OCS™ Liver System for the Resuscitation, Preservation, and Assessment of Donor Livers

July 14, 2021

Gastroenterology and Urology Devices Panel

TransMedics®

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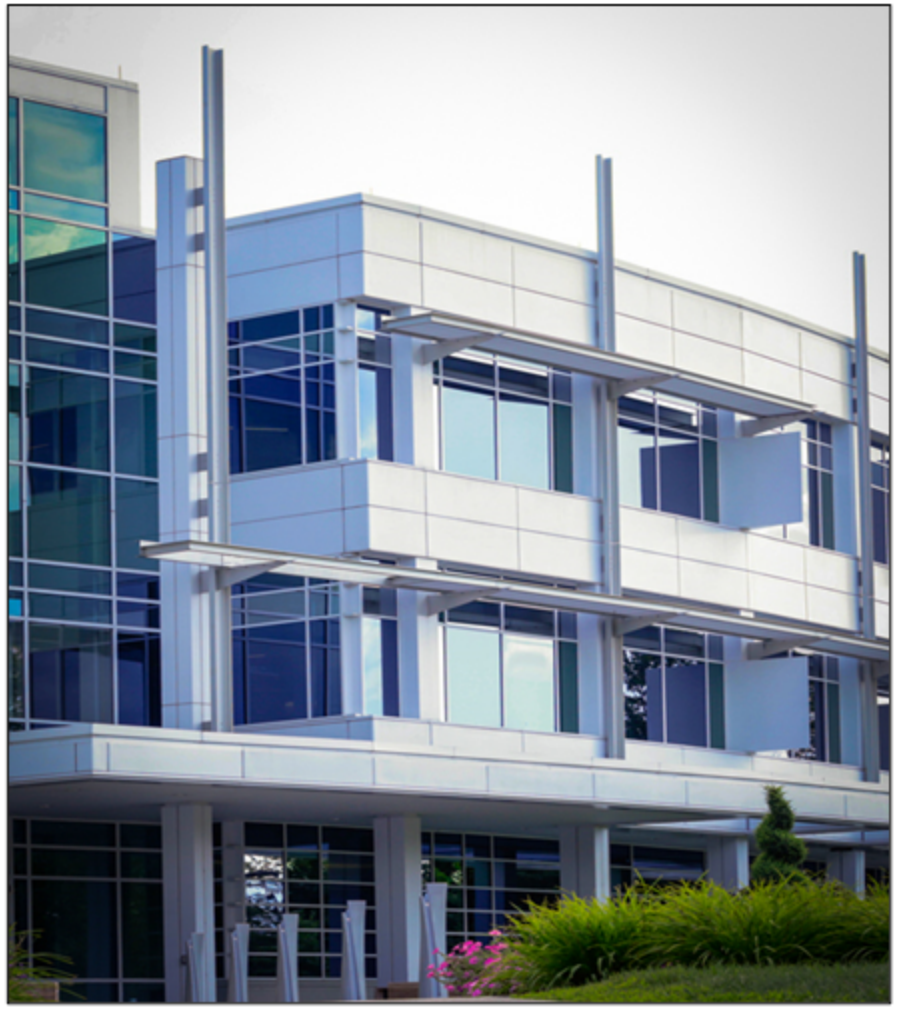
Introduction

Waleed Hassanein, MD

President and CEO

TransMedics, Inc.

About TransMedics and Organ Care System (OCS™)



Founded in 1998 to develop OCS technology to increase donor organ utilization for transplantation and improve post-transplant clinical outcomes

Clinically driven organization that pioneered concept of extracorporeal perfusion of donor hearts, lungs, and livers for transplantation

- Sponsored 8 US FDA pivotal trials

The OCS is developed and manufactured in the US

- OCS Lung FDA-approved for 2 indications
- OCS Heart under FDA review for extended-criteria
- OCS Liver CE-marked in Europe

Limitations of Cold Storage for Liver Transplantation

Cold Storage

- Severe time-dependent ischemic injury
- No organ optimization capabilities
- No assessment of organ viability

→ **Early Allograft Dysfunction (EAD)**

→ **Limits utilization of liver allografts**

~3 in 4 DCD donor livers go unutilized[2]

1. Hudcova et al, *Clin Transpl* 2017; 2. UNOS/SRTR Database.

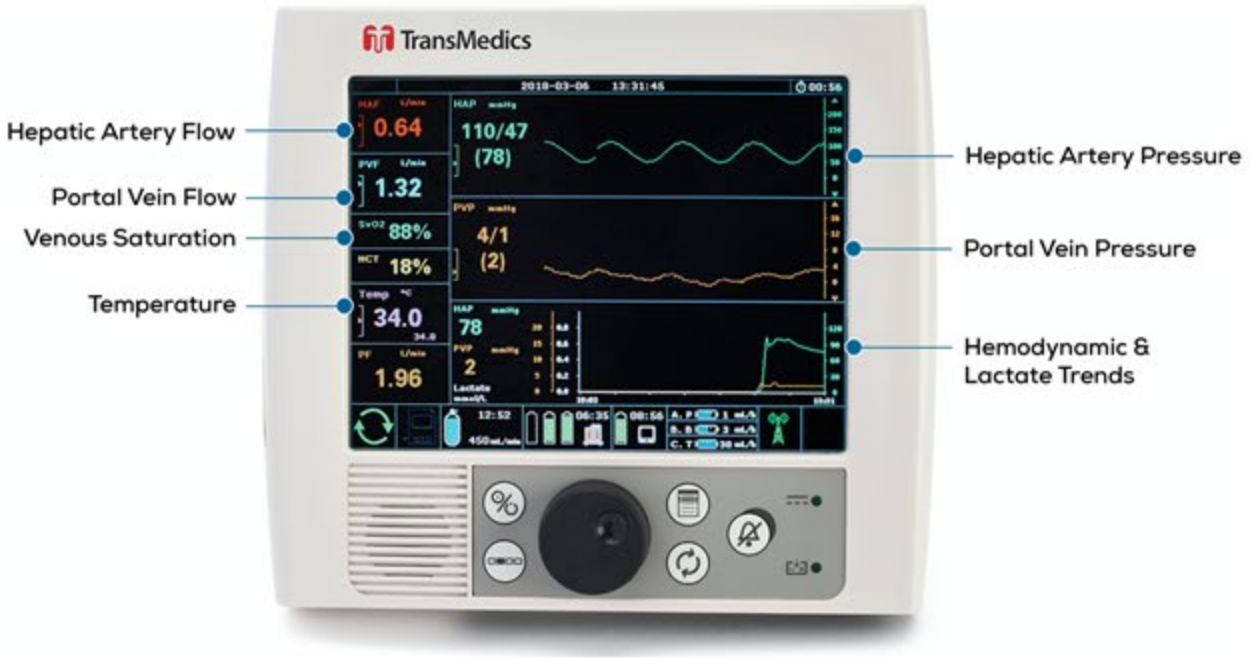
OCS Liver System: Integrated Portable Platform Designed To Overcome Limitations of Cold Storage and Increase Utilization

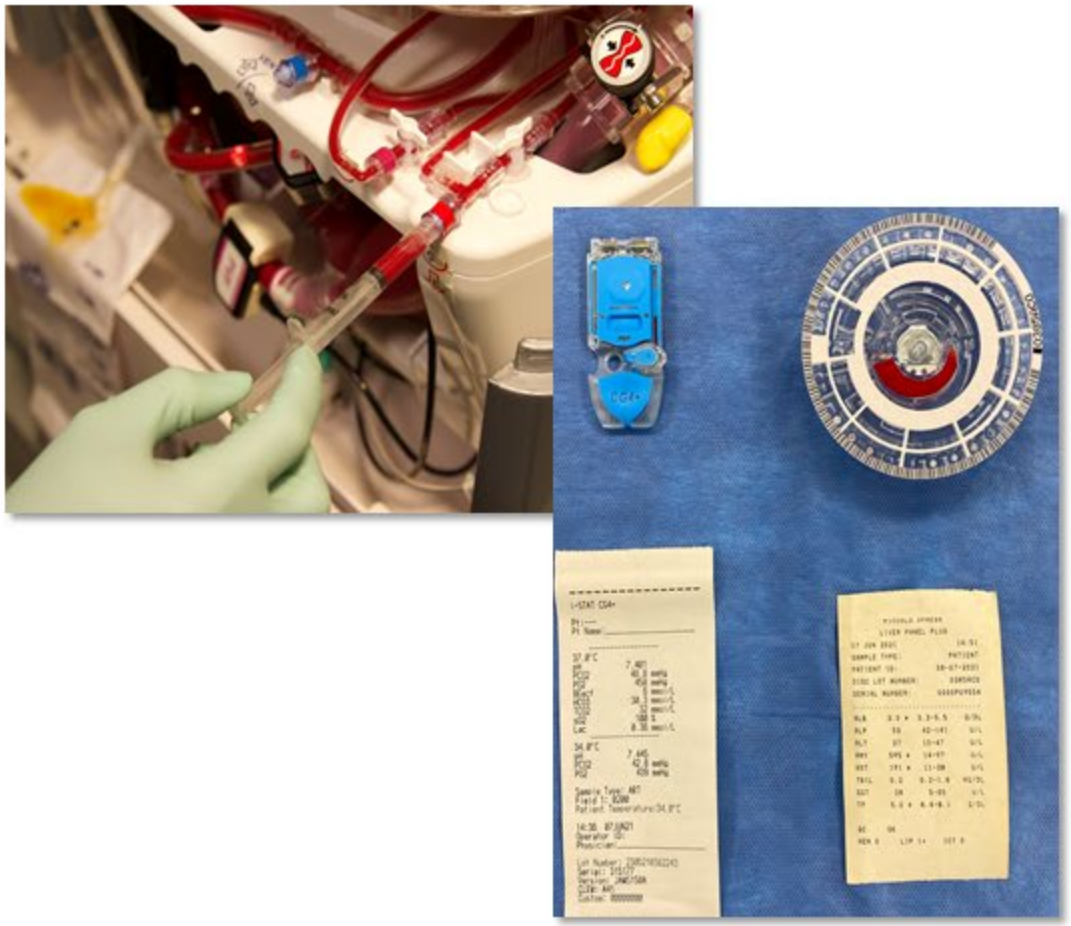
OCS™ Liver Console

OCS™ Liver Perfusion Set

OCS™ Liver Bile Salts

OCS Liver Enables Continuous Assessment of Metabolic and Functional State of the Donor Liver *Ex Vivo*





VIDEO

OCS Liver System Enables Several Clinical Advantages

Features of OCS Liver System	Clinical Advantages
Highly portable system	▪ Minimizes ischemic injury on liver allograft ▪ Eliminates time and distance limitations on donor liver procurement
Optimizes donor liver *ex vivo*	▪ Enables oxygen and substrate delivery ▪ Resuscitates donor livers that might not be transplantable on cold storage
Assesses metabolic & functional state of donor livers *ex vivo*	▪ Increases clinical confidence about transplantability ▪ Minimizes risk of transplanting questionable donor livers into recipients

Summary of Key PROTECT Trial Results

- OCS **superior** to control on primary effectiveness endpoint of EAD (p = 0.0096)
- Histopathological evidence of **reduced IR injury** with OCS
- OCS achieved significant **reduction in ischemic biliary complications**
- **Double** the number of **DCD donor livers utilized** with OCS vs cold storage
- PROTECT confirmed **that EAD is a valid surrogate** for risk of graft failure and prolonged ICU and hospital stay

Proposed Indications for Use

The TransMedics® Organ Care System (OCS™) Liver is a portable extracorporeal liver perfusion and monitoring system indicated for the resuscitation, preservation, and assessment of liver allografts from donors after brain death (DBD) or donors after circulatory death (DCD) ≤ 55 years old in a near-physiologic, normothermic and functioning state intended for a potential transplant recipient.

Agenda

Clinical Needs in Liver Transplantation	**Malcolm MacConmara, MD** Assistant Professor, Division of Surgical Transplantation UT Southwestern Medical Center
PROTECT & PROTECT CAP Trial Design & Results	**James Markmann, MD, PhD** Chief, Division of Transplant Surgery, Mass General Hospital Claude E. Welch Professor of Surgery, Harvard Medical School
Pathology Results	**Anthony J Demetris, MD** Starzl Professor of Liver and Transplant Pathology University of Pittsburgh
TransMedics Positions on FDA Discussion Questions	**Waleed Hassanein, MD** President and CEO TransMedics, Inc.
Clinical Perspective & Benefit-Risk Assessment	**Parsia Vagefi, MD, FACS** Chief, Division of Surgical Transplantation UT Southwestern Medical Center

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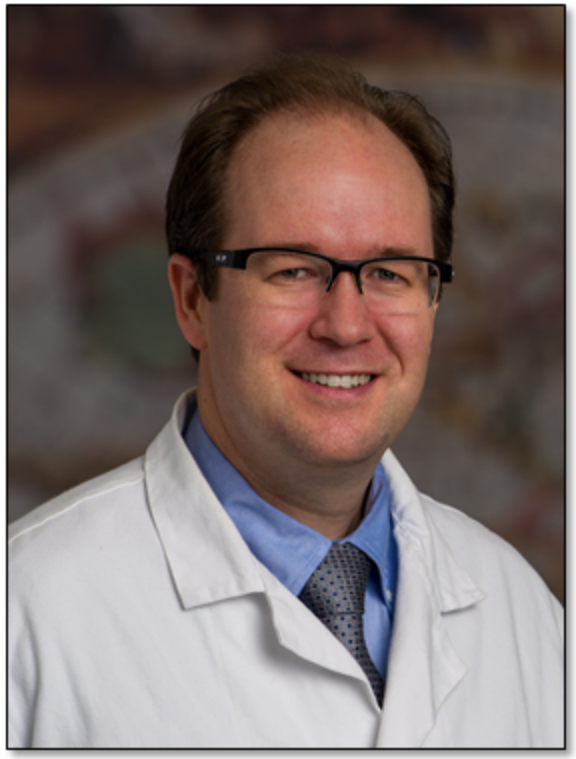

Clinical Needs in Liver Transplantation

Malcolm MacConmara, MD

Assistant Professor
Division of Surgical Transplantation
UT Southwestern Medical Center

Current Challenges in Liver Transplantation

High waiting list mortality due to organ scarcity[1]

High rates of post-transplant complications with cold storage[2-3]

3 of 4 DCD donor livers discarded[4]

Donor pool increasingly made up of higher-risk donors[1]

1. MacConmara et al, *Ann Surg* 2020; 2. Olthoff et al, *Liver Transplant* 2010; 3. Hudcova et al, *Clin Transplant* 2017; 4. UNOS/SRTR Database.

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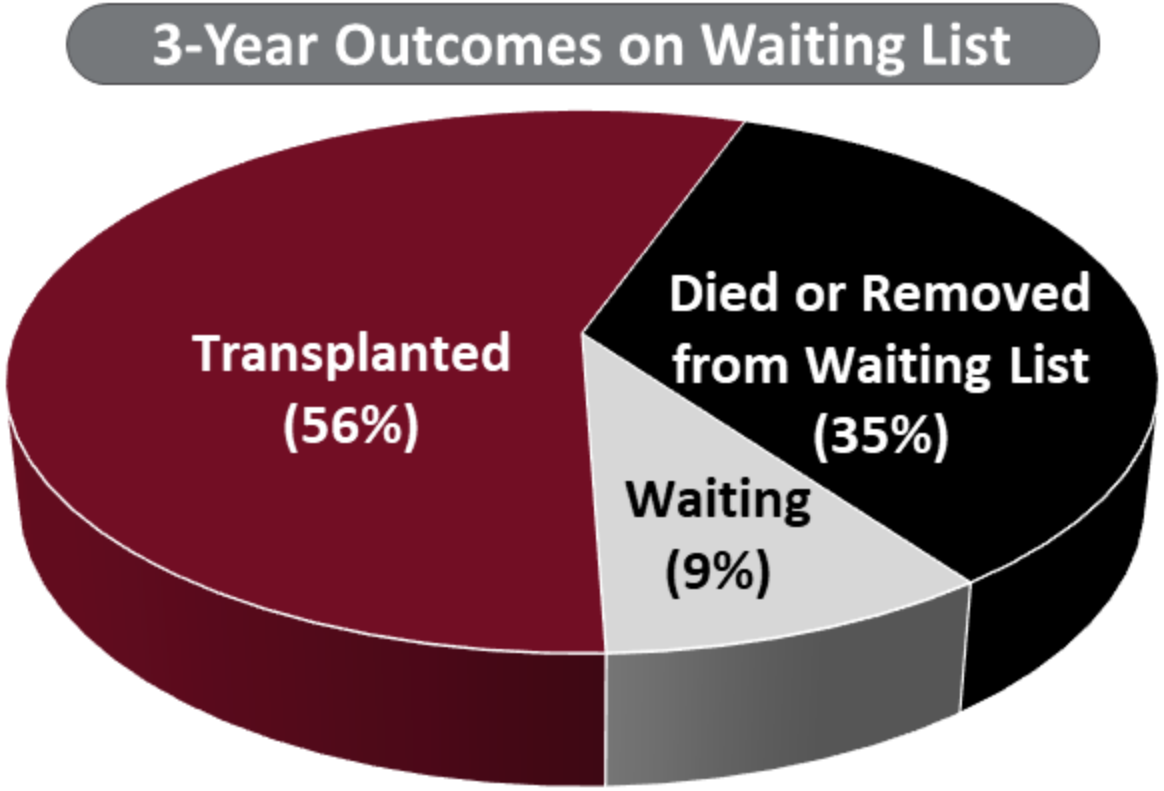
Inadequate Supply of Donor Livers Results in Substantial Waiting List Mortality

- 12,767 candidates on waiting list with only 8,896 transplants



SRTR/OPTN Annual Report, 2019

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Cold Storage Subjects Donor Livers to Time-Dependent Ischemic Injury

- Time donor liver on ice associated with degree of ischemic injury sustained
- Increased risk for post-transplant complications
  - Early allograft dysfunction (EAD)
  - Ischemic biliary complications
- Logistical time/distance constraints on utilization

EAD: Most Common Severe Complication after Liver Transplantation

- Cohort study of 300 deceased donor liver transplants at 3 US programs
- Conducted to create validated definition of EAD
- EAD defined as composite of
  - AST or ALT > 2,000 IU/L within first 7 days
  - Bilirubin ≥ 10 mg/dL on day 7
  - INR ≥ 1.6 on day 7
- Olthoff EAD definition is the gold standard for EAD

Olthoff et al, *Liver Transplant* 2010.

