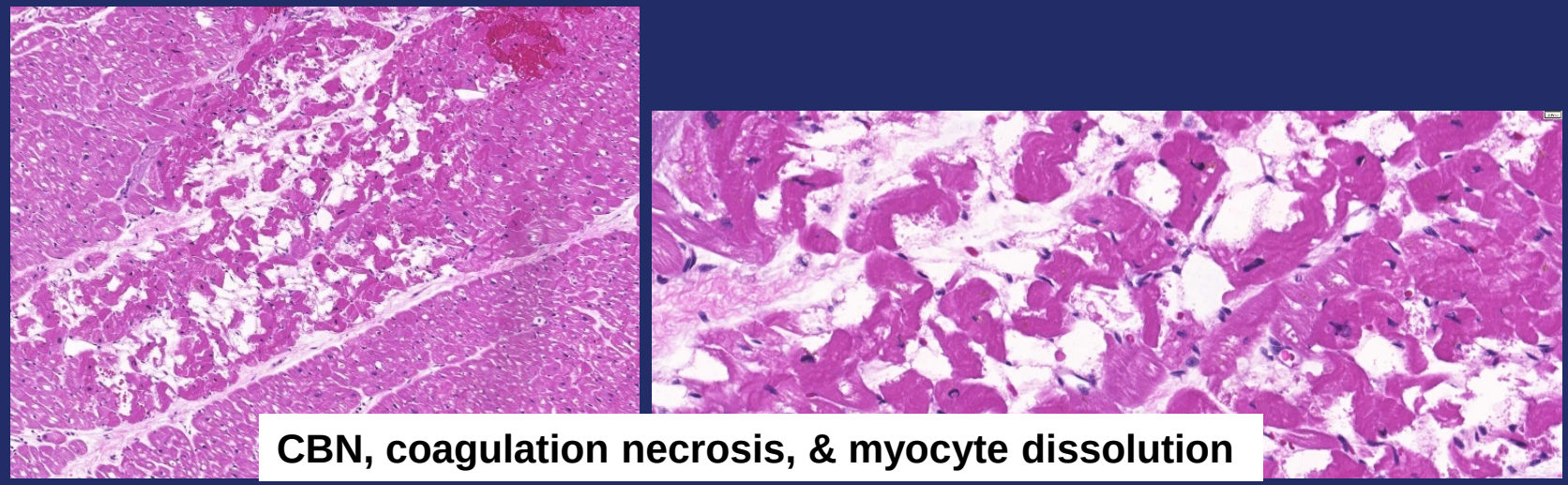
Gross Cardiac Pathology
Example 2: EXPAND Turned Down Heart

- Focal hemorrhage in posterior and lateral walls
- Left ventricular hemorrhagic mottling, mostly in left anterior and left lateral walls