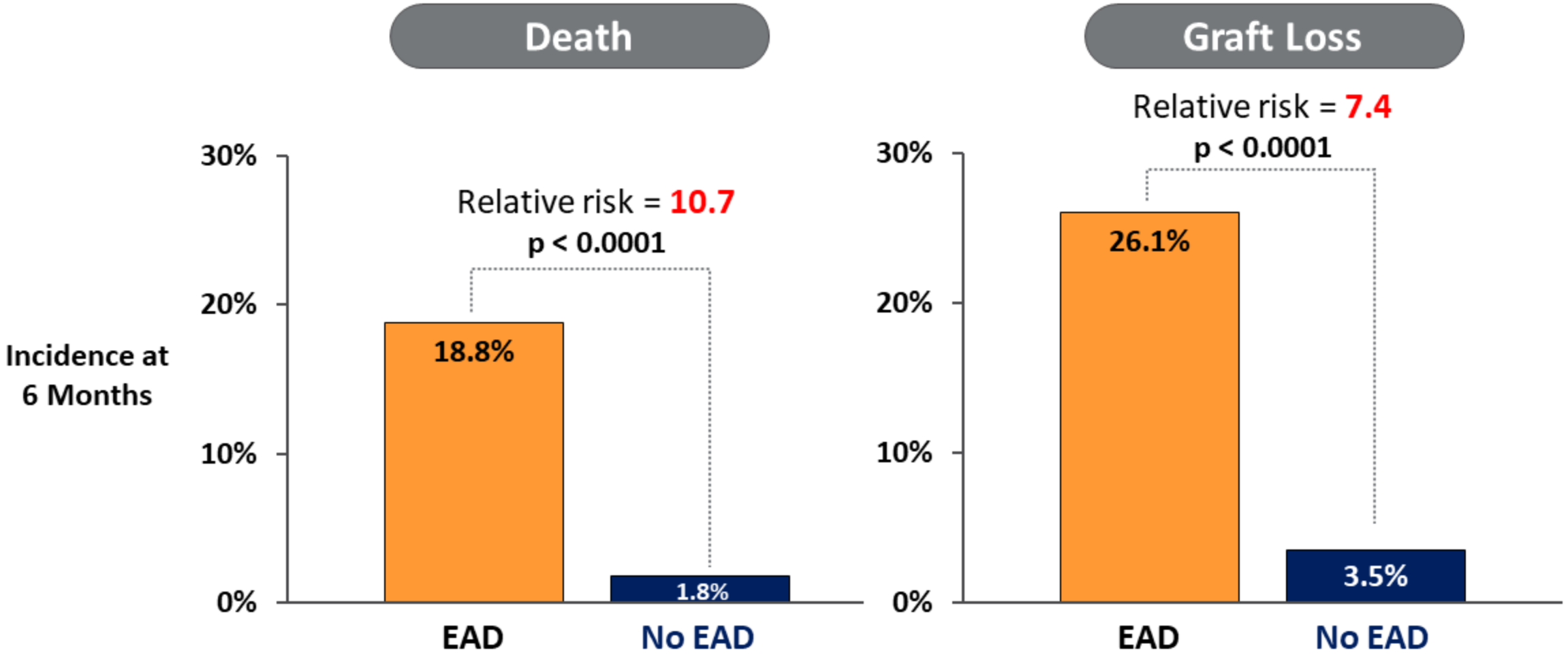
All Components of EAD Predict Mortality and Graft Failure

EAD Component(s) Met	Patients (% of total)	6-Month Outcomes	
		Mortality	Graft Failure
INR only	5 (7%)	40%	40%
Bilirubin only	28 (41%)	11%	14%
ALT/AST only	26 (38%)	19%	27%
INR + Bilirubin	4 (6%)	25%	50%
Bilirubin + AST/ALT	2 (3%)	0%	0%
INR + Bilirubin + AST/ALT	4 (6%)	50%	75%

- Discriminant validity for mortality highest with composite definition

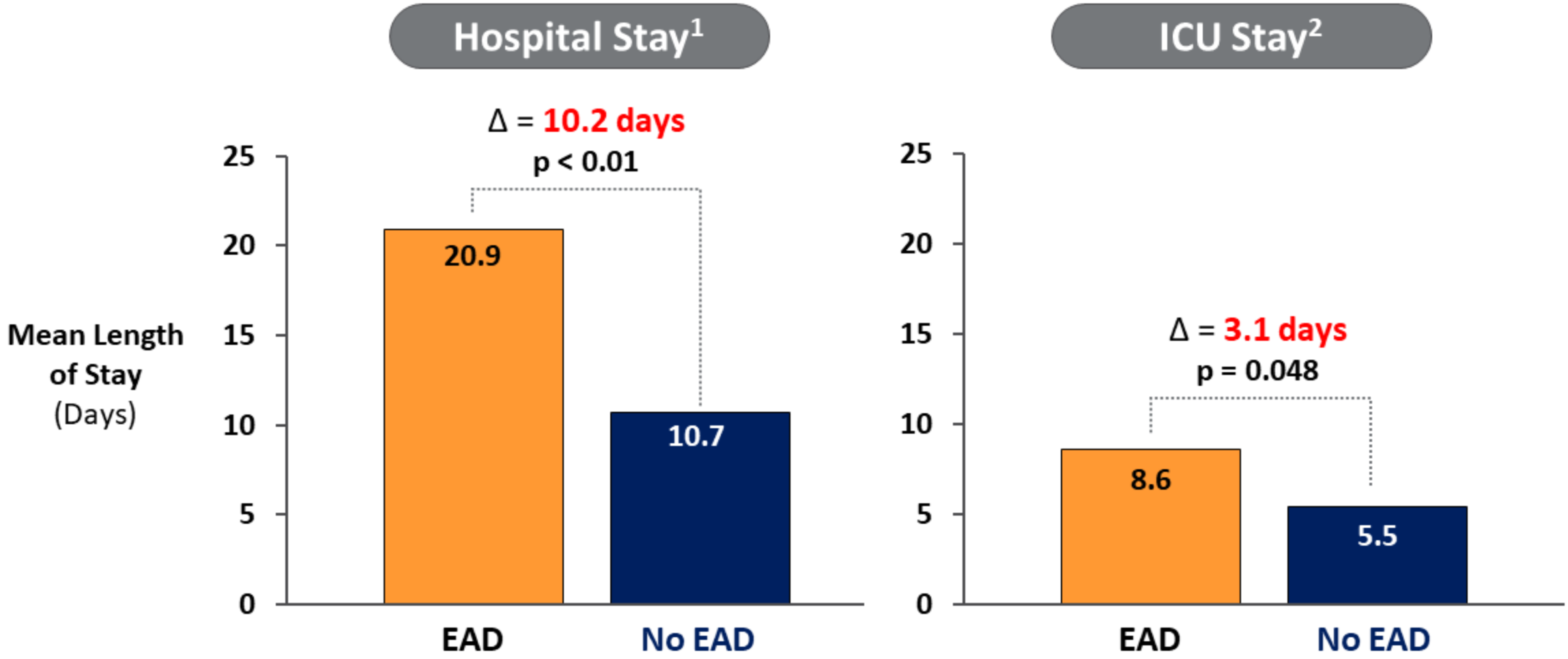
Olthoff et al, *Liver Transplant* 2010.

EAD: Validated Predictor of Death and Graft Loss



Olthoff et al, *Liver Transplant* 2010.

EAD: Associated with Longer ICU and Hospital Lengths of Stay



1. Lee et al, *Ann Hetapol* 2016; 2. Croome et al, *Transplant Proc* 2013.

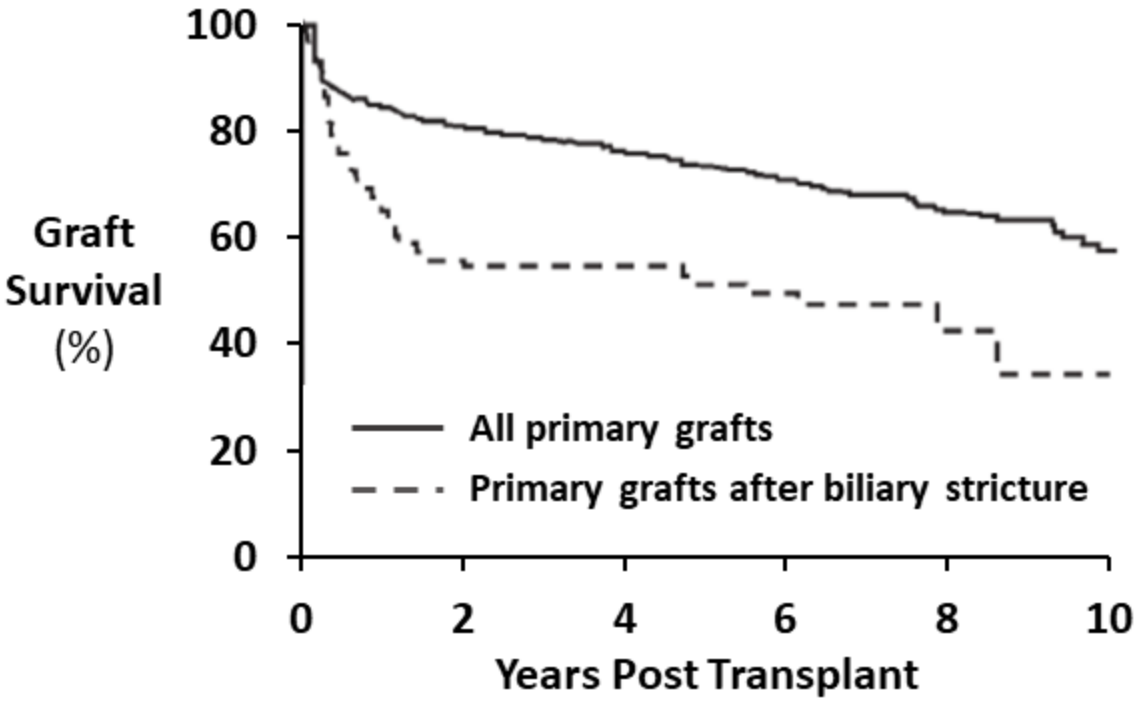
Ischemic Biliary Complications: More Common in DCD Donors, Donors with Long Ischemic Times, and Older Donors

- Ischemic biliary complications: biliary strictures, bile leaks, bile duct stones/casts, ischemic biliary injury[1]
- **10-15%** incidence overall[1] and up to **40%** in DCD livers[2]
- Key risk factors[3-5]
  - Longer cold ischemic times
  - Older donor age
  - DCD donors
- Concern for biliary strictures is one of the most common reasons for discard

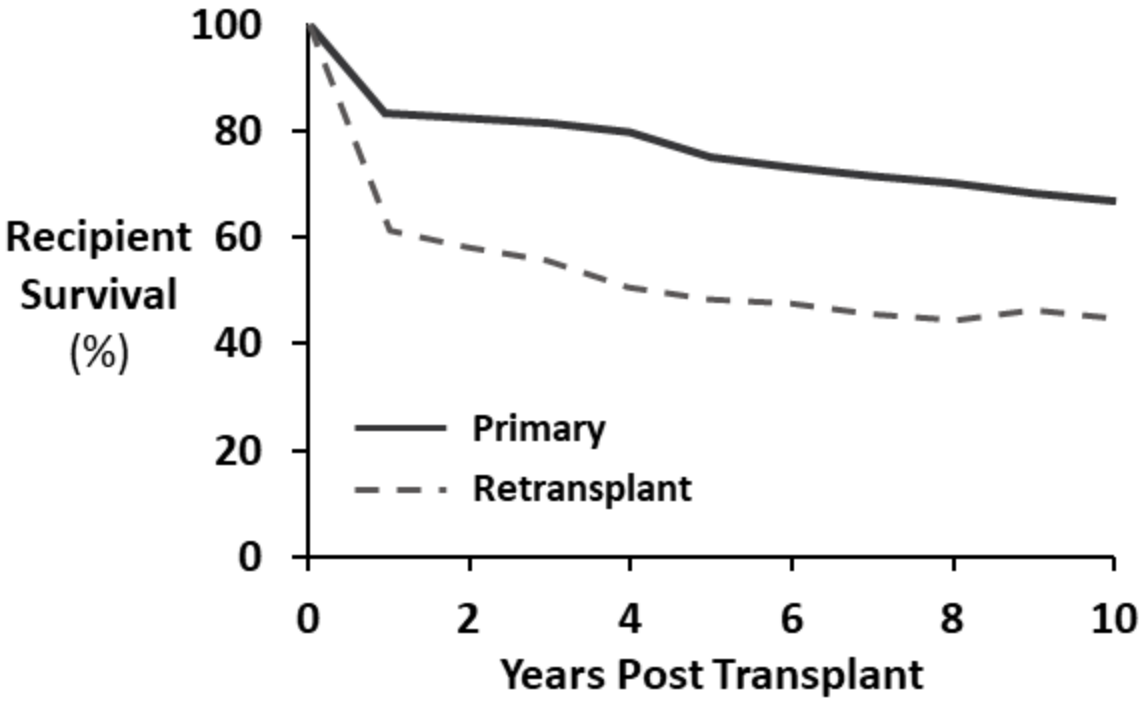
1. Daniel et al, *Clin Liver Dis* 2017; 2. Lee et al, *Liver Transpl* 2014;
3. Foley et al, *Ann Surg* 2011; 4. Chan et al, *Liver Transpl* 2008; 5. Sanchez-Urdazpal et al, *Hepatology* 1992.

Ischemic Biliary Complications Increase Risk for Primary Graft Failure, Retransplantation, and Death

Primary Graft Survival[1]



Retransplant Survival[2]



1. Guichelaar et al, *Am J Transplant* 2003; 2. Markmann et al, *Ann Surg* 1997.

New National Liver Distribution Policy Will Exacerbate Issues with Time-Dependent Ischemic Injury on Cold Storage

- New national liver distribution policy emphasizes
  - **Medical urgency**
  - **Distance** between donors and recipients
- Longer travel times on cold storage put recipients at greater risk for post-transplant complications
- Fulfilling national mandate will be difficult without technologies to reduce ischemic injury during preservation

Current Challenges in Liver Transplantation

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High rates of post-transplant complications with cold storage[2-3]

3 of 4 DCD donor livers discarded[4]

Donor pool increasingly made up of higher-risk donors[1]

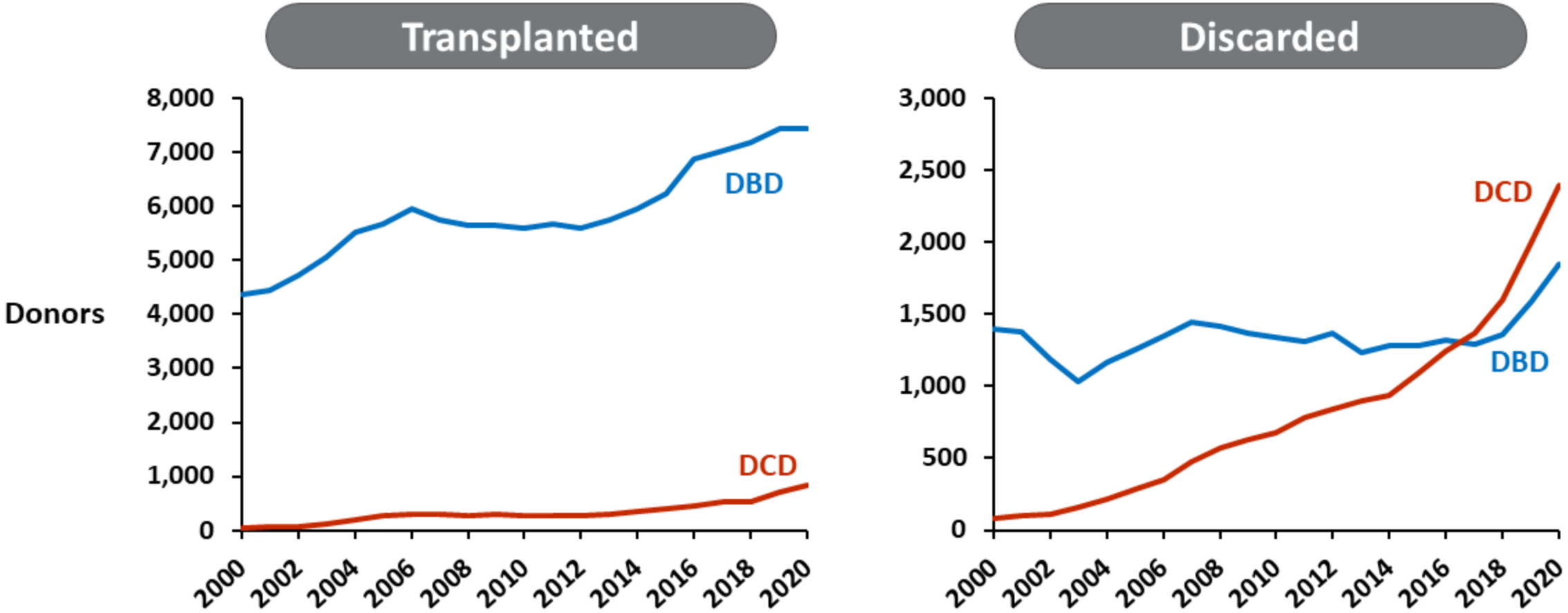
1. MacConmara et al, *Ann Surg* 2020; 2. Olthoff et al, *Liver Transplant* 2010; 3. Hudcova et al, *Clin Transplant* 2017; 4. UNOS/SRTR Database.

Cold Storage Severely Limits Utilization of DCD Donor Livers

- In early 1990s, early attempts made to utilize DCD livers
- Prolonged warm ischemia time and reperfusion injury after cold storage led to poor outcomes[1-3]
  - Recipient mortality
  - Primary graft non-function or allograft failure
  - Hepatic artery thrombosis
  - Ischemic biliary complications (ischemic cholangiopathy)

1. Merion et al, *Ann Surg* 2006; 2. Lee et al, *Liver Transpl* 2014; 3. Abt et al, *Ann Surg* 2004.

3 of 4 Livers from DCD Donors Are Not Transplanted



UNOS/SRTR Database

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Overall Quality of Donor Pool Is Declining

- Donor population increasingly comprised of higher-risk allografts
  - Older donors
  - Higher prevalence of obesity
  - Higher prevalence of fatty liver disease
- Cold storage has no ability to optimize livers or assess viability for transplant
  - Limits utilization of donor livers with risk factors
  - May lead to transplantation of unsuitable donor livers
- Number of donor livers discarded or not pursued likely to increase while cold storage remains only option for preservation

MacConmara et al, *Ann Surg* 2020.

Unmet Need to Address Limitations of Cold Storage

- **1 of every 3 patients die or delisted** before receiving a liver transplant
- **Post-transplant complications** common with cold static storage
  - **1 in 3** experience EAD
  - **1 in 6** experience an ischemic biliary complication
- **75%** of DCD donor livers are discarded
- Future trends in donor pool will **exacerbate issues with cold storage**
- **New technologies needed** to improve post-transplant outcomes and expand utilization

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PROTECT and PROTECT CAP Trial Design and Results

James Markmann, MD, PhD

Chief, Division of Transplant Surgery,
Massachusetts General Hospital
Claude E. Welch Professor of Surgery,
Harvard Medical School

PROTECT Trial Design

- Prospective, randomized trial of 300 recipients at 20 US liver transplant sites
- 1:1 randomization to OCS Liver or Control (cold storage)
- Designed to compare safety and effectiveness of preservation techniques among donor livers with at least one of the following characteristics
  - Donor age ≥ 40 years
  - Expected total cross-clamp/cold ischemic time ≥ 6 hours
  - DCD donor with age ≤ 55 years
  - Steatotic liver > 0% and ≤ 40% macrosteatosis at time of retrieval*

PROTECT Evaluated Donor Livers that Are Challenging to Preserve on Cold Storage

* Based on retrieval biopsy readout only if the donor liver was suspected to be fatty at time of retrieval

Donor Exclusion Criteria

- Living donors
- Liver intended for split transplants
- Positive serology for HIV, hepatitis B, or hepatitis C
- Presence of moderate or severe traumatic liver injury, or anatomical liver abnormalities that would compromise ex-vivo perfusion (i.e., accessory blood vessels or other abnormal anatomy that require surgical repair) and livers with active bleeding (e.g., hematomas)
- Donor livers with macrosteatosis of > 40% based on retrieval biopsy readout

Recipient Inclusion and Exclusion Criteria

Recipient Inclusion Criteria

- Registered male or female primary liver transplant candidate
- Age ≥ 18 years
- Provided informed consent

Recipient Exclusion Criteria

- Acute, fulminant liver failure
- Prior solid organ or bone marrow transplant
- Chronic use of hemodialysis or diagnosis of chronic renal failure
- Multi-organ transplant
- Ventilator dependent
- Dependent on > 1 IV inotrope to maintain hemodynamics

Primary Effectiveness Endpoint

- Early allograft dysfunction (EAD), defined as presence of at least one of the following
  - AST level > 2000 IU/L within the first 7 postoperative days
  - Bilirubin ≥ 10 mg/dL on postoperative day 7
  - INR ≥ 1.6 on postoperative day 7
  - Primary non-functioning graft within the first 7 days (irreversible graft dysfunction requiring emergency liver retransplantation or death, in the absence of immunologic or surgical causes)
- Hypothesis testing
  - Non-inferiority at margin of 0.075
  - Superiority (if non-inferiority criterion met)

Rationale for Use of Surrogate Endpoints in Clinical Trials

- Substitute for clinically meaningful endpoint that is expected to predict the effect of the therapy
- Appropriate in cases when proposed clinical benefit (e.g., survival) might not be detectable in trials of reasonable duration or size

Section 507(e)(9) of the Federal Food, Drug, and Cosmetic Act

EAD Is a Well-Accepted Surrogate Endpoint in Liver Transplantation

- Repeatedly shown to be valid predictor of important clinical outcomes[1-4]
  - Recipient survival
  - Graft survival
  - Postoperative complications
  - Longer hospital length of stay
  - Longer ICU length of stay
  - Greater total cost of care
- Powering PROTECT to demonstrate survival benefit not feasible
- EAD appropriate primary endpoint for PROTECT

1. Olthoff et al, *Liver Transpl* 2010; 2. Lee et al, *Ann Hetapol* 2016; 3. Croome et al, *Transplant Proc* 2013; 4. Eisenbach et al, *Transplant Proc* 2009.

OCS Donor Liver Assessment Endpoints

- OCS assessment during perfusion, defined as proportion of livers on which measurements of all of the following were available on OCS before transplant
  - Lactate level (every 2 hours)
  - Average bile production rate (based on total bile production volume and duration of OCS perfusion)
  - Hepatic artery pressure (continuously)
  - Portal vein pressure (continuously)
- Hypothesis testing
  - Evaluated against performance goal of 85% in OCS group

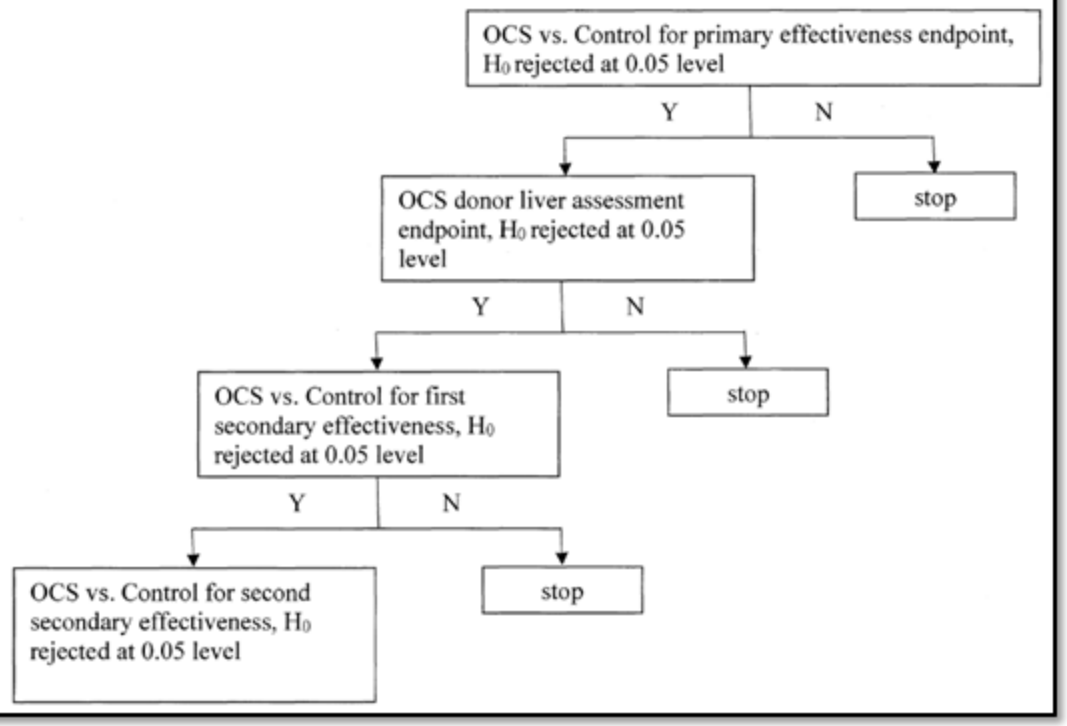
Secondary Effectiveness Endpoints

- Two secondary effectiveness endpoints
  1. Patient survival at Day 30 post transplantation
  2. Patient survival at initial hospital discharge post transplantation
- Hypothesis testing
  - Non-inferiority at margin of 0.075
  - Superiority (if non-inferiority criterion met)

PROTECT Prespecified Appropriate Type-I Error Control

5.8. Multiple Comparisons / Multiplicity

No adjustments for multiple comparisons/multiplicity will be made. Because fixed sequence testing will be used for the secondary effectiveness endpoints, no adjustment for the multiplicity of these endpoints needs to be made. The fixed sequence testing is shown below.



Page 20 of PROTECT SAP

Because fixed sequence testing will be used for the secondary endpoints, no adjustment for the multiplicity of these endpoints needs to be made. The endpoints will be tested in the order listed above. The test for non-inferiority for the first secondary effectiveness endpoint will be performed only if the null hypothesis has been rejected for the OCS donor liver assessment endpoint. The test for non-inferiority for the second secondary effectiveness endpoint will be performed only if the null hypothesis has been rejected in favor of the alternative hypothesis of non-inferiority of the OCS treatment to the Control treatment for the first secondary effectiveness endpoints. Similarly, the test for superiority for the second secondary effectiveness endpoint will be performed only if the null hypothesis of equality has been rejected in favor of superiority of the OCS treatment to the Control treatment for the first secondary effectiveness endpoints (and non-inferiority has been demonstrated for the given secondary effectiveness endpoint). Due to statistical power limitations, it is not expected that non-inferiority will be demonstrated for patient survival at day 30 or at initial hospital discharge.

Page 44 of PROTECT Protocol
Pages 31-32 of PROTECT SAP

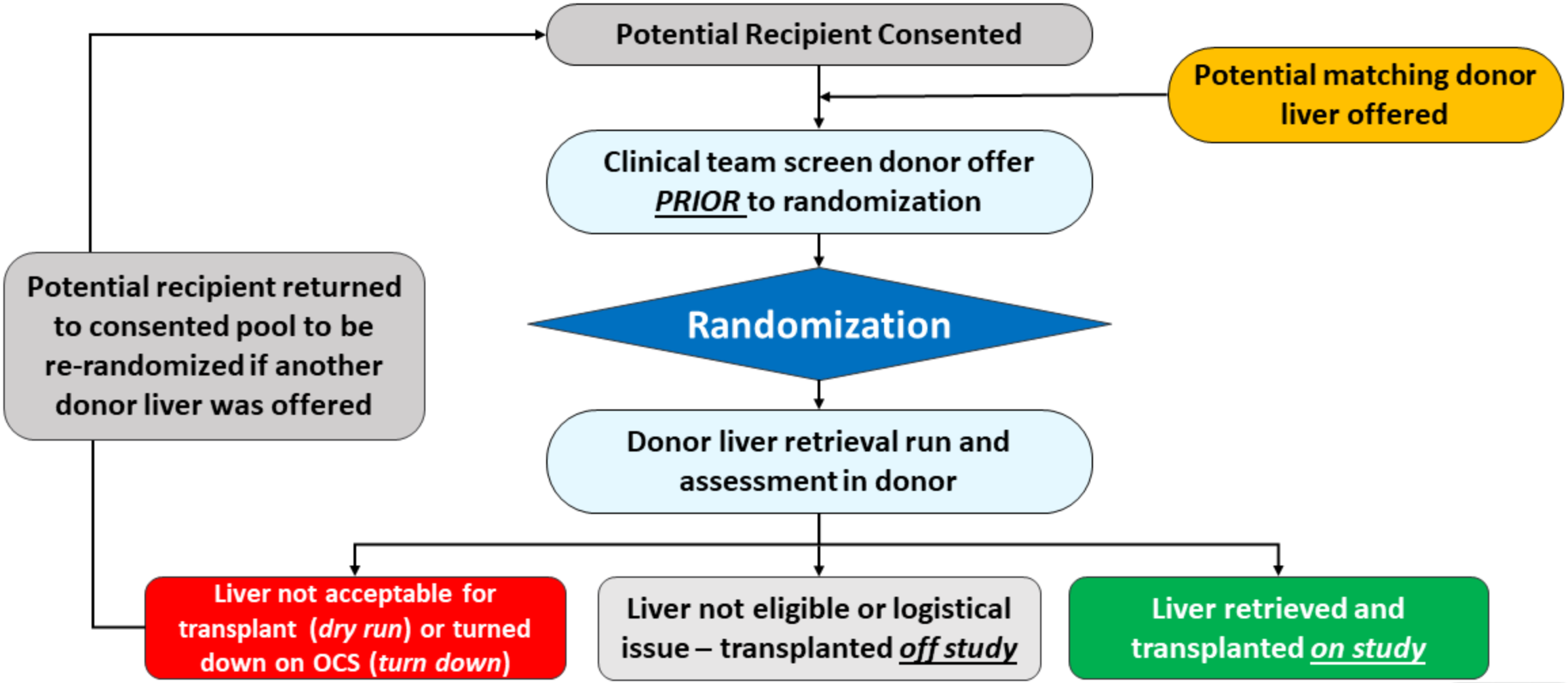
Safety Endpoint

- Incidence of liver graft-related serious adverse events (LGRSAEs) in first 30 days
  - Primary non-function
  - Ischemic biliary complications (ischemic biliary strictures and non-anastomotic bile duct leaks)
  - Vascular complications
  - Liver allograft infections
- Hypothesis testing
  - Non-inferiority at margin of 1.0 event/patient
  - Superiority (if non-inferiority criterion met)
- No multiplicity adjustment necessary

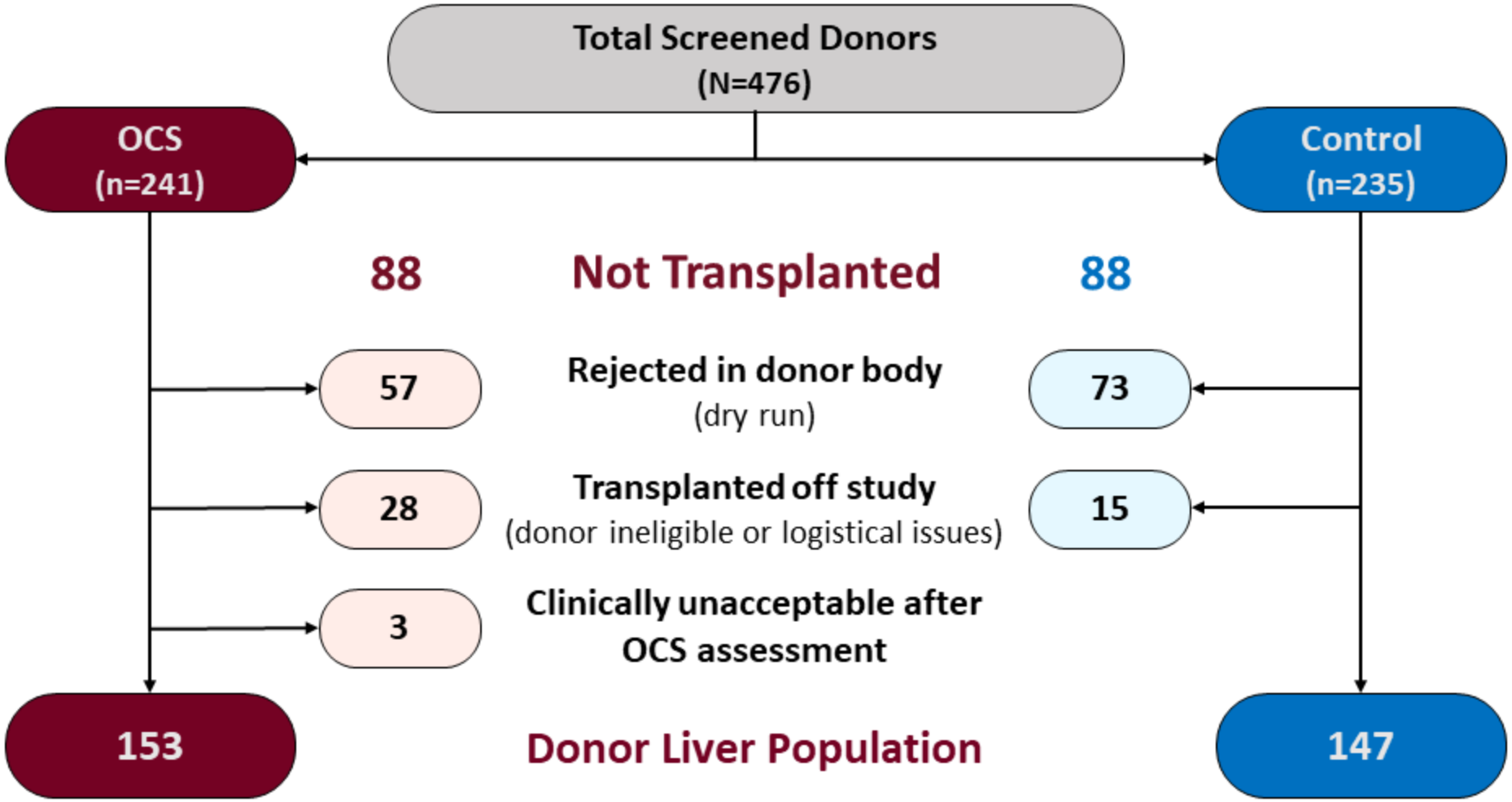
Other Clinical Endpoints Pre-Specified in PROTECT Protocol

- Ischemic biliary complications diagnosed at 6 and 12 months
  - Ischemic biliary strictures or non-anastomotic bile leaks
- Pathology sample score for liver tissue samples
- Extent of reperfusion syndrome based on the rate of increase of lactate
- Length of initial post-transplant ICU stay
- Length of initial post-transplant hospital stay