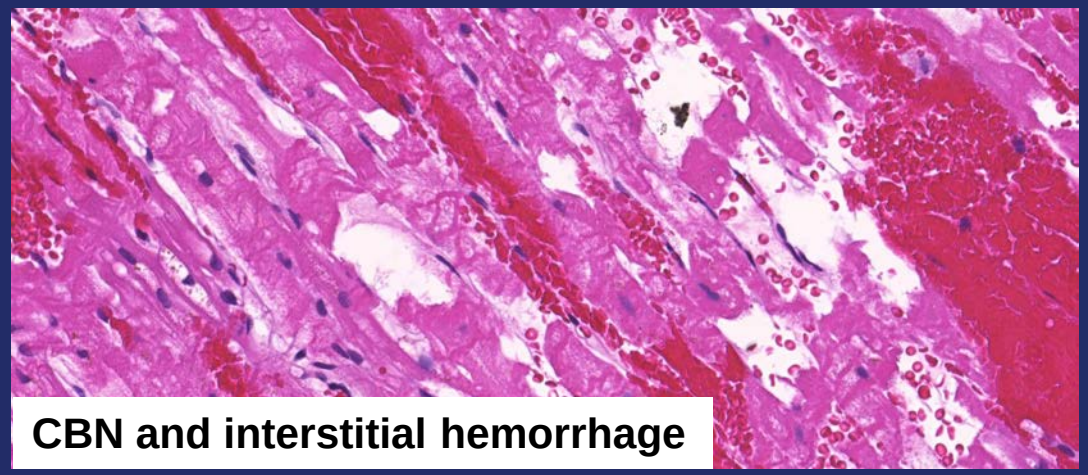


Myocardial Histology Example 2: EXPAND Turned Down Heart

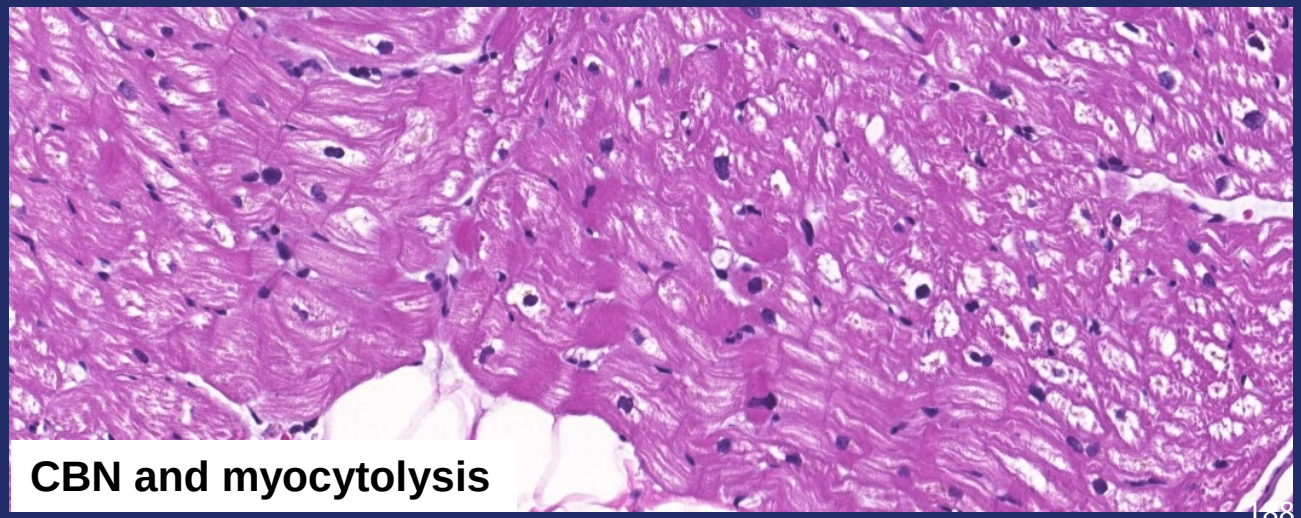
- Nearly all sections from the LV, RV, and interventricular septum showed:
  - Contraction band necrosis (CBN)
  - Wavy myofibers
  - Interstitial edema
  - Focal coagulation necrosis
  - Early loss of nuclei
- Findings consistent with widespread acute ischemic injury