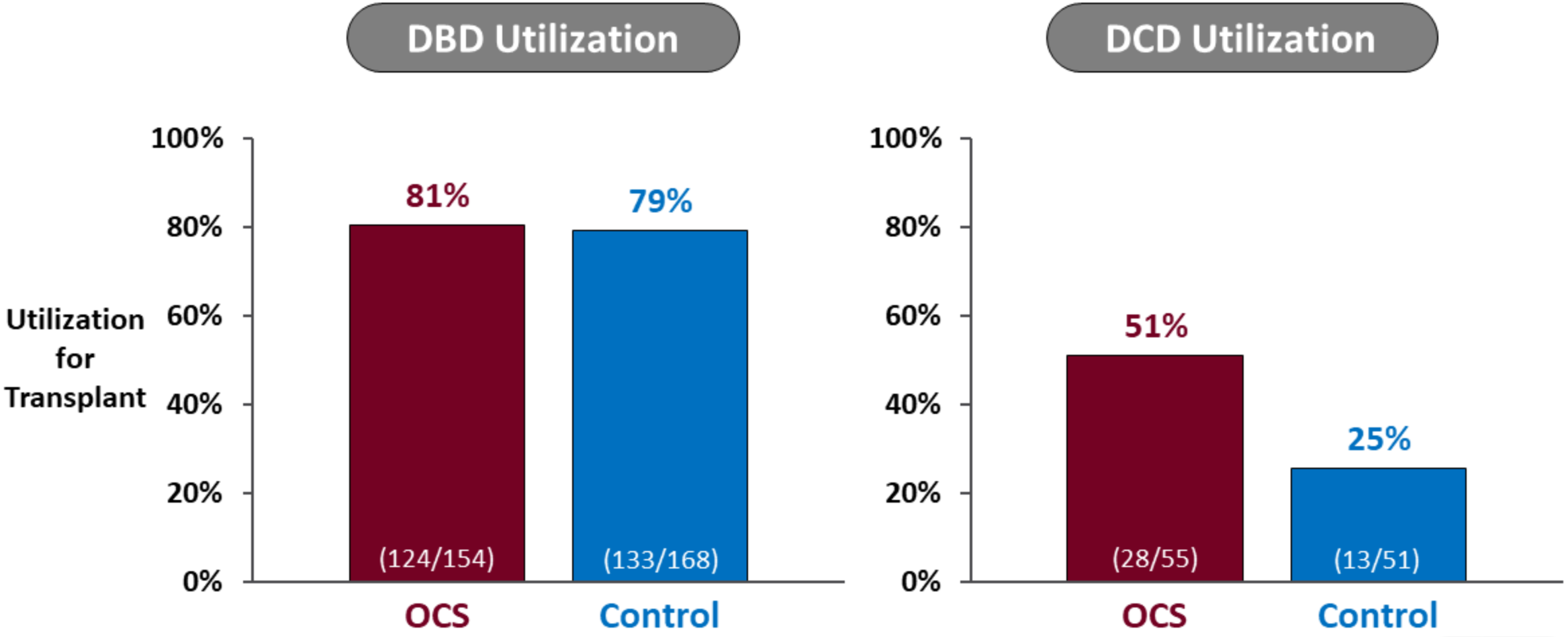
PROTECT Trial Randomization Process



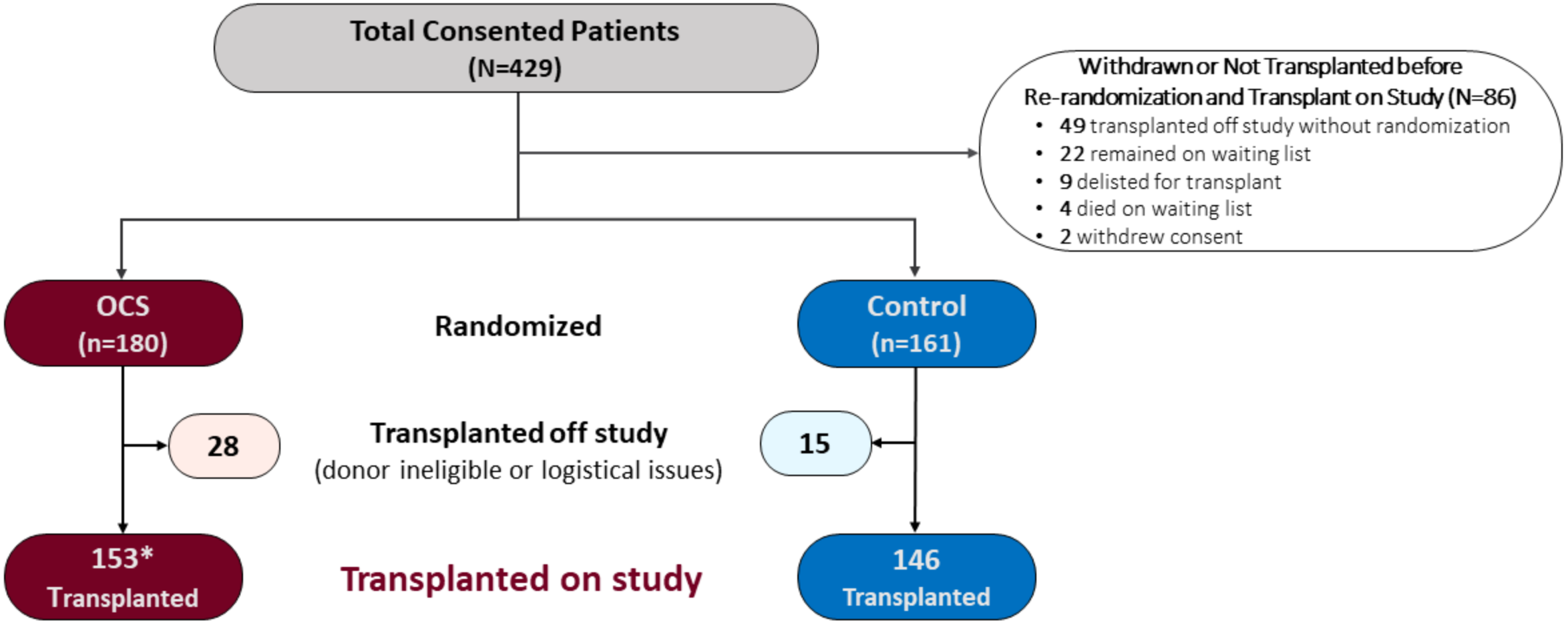
Donor Screening in PROTECT Trial



OCS Assessment Capabilities Enabled Higher Utilization of DCD Donor Livers

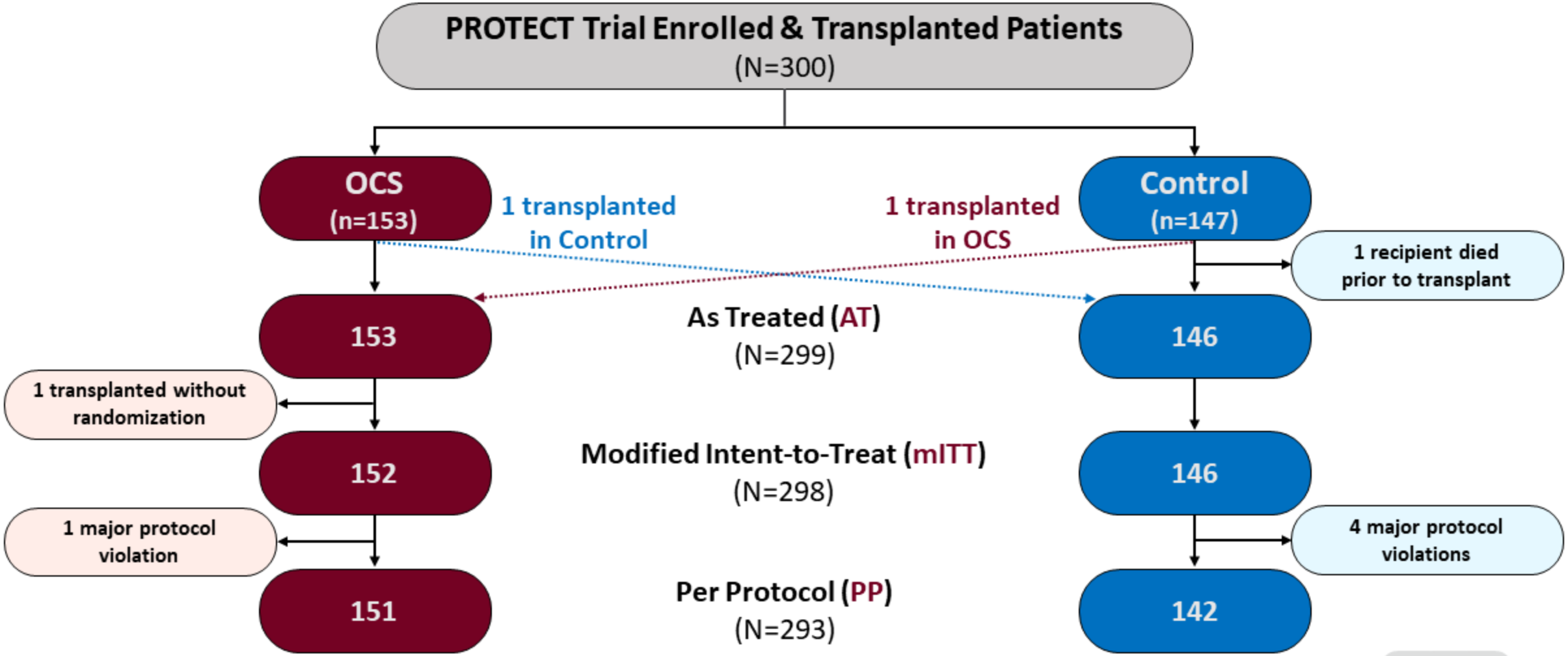


Recipient Screening in PROTECT Trial



* Includes 1 patient transplanted with a donor liver preserved on OCS without randomization

Accountability of Randomized and Transplanted Patients



Analysis Populations

Population	Definition	Role in Analyses
Per Protocol (PP)	All randomized patients who were transplanted with no major protocol violations and received complete preservation procedure as per randomization assignment – *analyzed as randomized*	**Primary analysis population for effectiveness endpoints**
As Treated (AT)	All transplanted patients in the trial – *analyzed as treated*	**Primary analysis population for safety endpoints**
Modified Intent-to-Treat (mITT)	All randomized patients who were transplanted – *analyzed as randomized*	Secondary analysis population for effectiveness endpoints

Donor Demographic and Baseline Characteristics

Donor Characteristics	OCS (N=152)	Control (N=146)
Age (years), mean ± SD	45.8 ± 14.9	47.0 ± 15.2
≥ 40 years old	102 (67%)	93 (64%)
Total cross-clamp ≥ 6 hours	48 (32%)	56 (38%)
DCD ≤ 55 years old	28 (18%)	13 (9%)
Steatotic liver > 0% and ≤ 40% macrosteatosis at retrieval	95 (63%)	86 (59%)
Multiple donor characteristics	95 (63%)	85 (58%)
Cause of death		
Cerebrovascular hemorrhage	44 (29%)	50 (34%)
Head trauma	35 (23%)	29 (20%)
Cardiac	13 (9%)	10 (7%)
Other	60 (39%)	57 (39%)

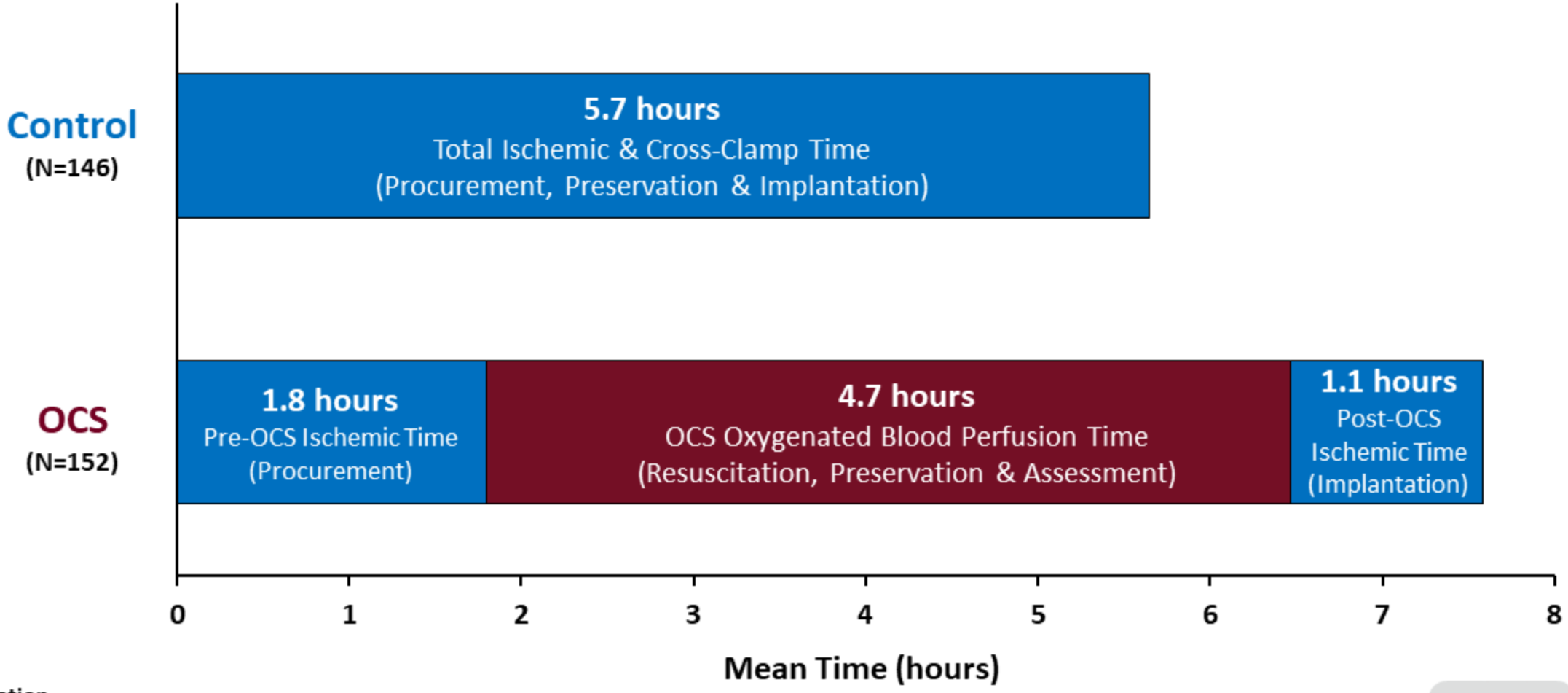
AT Population

Recipient Demographic and Baseline Characteristics

Recipient Baseline Characteristics	OCS (N=153)	Control (N=146)
Age (years), mean ± SD	57.1 ± 10.3	58.6 ± 10.0
Male	102 (67%)	100 (68%)
BMI (kg/m^2), mean ± SD	29.7 ± 5.4	29.5 ± 5.5
MELD score, mean ± SD	28.4 ± 6.9	28.0 ± 5.7
History of diabetes	44 (29%)	44 (30%)
History of liver cancer	60 (39%)	63 (43%)
Primary diagnosis		
Cholestatic diseases	9 (6%)	8 (5%)
Chronic hepatitis	27 (18%)	36 (25%)
Alcoholic cirrhosis	54 (35%)	48 (33%)
Primary hepatic tumors	14 (9%)	15 (10%)
NASH	24 (16%)	20 (14%)
Other	25 (16%)	19 (13%)

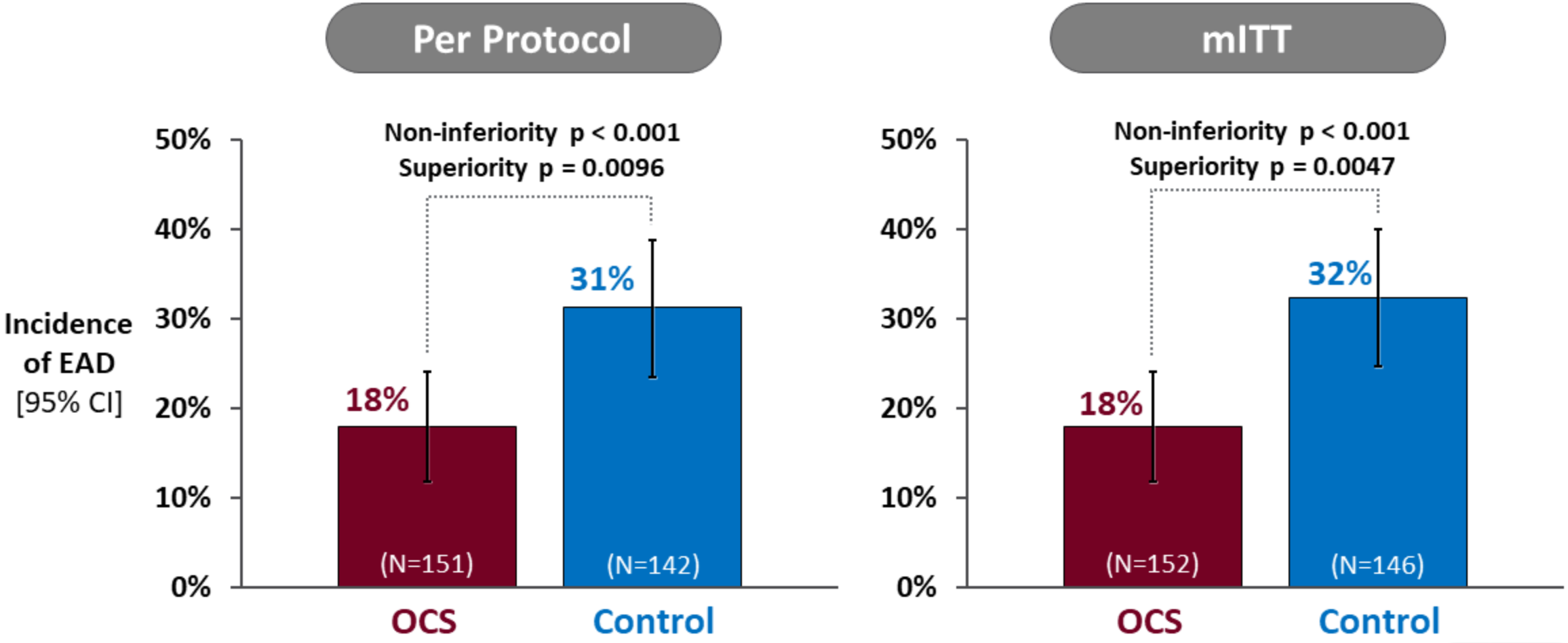
AT Population

OCS Substantially Reduced Cold Ischemic Time And Allowed For Longer Cross-Clamp Time



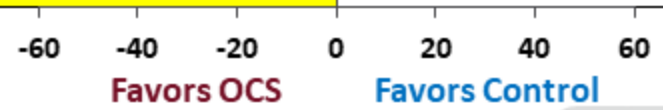
mITT Population

Primary Effectiveness Endpoint Met: OCS Superior to Control in Reducing Incidence of EAD



OCS Associated with Lower EAD Rate in All Subgroups

Factor	Criteria	OCS		Control		Difference (Percentage Points)
Macrosteatosis	≤ 20%	147	16%	134	28%	-12
	> 20%	4	50%	4	100%	-50
Donor Age	≤ 50 yrs	82	21%	82	38%	-17
	> 50 yrs	69	13%	63	24%	-11
MELD Score	≤ 25	45	18%	39	36%	-18
	>25	106	17%	106	30%	-13
DBD Cross-Clamp Time	< 6 hrs	34	6%	82	22%	-16
	≥ 6 hrs	89	19%	50	34%	-15
Donor Inclusion criteria	Age ≥ 40 yrs	102	16%	91	22%	-6
	Cross-clamp ≥ 6 hrs	47	23%	56	36%	-12
	DCD & Age ≤ 55 yrs	28	25%	13	85%	-60
	Steatotic liver	93	19%	87	30%	-11
Donor Type	DCD	28	25%	13	85%	-60
	DBD	123	15%	132	27%	-11



mITT Population

Pre-Specified EAD Composite by Component

	OCS (N=151)	Control (N=145)
Pre-Specified EAD Composite	**27/151 (18%)**	**47/145 (32%)**
EAD Component	**(N=27 cases)**	**(N=47 cases)**
AST only	17 (63%)	36 (77%)
Bilirubin only	4 (15%)	2 (4%)
INR only	3 (11%)	2 (4%)
AST + Bilirubin	0	3 (6%)
AST + INR	1 (4%)	2 (4%)
AST + Bilirubin + INR	2 (7%)	2 (4%)

mITT Population

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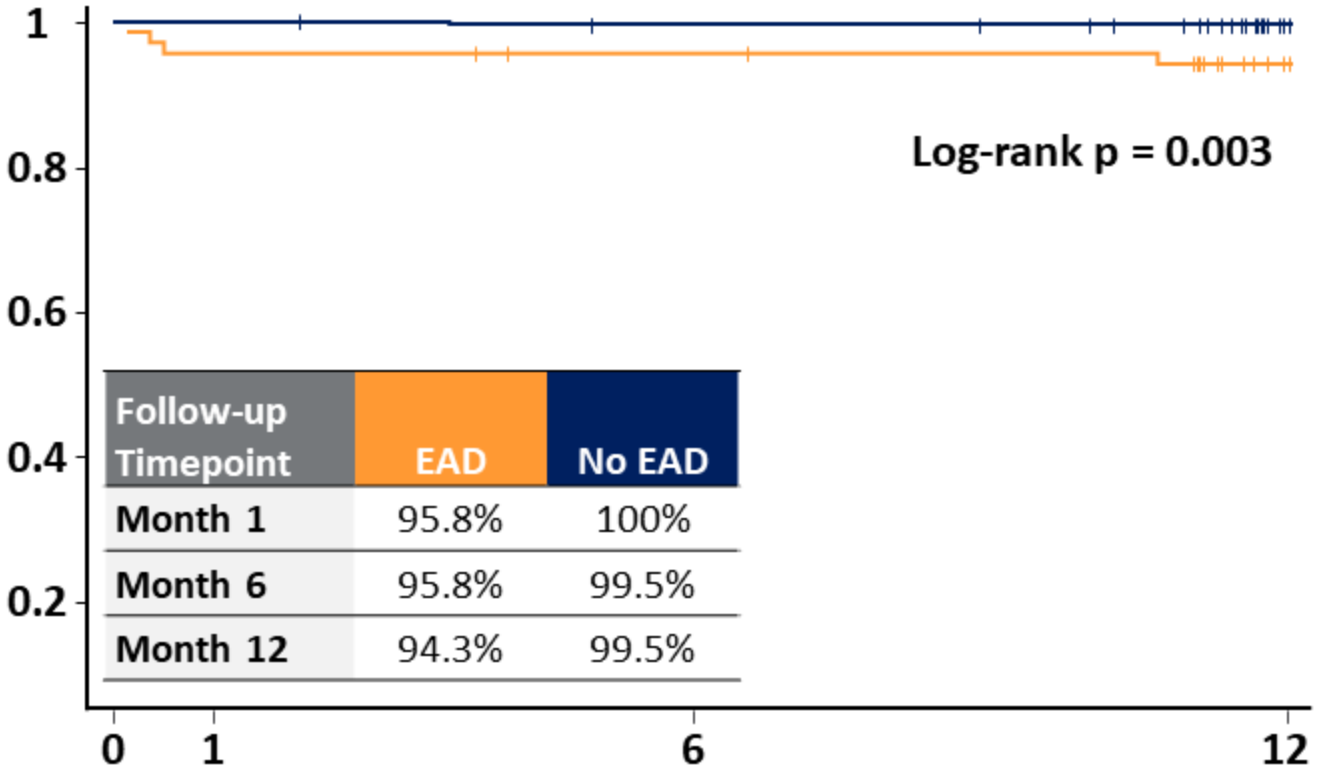
Clinical Benefits of Preventing EAD in PROTECT