CBN, coagulation necrosis, & myocyte dissolution



CBN and interstitial hemorrhage



CBN and myocytolysis

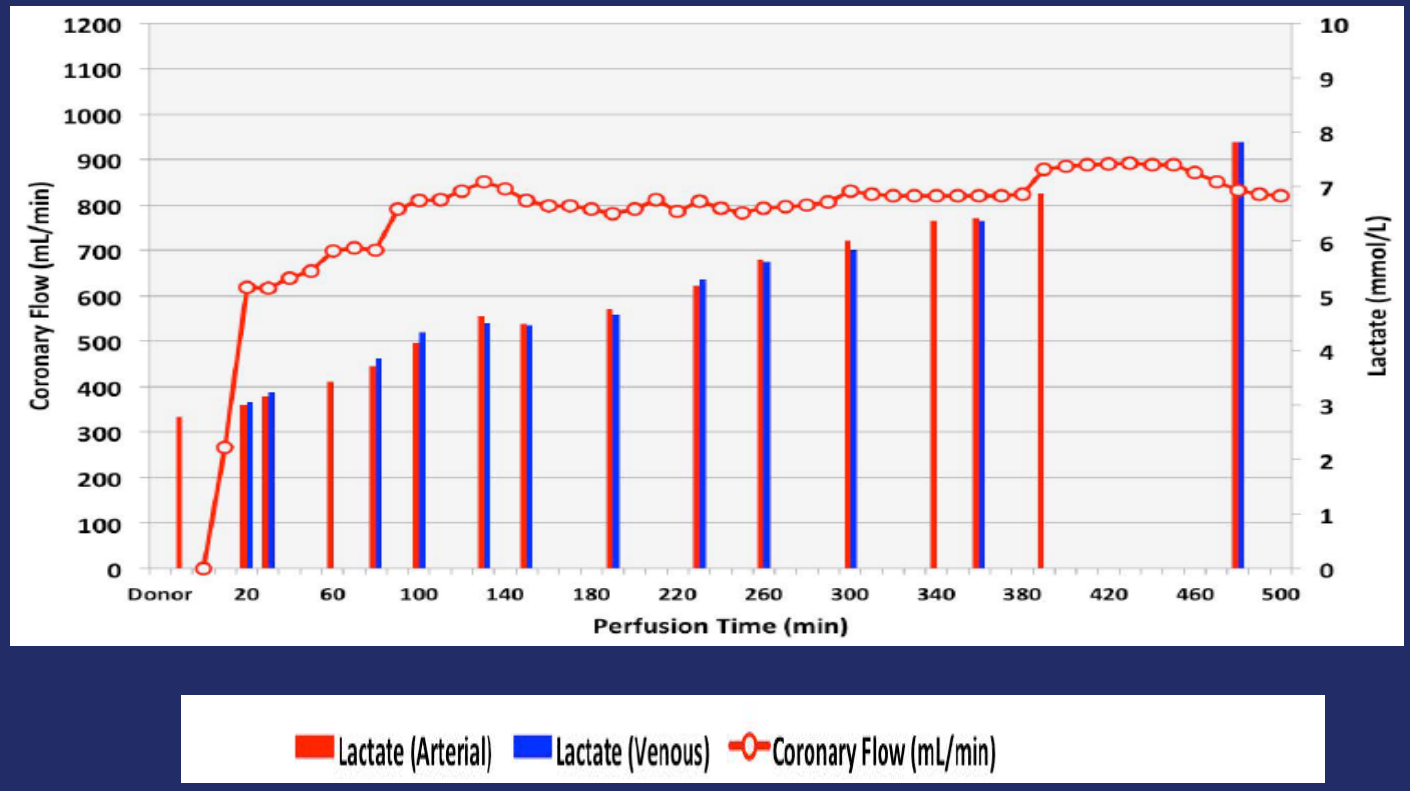
Example 3: EXPAND Turned Down Heart

Donor: 17-year old male with an intracranial hemorrhage secondary to an AVM approximately 2.5 days pre-cardiectomy

- No cardiac arrest
- No troponin elevation
- Echo within 48 hours prior to cardiectomy showed LVEF 65%
- Stable vital signs prior to cardiectomy
- Single inclusion criterion met: Projected cross-clamp time ≥4 hours