Absence of EAD Associated with Lower Risk of Graft Failure



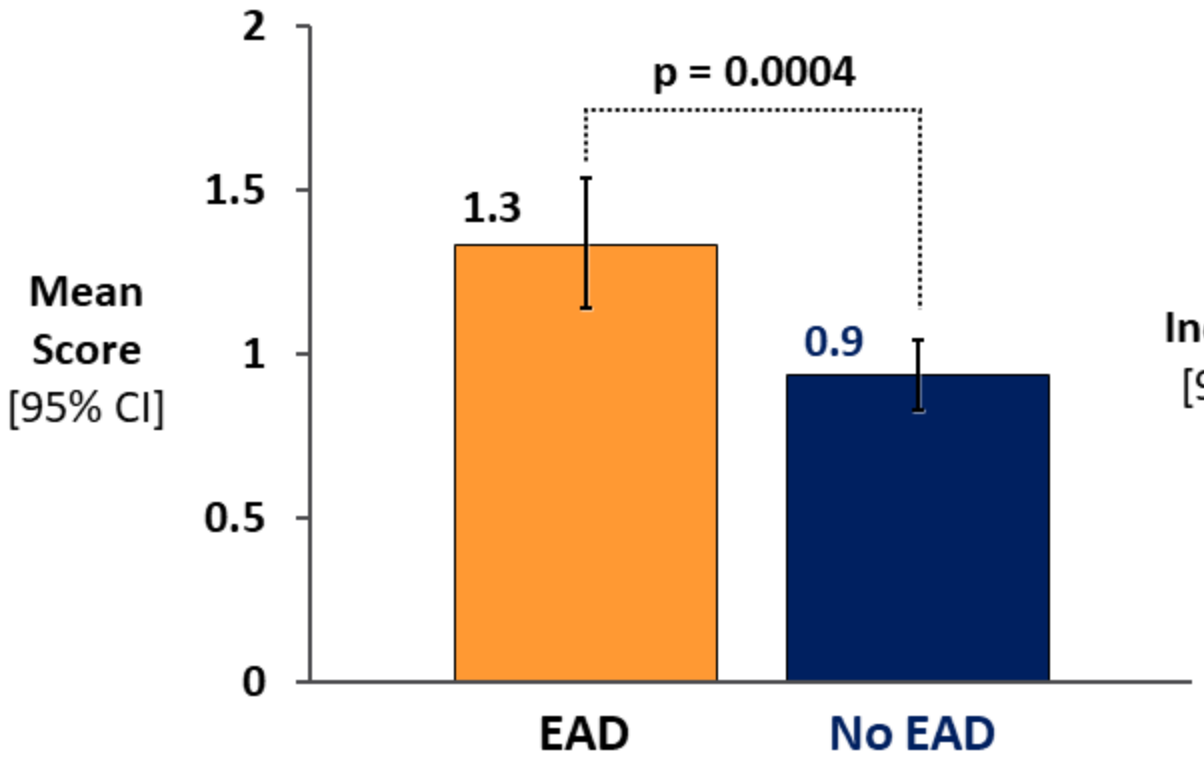
Follow-up Timepoint	EAD	No EAD
Month 1	95.8%	100%
Month 6	95.8%	99.5%
Month 12	94.3%	99.5%

EAD	71	68	66	43
No EAD	220	220	215	166

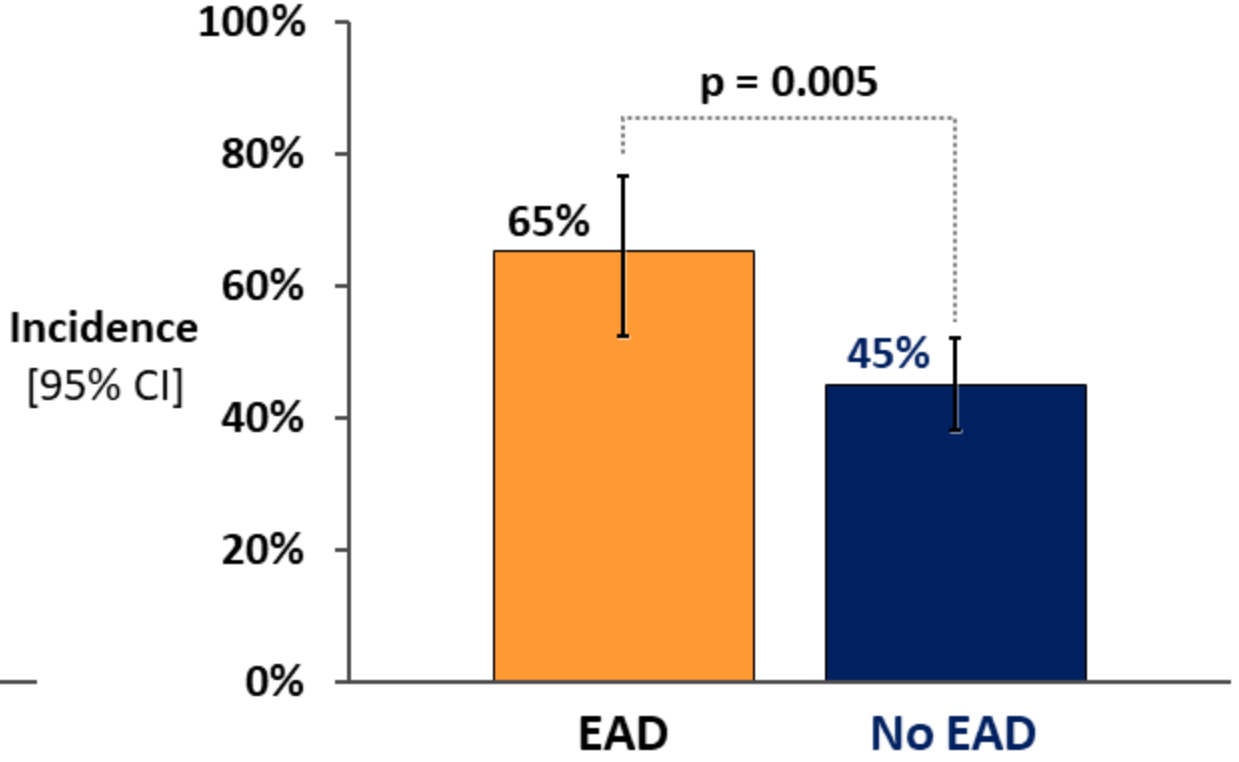
PP Population

Absence of EAD Associated with Less Reperfusion Injury Based on Blinded Pathology Scoring and Lower Incidence of Reperfusion Syndrome

Histopathology Scoring



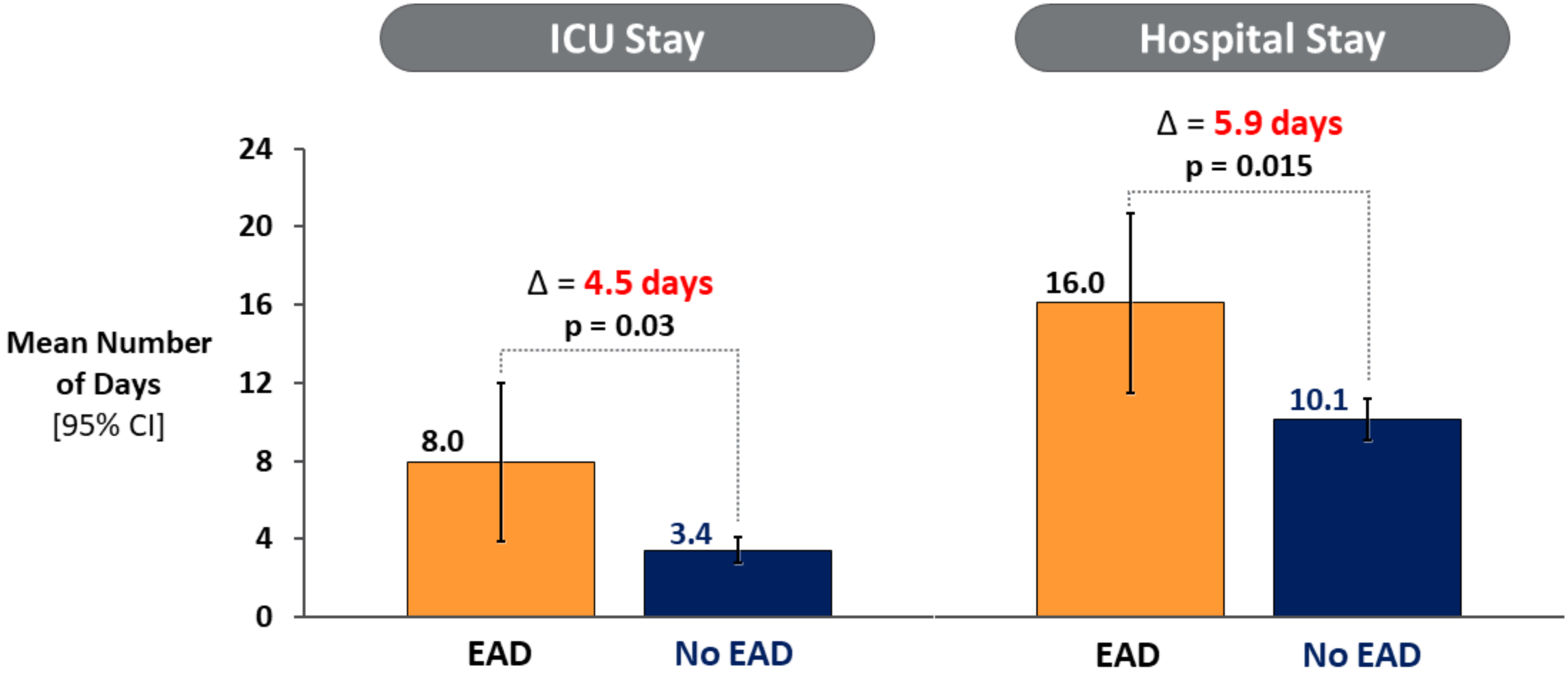
Reperfusion Syndrome*



PP Population

* As determined by increasing lactate trend

Absence of EAD Associated with Shorter ICU and Hospital Stays



PP Population

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Secondary Effectiveness Endpoints and Other Endpoints

OCS Donor Liver Assessment Endpoints Met

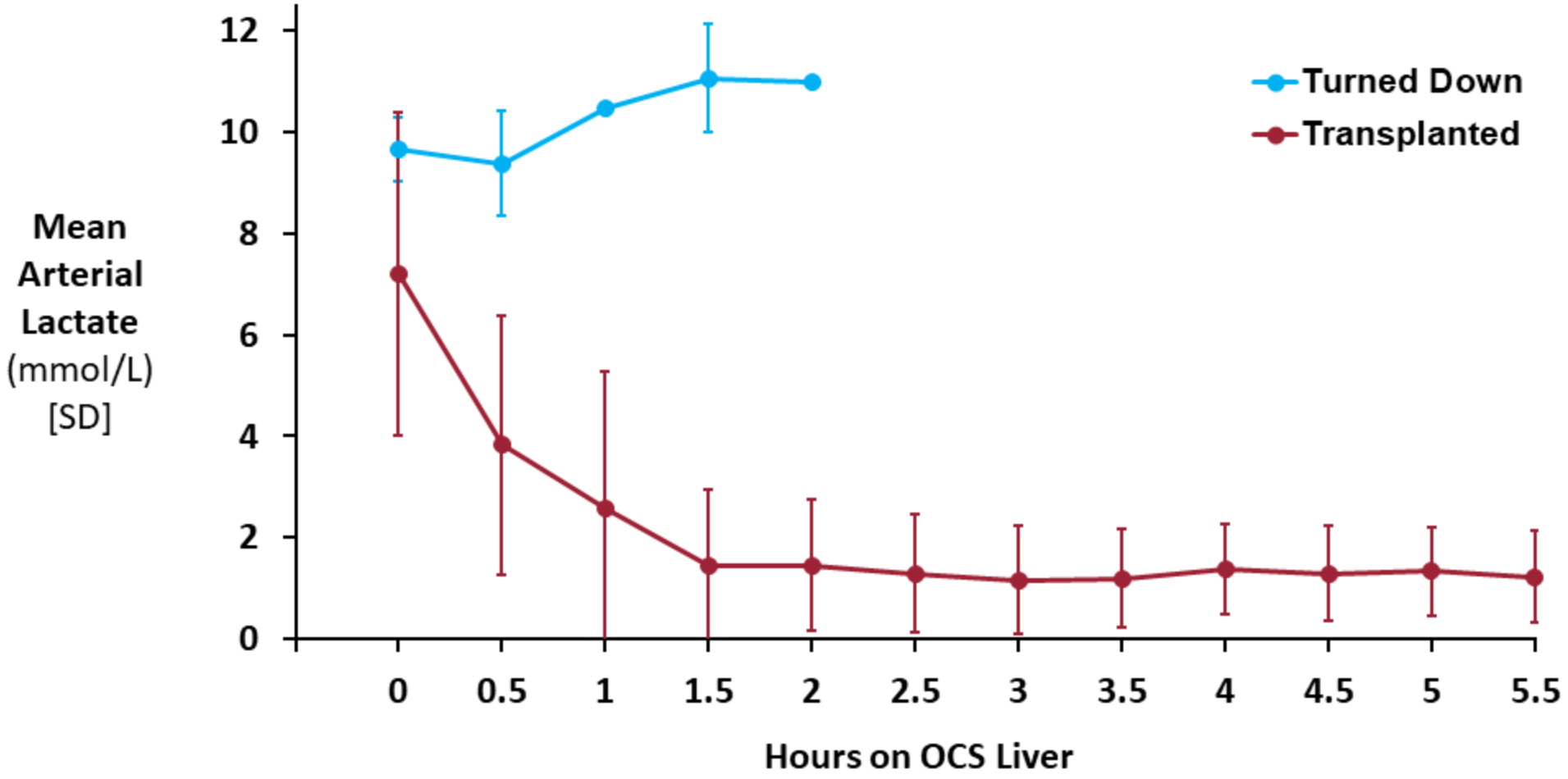
OCS Liver System Assessment Parameters During Perfusion	OCS Measurements Available (N=155)
Lactate level	145 (94%)
Hepatic artery pressure	155 (100%)
Portal vein pressure	155 (100%)
Average bile production rate	154 (99%)
Overall	**144 (93%)**
Lower 95% CI	**88.5%**
P-value vs 85% performance goal	**0.002**

OCS Donor Liver Population

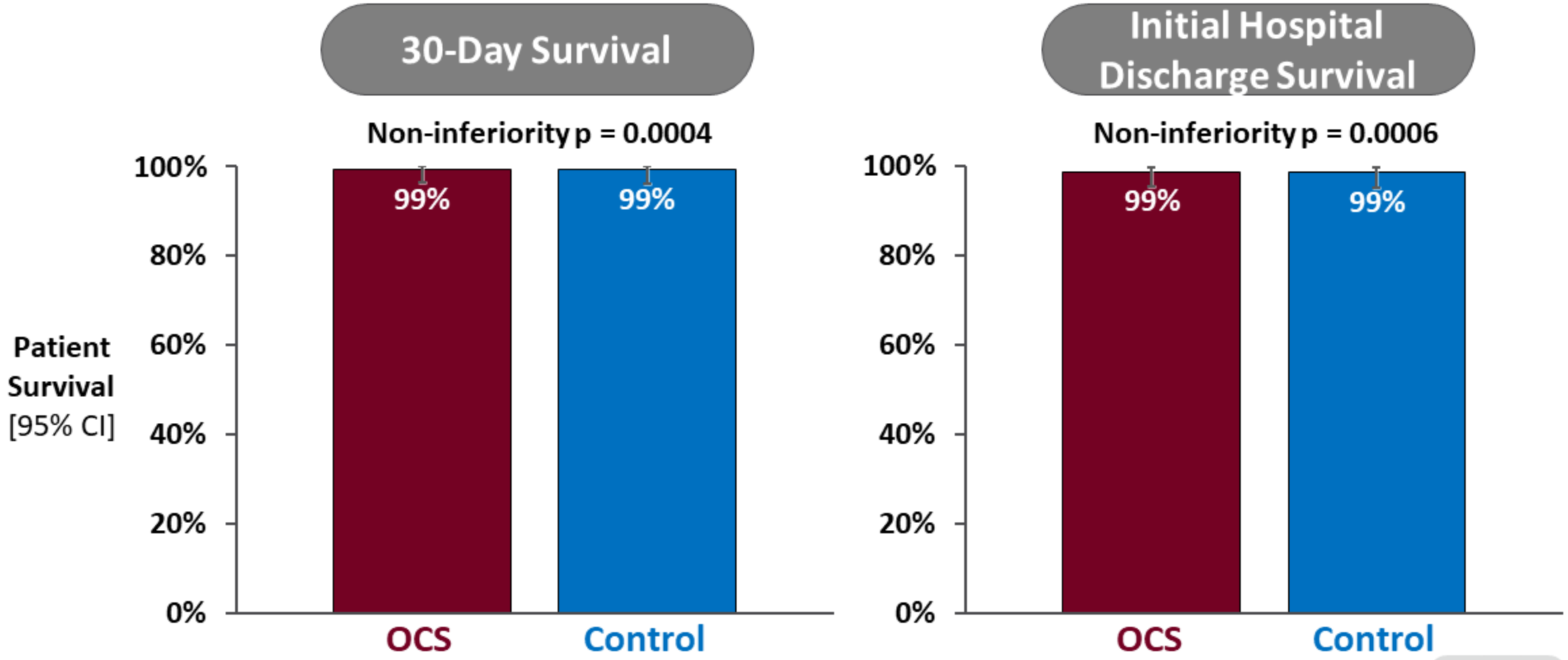
OCS Assessment Capabilities Resulted in Turning Down 2 DCD Livers with Significant Pre-Existing Pathology

- **DCD Liver 1** turned down based on pathology finding of bridging fibrosis
  - Would have been detected regardless of preservation method
- **DCD Livers 2 & 3** turned down based on lactate trend and perfusion parameters
  - Severe confluent lobular necrosis by core pathology lab
- Use of OCS to assess and turn down DCD Livers 2 & 3 may have saved recipients from EAD or primary non-function (PNF)

OCS Arterial Lactate Trends Identified 2 Livers for Turn Down

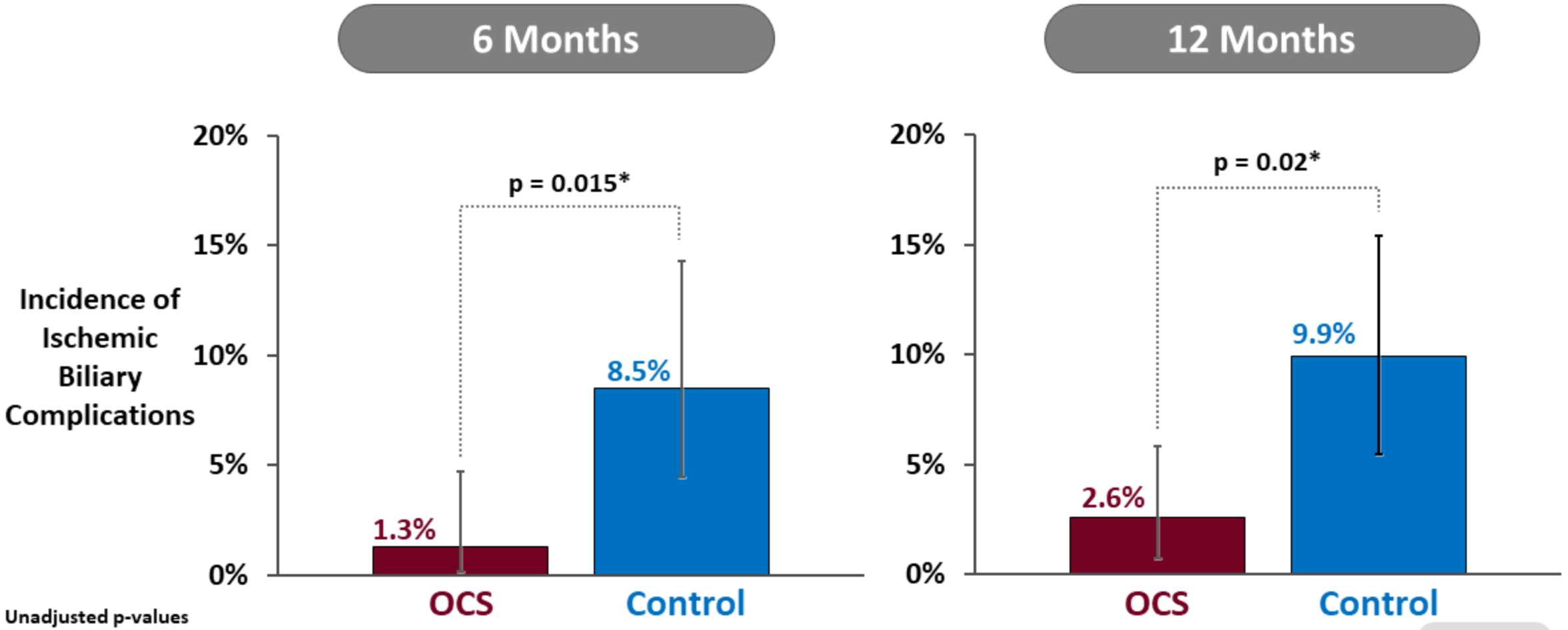


Secondary Endpoints Met: Non-Inferior Survival at Day 30 and at Initial Hospital Discharge



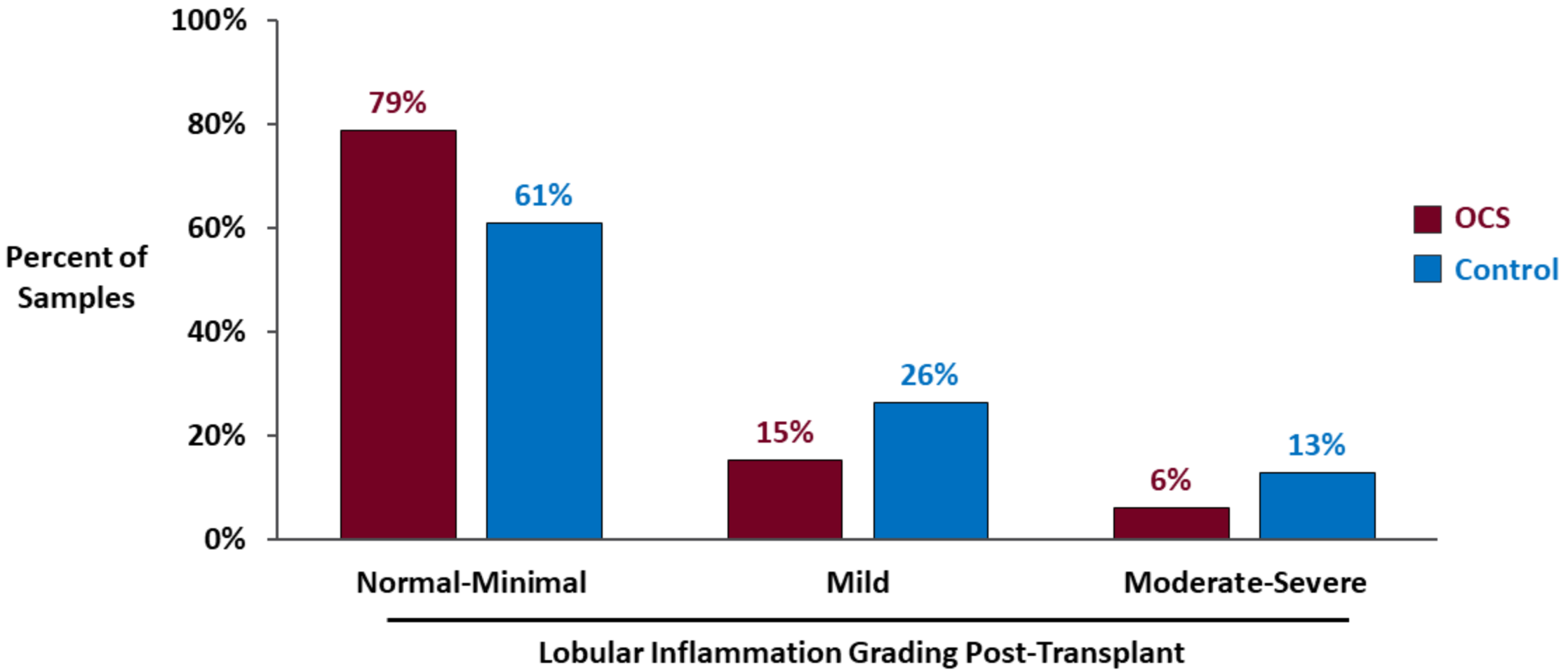
PP Population

Significantly Lower Incidence of Ischemic Biliary Complications with OCS than Cold Storage through 12 Months



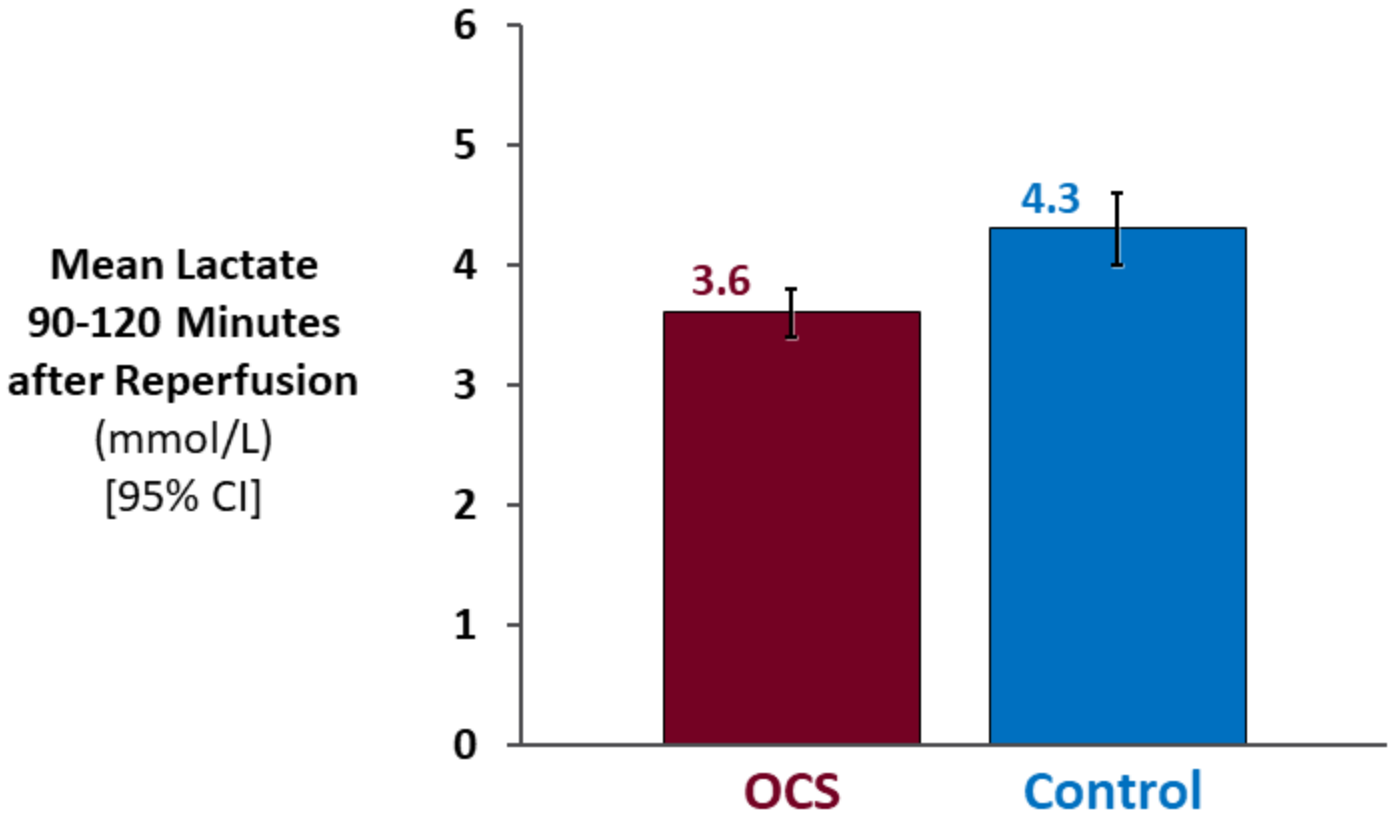
* Unadjusted p-values
PP Population

Histopathological Evidence of Reduced IR Injury with OCS



mITT Population

OCS Associated with Lower Post-Transplant Reperfusion Syndrome as Assessed by Lactate Levels



PP Population

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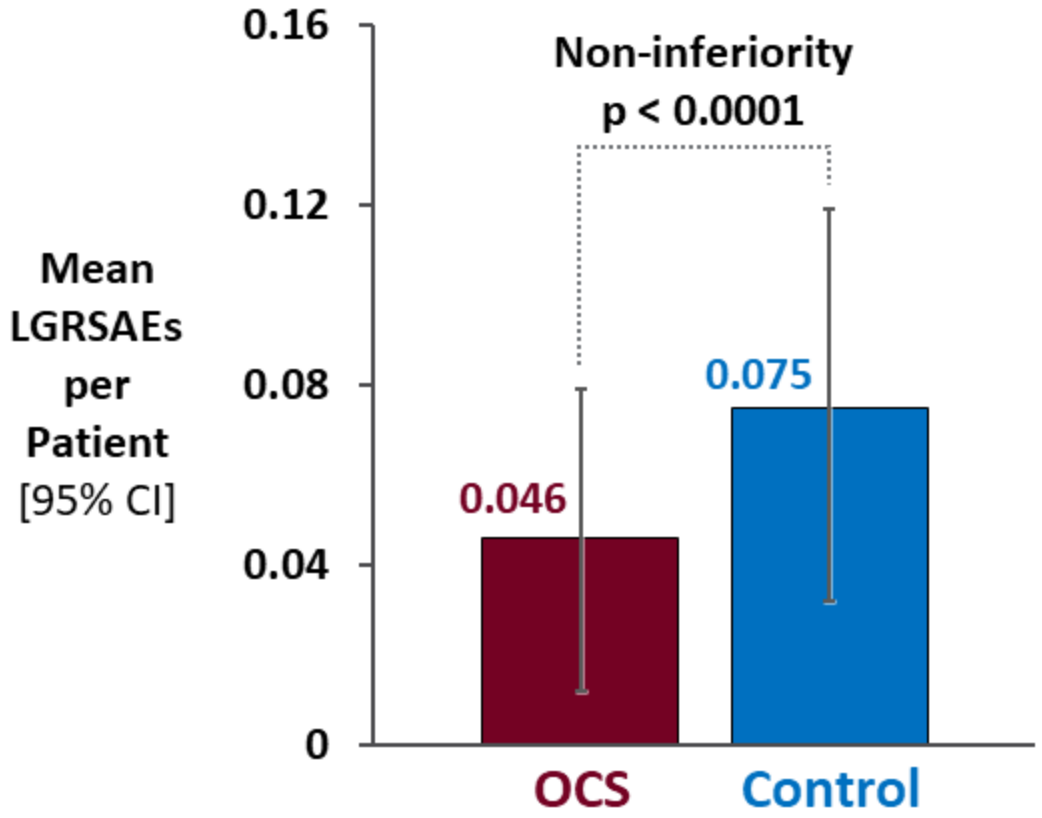
Safety

Safety Endpoint Met: OCS Non-Inferior to Control in LGRSAEs



LGRSAE within 30 Days Post Transplant	OCS (N=153)		Control (N=146)	
	Patients	Events	Patients	Events
Any LGRSAE	7 (5%)	8	11 (8%)	13
Non-functioning graft	0	0	0	0
Ischemic biliary complication	0	0	2 (1%)	2
Vascular complication	7 (5%)	8	9 (6%)	11
Liver allograft infection	0	0	0	0

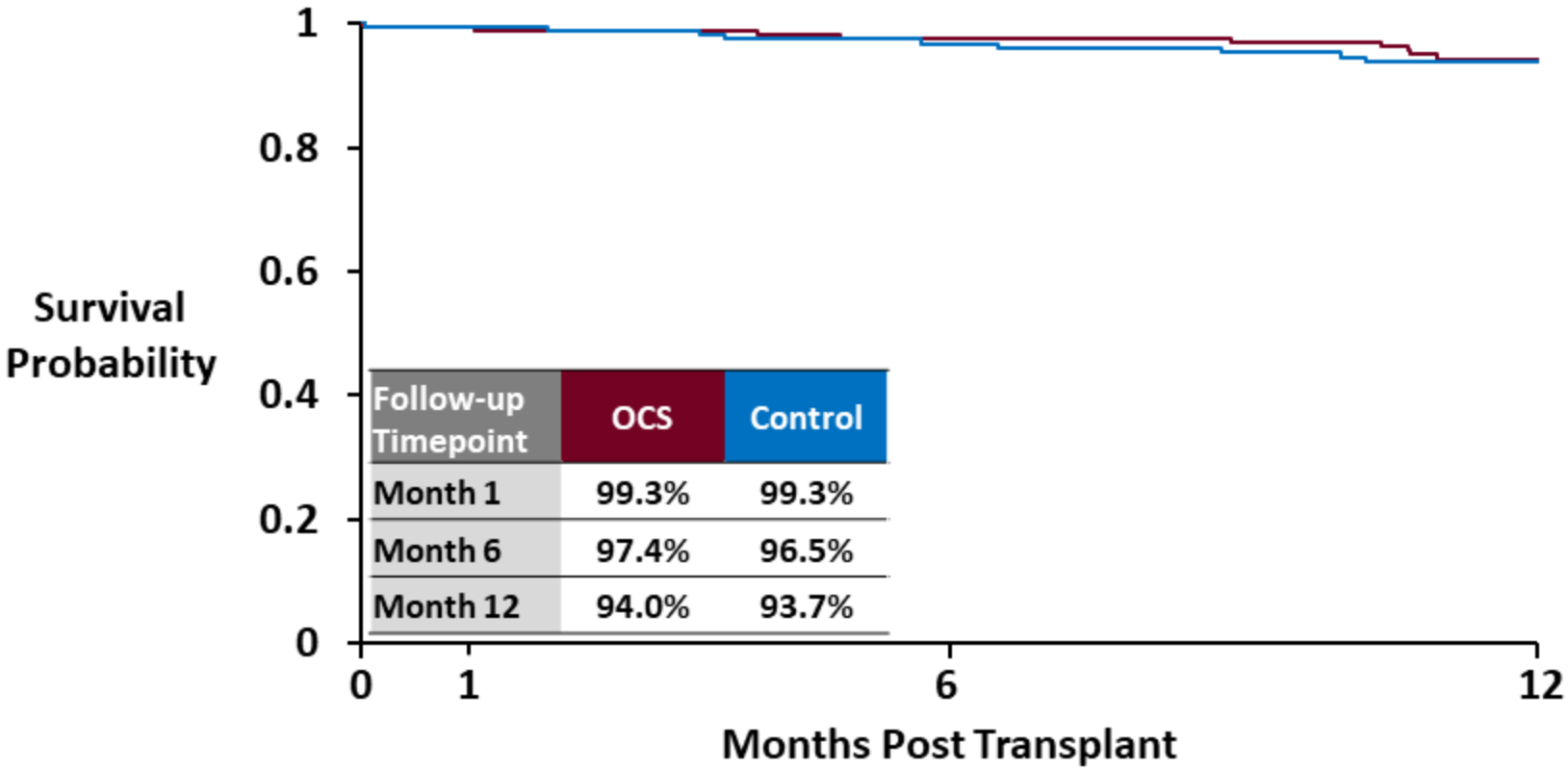
AT Population. Non-inferiority margin = 1.0