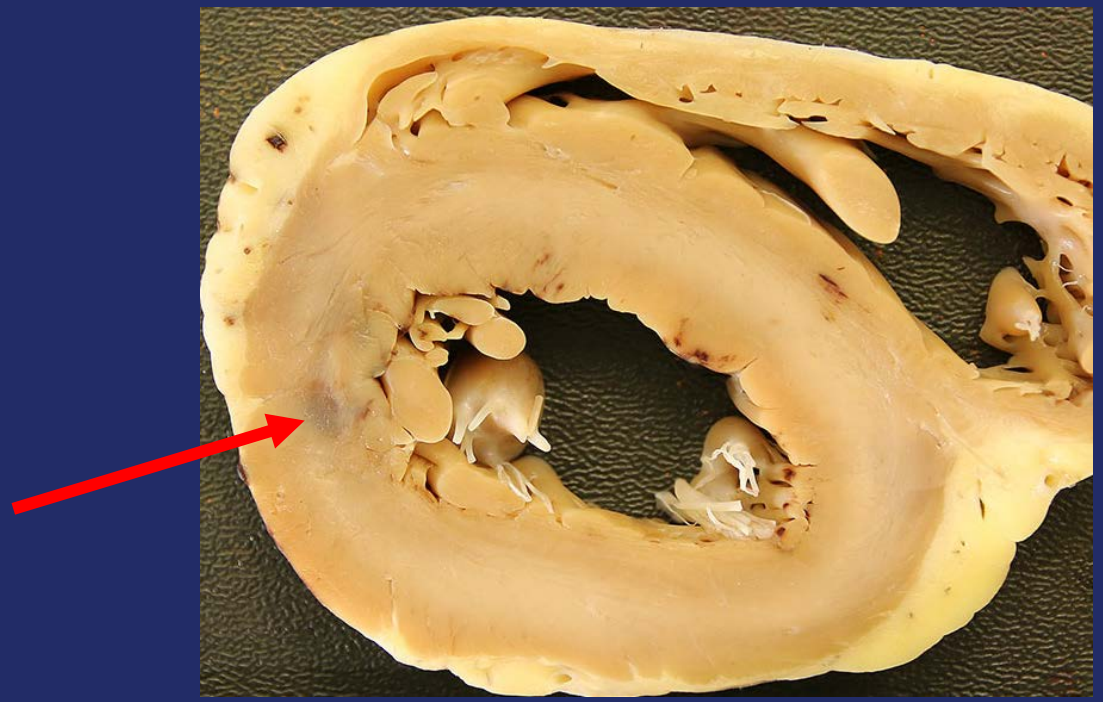
Example 3: EXPAND Turned Down Heart

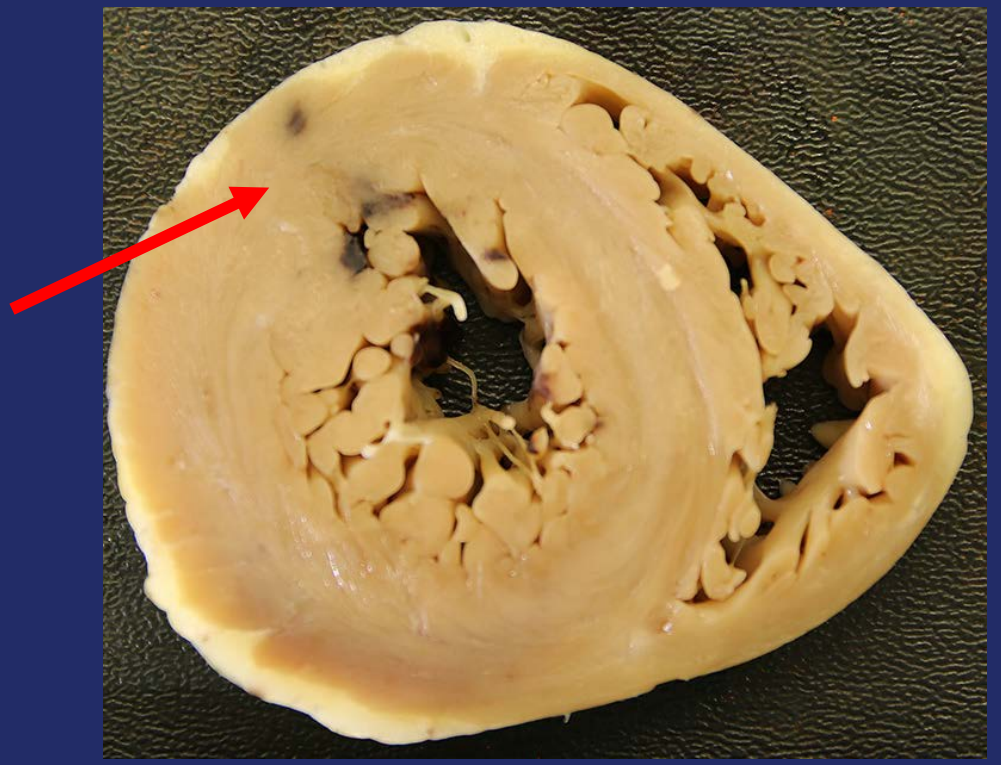
OCS Heart perfusion time, coronary flow, and lactate levels