Post-Hoc Safety Analyses Requested by the FDA

AE within 30 Days Post Transplant	OCS (N=153)	Control (N=146)
Anastomotic biliary complication	12 (7.8%)	6 (4.1%)
Post-transplant bile leak	4 (2.6%)	11 (7.5%)

AT Population

Similar Overall Patient Survival through 12 Months

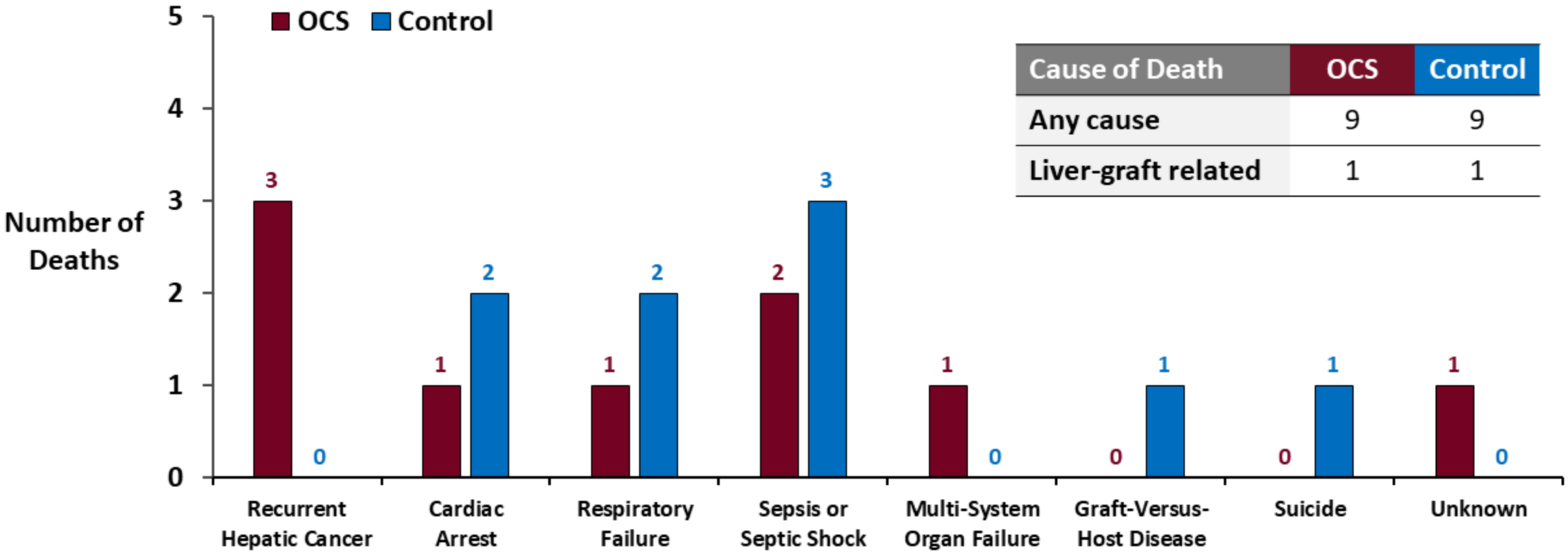


Follow-up Timepoint	OCS	Control
Month 1	99.3%	99.3%
Month 6	97.4%	96.5%
Month 12	94.0%	93.7%

OCS	151	150	147	105
Control	142	141	137	106

PP Population

Causes of Death through 12 Months



Cause of Death	OCS	Control
Any cause	9	9
Liver-graft related	1	1

mITT Population

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PROTECT Continued Access Protocol (CAP)

PROTECT CAP Summary

- 74 enrolled recipients
  - All have 30-day outcomes post transplant
- Generally similar recipient demographics and baseline characteristics
- Donor characteristics similar to PROTECT, except more DCD donors (23% vs 18%)
- No donor liver turn downs on OCS
- EAD rate: **25.7%**
- Excellent short-term (30-day) patient and graft survival: **98.7%**

Causes of Death in PROTECT CAP

Days After Transplant	CEC Adjudication	
	Liver Graft Related	Cause of Death
30	**No**	**Sepsis** secondary to perforated duodenal ulcer
59	**No**	**Sepsis** most likely originating from the lungs
75	**No**	**Respiratory failure** from pre-existing hepatopulmonary syndrome
108	**No**	**Mycobacterium lung abscess** secondary to respiratory failure and lung infection
111	**N/A** (patient died after retransplant with cold storage)	**Sepsis** (after retransplant)

Summary of Key PROTECT and PROTECT CAP Results

- OCS **superior** to control on primary endpoint of EAD (p = 0.0096)
- Histopathological evidence of **reduced IR injury** with OCS
- OCS achieved **significant reduction** in ischemic biliary complications
- **Double** the number of DCD donor livers utilized with OCS vs cold storage
- Other benefits of reducing EAD consistent with prior studies: significant reductions in graft failure, ICU and hospital stay, and reperfusion injury
- PROTECT CAP provides supportive evidence with more DCD donor livers

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Pathology Results

Anthony J Demetris, MD
Starzl Professor of Liver and Transplant Pathology
University of Pittsburgh

Background on Hepatic Ischemia-Reperfusion (IR) Injury

- IR injury is an unavoidable pathological process **regardless of preservation method**
  - Occurs when liver is reperfused
  - Begins on device with OCS or in recipient after transplant with cold storage
- IR injury may lead to increased liver enzymes, biliary strictures, and graft dysfunction[1]
- With cold storage, IR injury does not manifest **until the donor liver is transplanted into the recipient**
- OCS offers benefit of allowing for proactive identification, monitoring, and responding to IR injury *ex vivo* rather than reacting *in vivo* after transplant
  - Particularly beneficial for marginal or DCD donor allografts

1. Pine et al, *Liver Transpl* 2009.

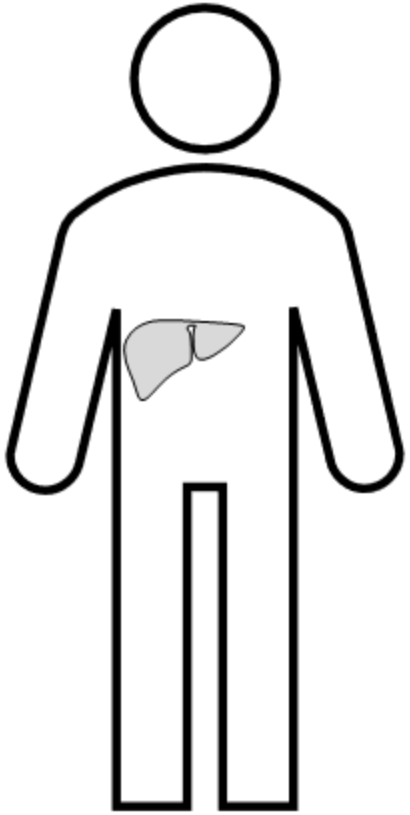
Methods for Histopathology Assessment

- Histopathological Evaluation
  - Conducted without any knowledge of treatment arm or donor organ type (DBD or DCD)
  - Scored 32 parameters with emphasis on findings important in predicting function and graft survival
    - Type and distribution of hepatocyte necrosis, lobular inflammation, and micro-circulatory disturbance
    - Histopathology predicts early allograft dysfunction[1-2]
    - Fibrosis and pre-existing or developing defects
- No difference between groups in overall biopsy metrics

1. Kakizoe et al, *Hepatology* 1990; 2. Ali et al, *Liver Transplant* 2015.

Pathology Sample 1

At Surgical Procurement from Donor



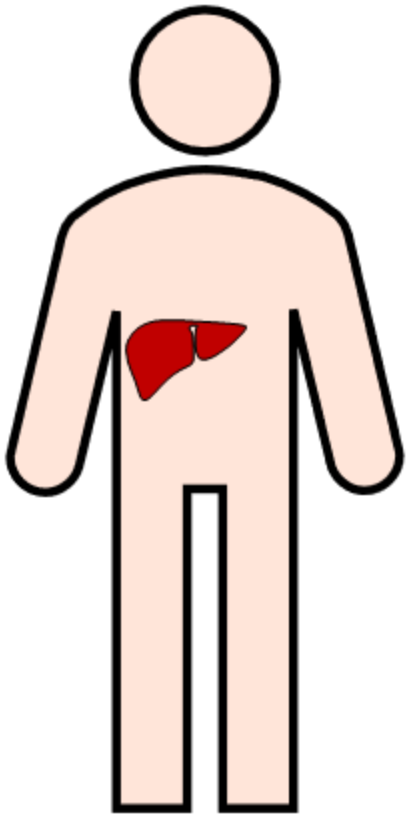
Pathology Sample 2

After Cold Storage or OCS Perfusion and Prior to Transplantation

IR injury first manifests on OCS

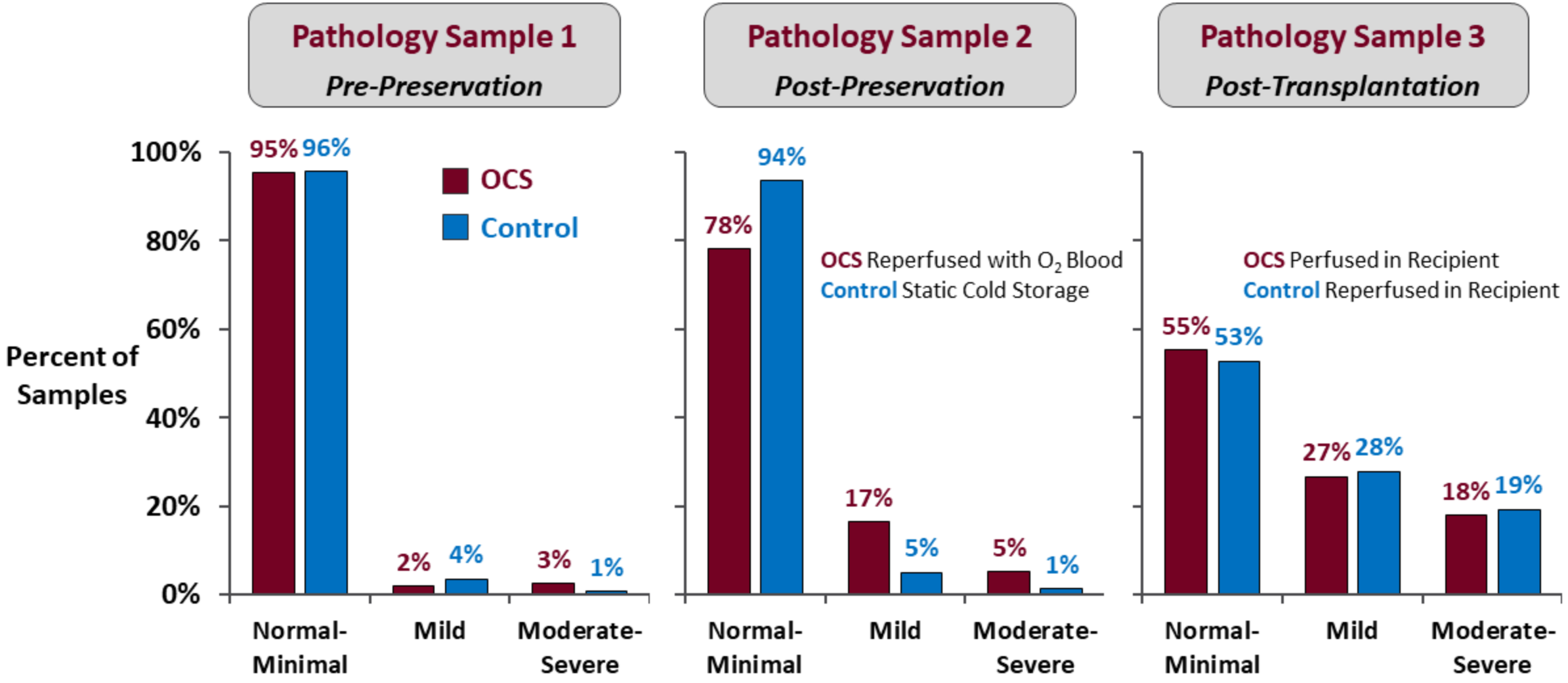
Pathology Sample 3

After Transplantation in Recipient



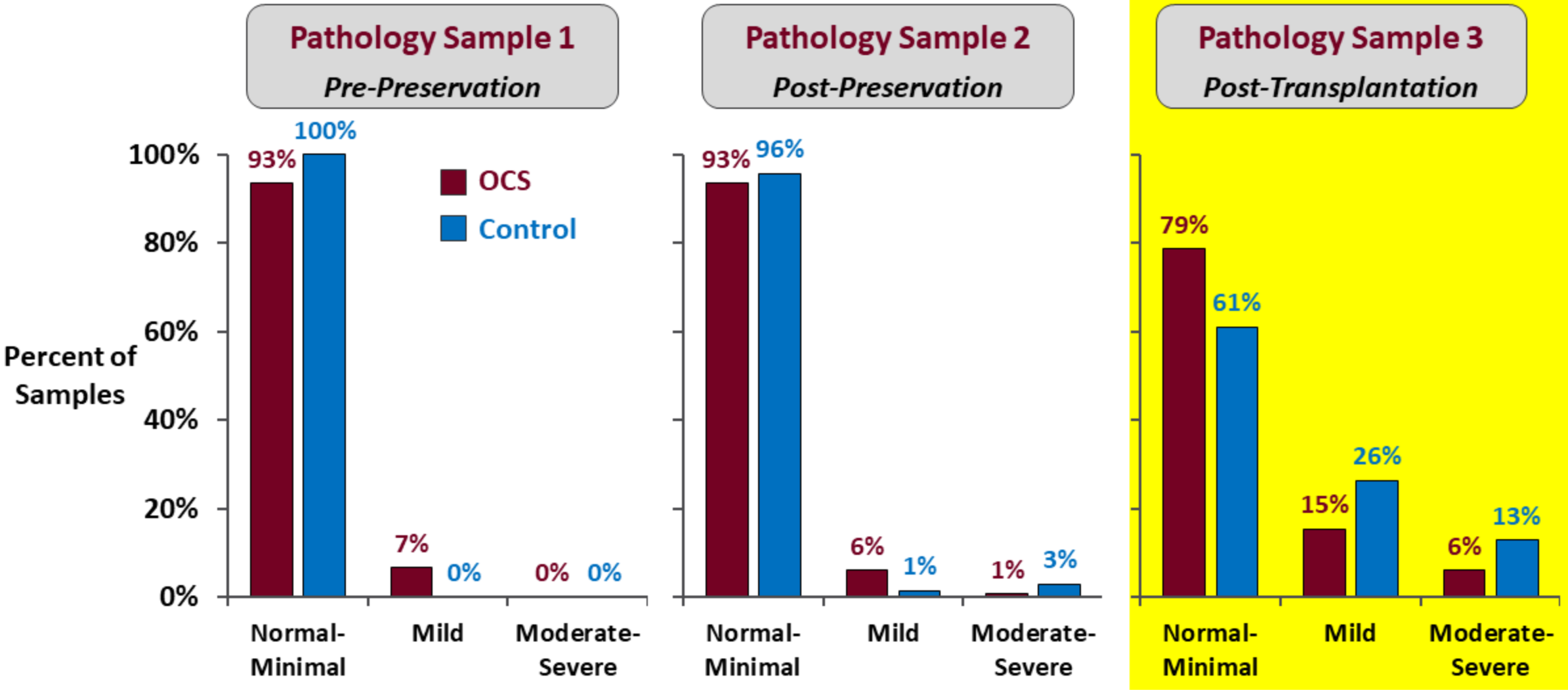
IR injury first manifests after Cold Storage

Assessment of Lobular Necrosis



mITT Population

Assessment of Lobular Inflammation

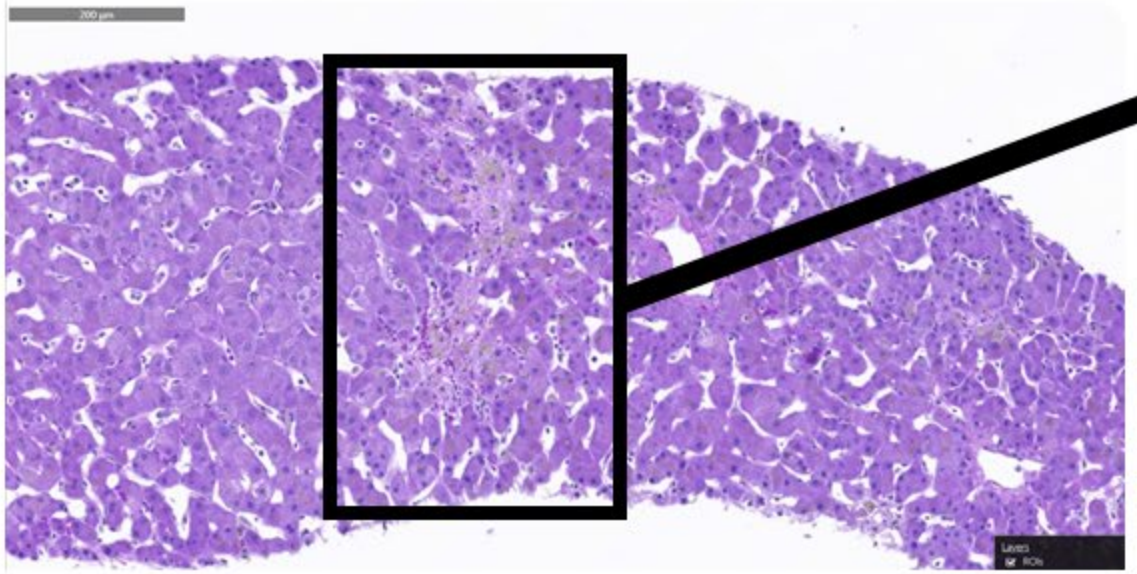


mITT Population

Important Concepts about Turndown Livers in PROTECT

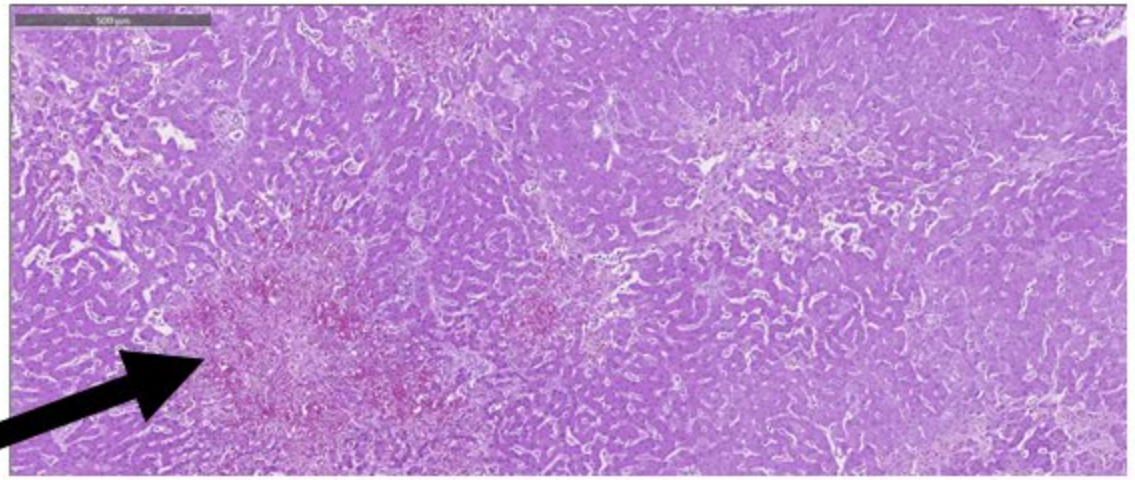
- FDA generated a table extracted from my reports that **omits key findings**
- Liver **biopsies sample 0.0002%** of the liver parenchyma
  - Even so, abnormalities were detected in all 3 pre-preservation biopsies
- **Whole liver examination** more closely mimics global OCS functional assessment
- Comparing the pre-preservation biopsy with the turndown whole liver examination **illustrates the utility of OCS** global functional assessment *ex vivo*