Gross Cardiac Pathology
Example 3: EXPAND Turned Down Heart

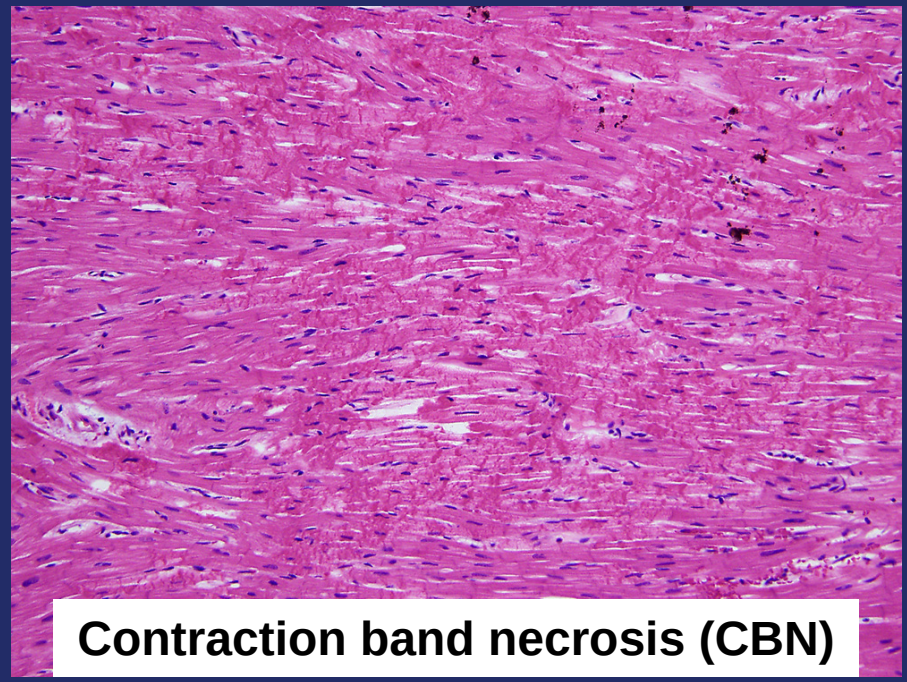
Focal subendocardial hemorrhage in anterior and lateral LV walls



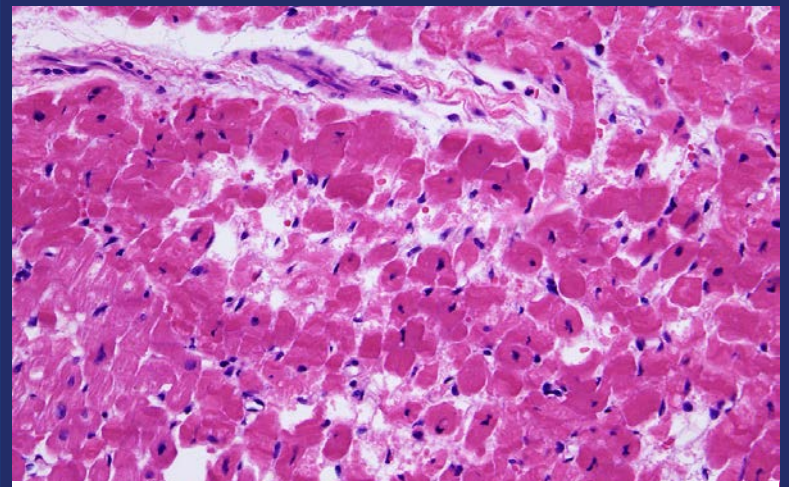


Myocardial Histology Example 3: EXPAND Turned Down Heart

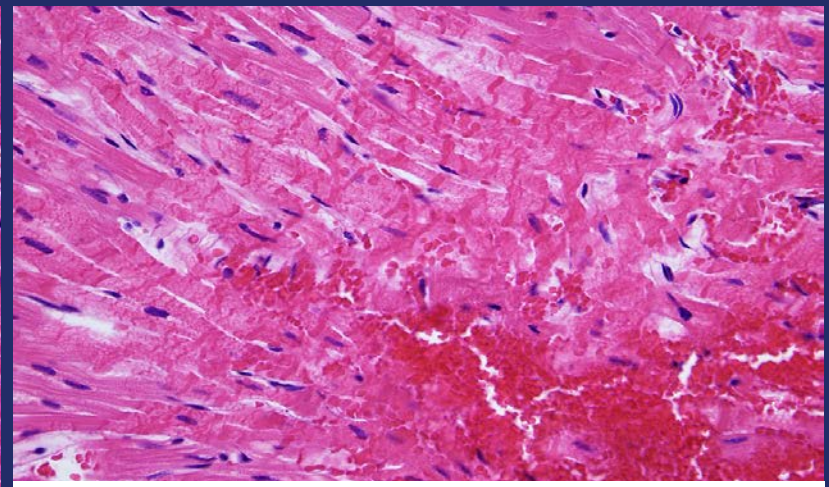
- Anterolateral LV subendocardial infarction with reperfusion and hemorrhage
- Other sections showed occasional acute microinfarcts with hypereosinophilia, contraction bands, & edema
- Other areas with hemorrhage
- No inflammation or myocardial lesions correlated with antemortem intracranial hemorrhage



Contraction band necrosis (CBN)



CBN and coagulation necrosis



CBN and interstitial hemorrhage

Clinical Observations

PROCEED II: OCS Heart vs. SOC RCT

- More deaths (within 30 and 38 days) in the OCS Heart group
- Longer ICU stays in the OCS Heart group
- Greater use of mechanical circulatory support in the OCS Heart group
- Longer hospital duration in the OCS Heart group

EXPAND: 4 OCS Heart recipients with acute severe PGD that directly contributed to death

- 3 cases within the first 24 hours, and 1 within 48 hours
- Pre-transplant echo showed normal LVEF for 3 of 4 hearts (echo not provided for 1 heart)
- Narrative summary reports: Mortality possibly related to preservation

Summary of Clinicopathologic Correlations

Pathologic analysis of OCS Heart turned down donor hearts with:

(1) stable antemortem hemodynamics;

(2) normal (or near normal) cardiac anatomy and normal ventricular function by echocardiography; and

(3) cardiac autopsy findings of acute diffuse or multifocal myocardial damage

Raise the possibility that in an important proportion of cases, the OCS Heart did not provide effective organ preservation or severely damaged what would have been an acceptable graft for transplant

Post Approval Study

Catherine P. Wentz, M.S.
Chemical/Biomedical Engineer
Lead Reviewer, Circulatory Support Devices Team (THT2B2)
Division of Circulatory Support, Structural and Vascular Devices (DHT2B)
Office of Heart Technology: Cardiovascular Devices (OHT2)
Office of Product Evaluation and Quality (OPEQ)

Post Approval Study

Proposed Studies

- A 175 patient, single-arm, prospective, observational registry
- A follow-up analysis on Tx EXPAND subjects

FDA Concerns

- Primary Endpoint: 12-month survival
  - Cardiac graft related death vs all cause mortality
- Performance goal of 86%
  - EXPAND = 95%

FDA Summary

Fernando Aguel
Assistant Division Director
Circulatory Support Devices Team
CDRH/FDA

FDA Summary

- **Study Design**
  - **Challenging to interpret the randomized results from PROCEED II and how they inform EXPAND study results**
  - **Single-arm study limitations for EXPAND and CAP datasets**

- **Study conduct**
  - **late adjudicated changes to investigators' assigned primary endpoint classifications for primary graft dysfunction**
  - **Modification to the assignments of donor heart inclusion criteria met**

FDA Summary

- **Definition of Extended Criteria Hearts**
  - **Difficulty in defining Extended criteria hearts and the possibility of substantial overlap between the definitions for standard and extended criteria donor hearts**

- **Lactate**
  - **Uncertainty regarding its use as a metric to determine the transplantability of a donor heart post-perfusion**

FDA Summary

- **Survival**
  - Trend of decreased survival for Randomized PROCEED II OCS hearts compared to SOC
  - Similar survival curve for EXPAND study hearts
- **OCS Heart Device Safety**
  - Unclear whether device may be associated with myocardial damage
- **Impact of OCS Heart System**
  - Uncertainty regarding the impact on pool of transplantable donor hearts and long-term survival for transplant recipients

FDA Summary

Thank you