Turndown DCD Liver #1



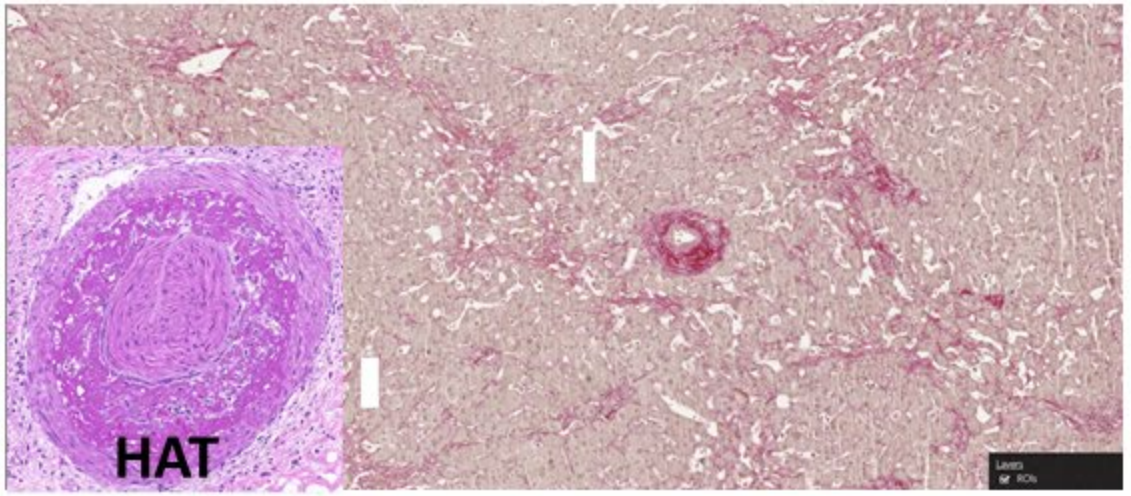
Pre-Preservation Biopsy

- Evidence of ischemic midzonal injury ~ 5-7 days in pre-retrieval biopsy

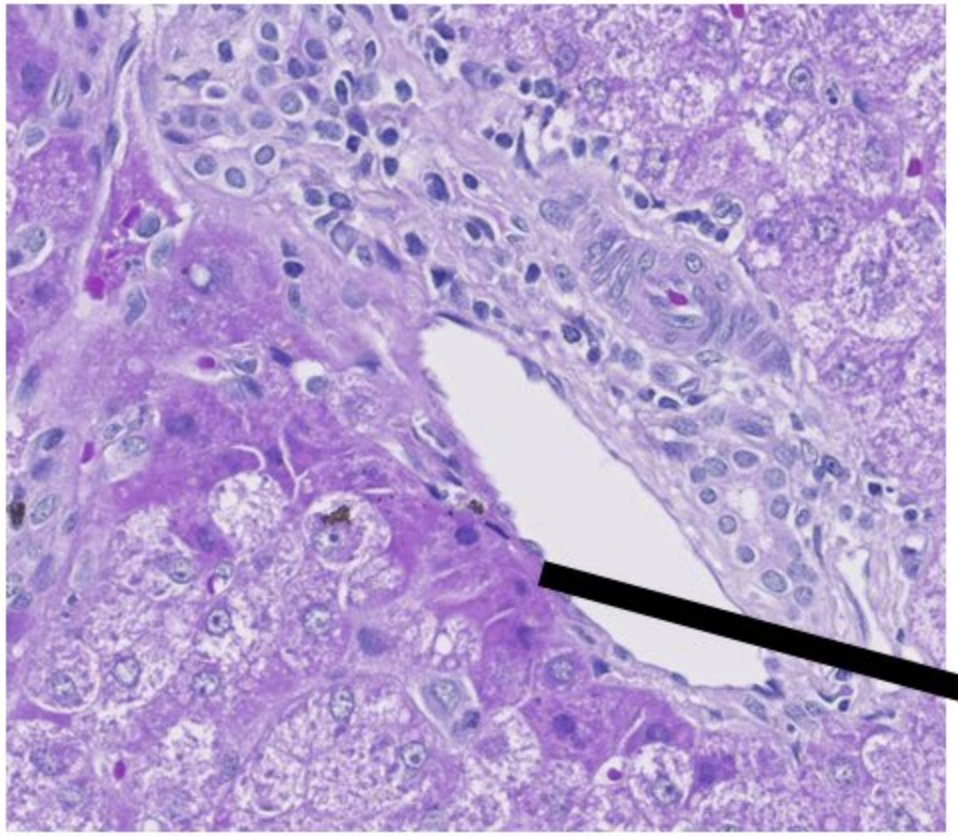


Turndown Whole Liver Examination

- Midzonal bridging fibrosis (> 7 days)
- HAT (> 2-3 days old)

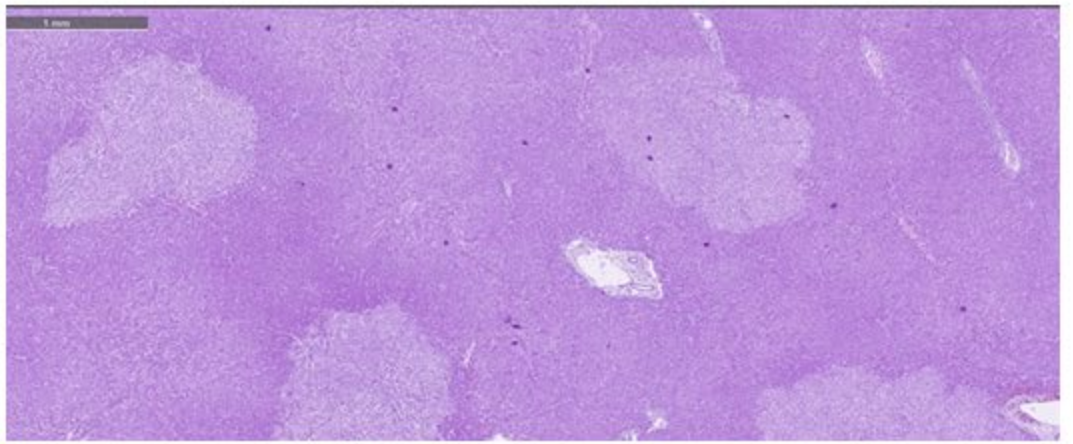


Turndown DCD Liver #2



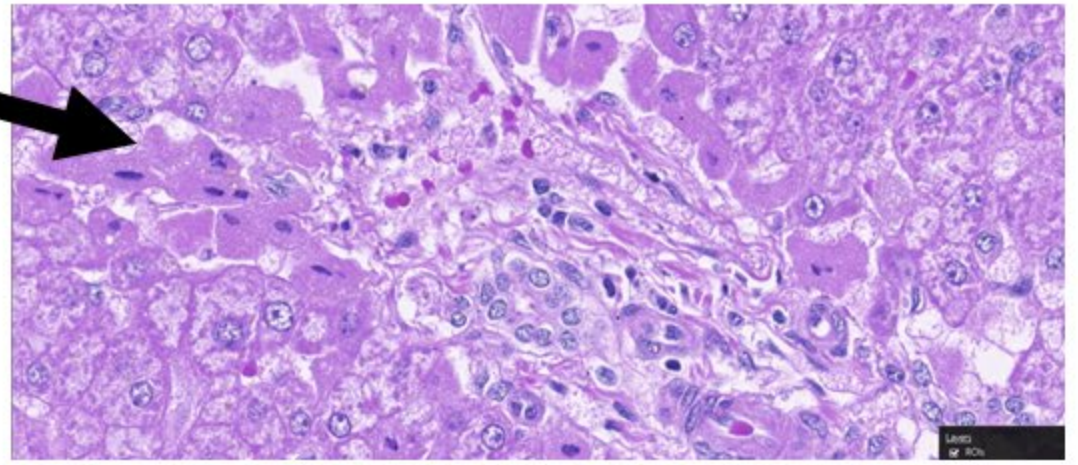
Pre-Preservation Biopsy

- Evidence of early periportal hepatocyte necrosis in pre-retrieval biopsy

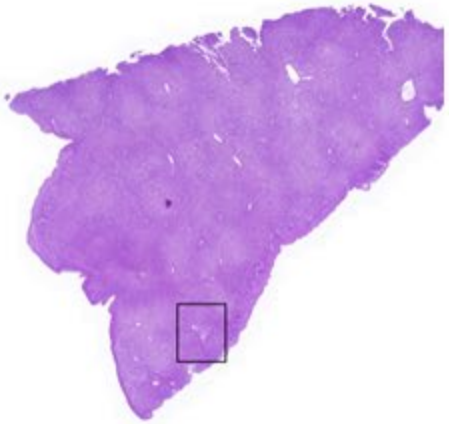


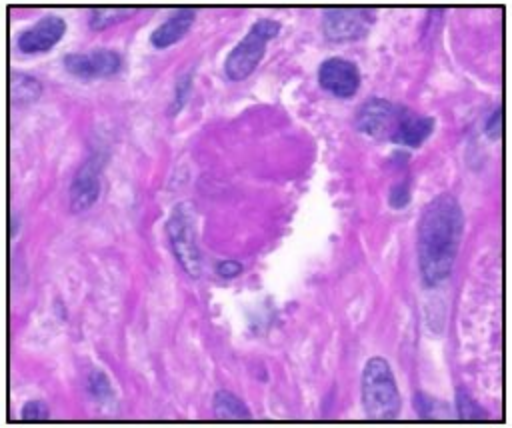
Turndown Whole Liver Examination

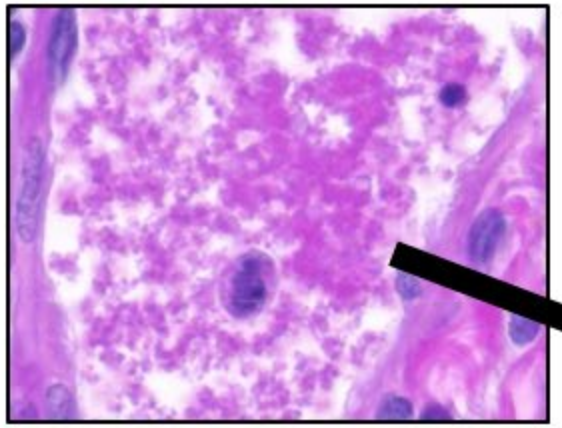
- Confluent perivenular and periportal necrosis
- Multiple glycogenic foci → pre-neoplastic with Warburg effect (Lefkowitch et al, *Semin Liver Dis* 2015)



Turndown DCD Liver #3

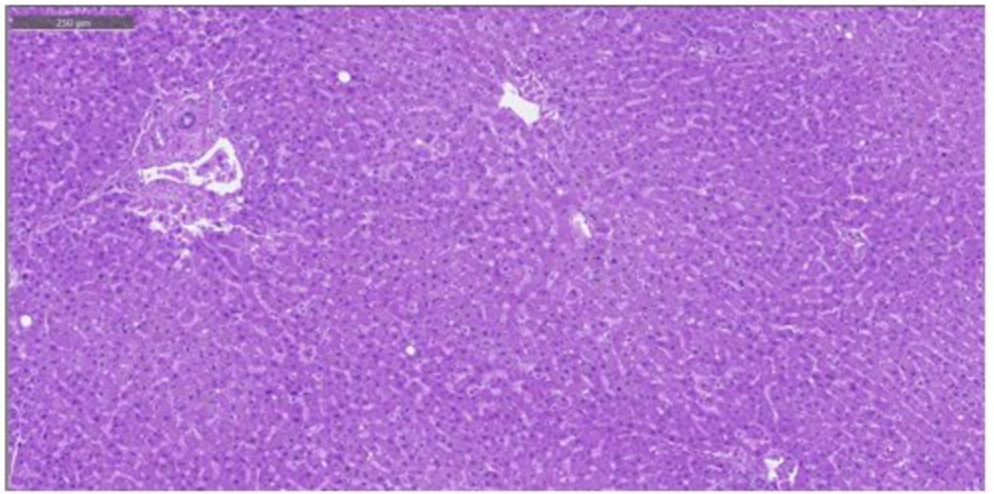






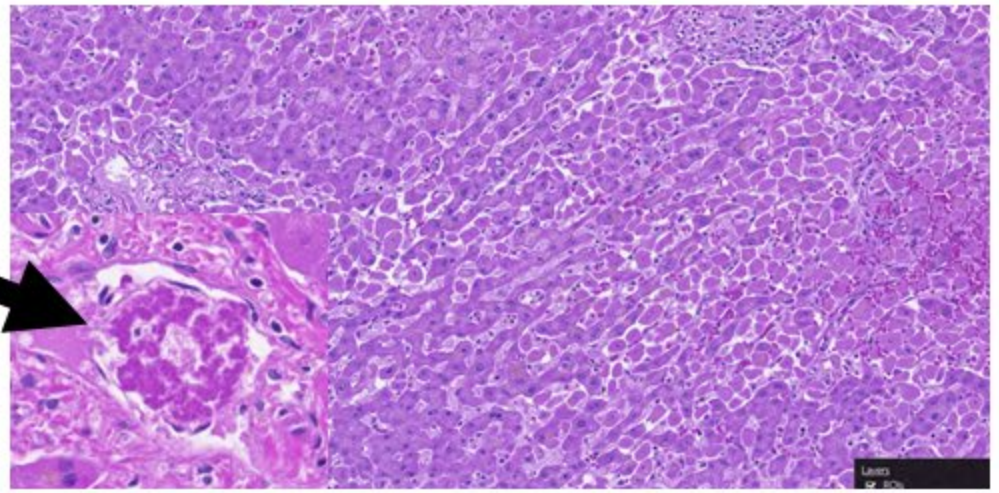
Pre-Preservation Biopsy #1

- Platelet-fibrin thrombi in vessels in pre-retrieval biopsy



Turndown Whole Liver Examination

- Platelet-fibrin thrombi triggered early coagulative necrosis in post-transplant biopsy



Conclusions from Histopathological Assessment

- In liver transplantation, IR injury is unavoidable regardless of preservation method
- No net differences between groups in lobular necrosis
- Less lobular inflammation in OCS group after transplant
  - Correlates with decreased EAD rate, as in other studies
- OCS revealed serious pre-existing issues in turndown livers

Histopathology and Clinical Data Demonstrate that Quality of Donor Liver Preservation Better with OCS than Cold Storage

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TransMedics Positions on FDA Discussion Questions

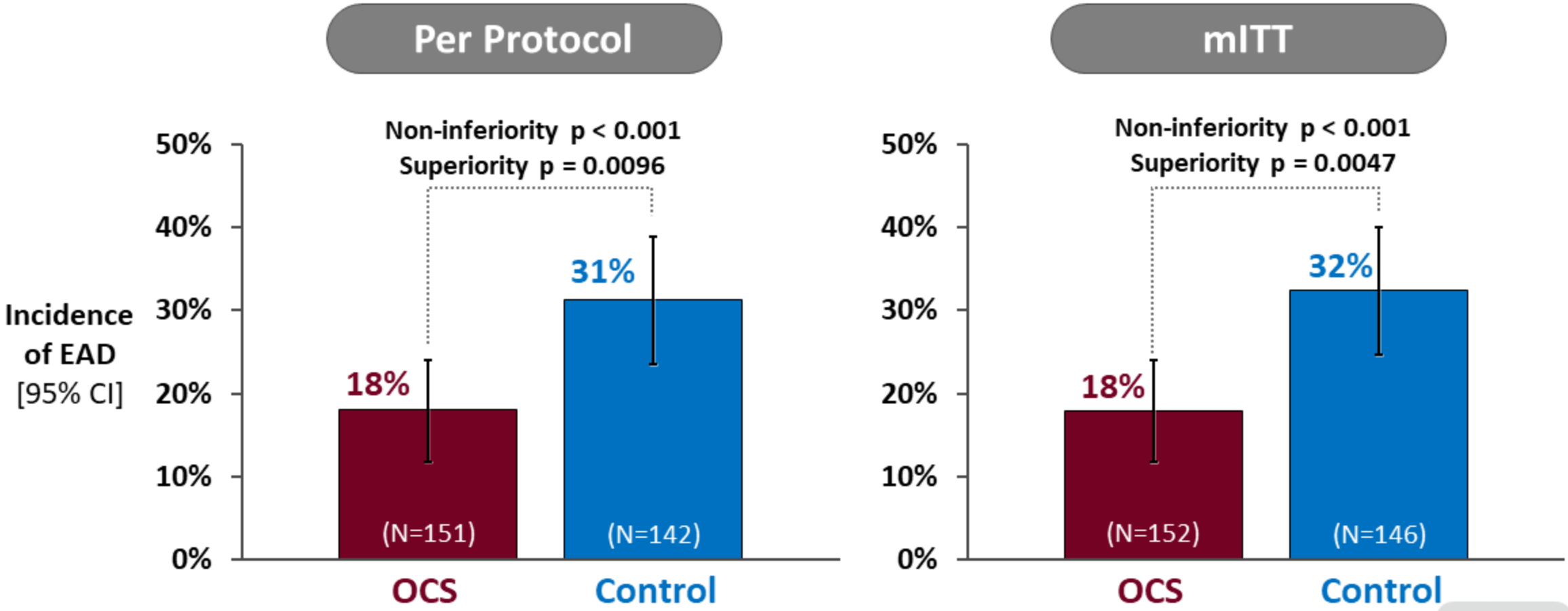
Waleed Hassanein, MD

President and CEO

TransMedics, Inc.

Question 1a: Primary Effectiveness Endpoint

Primary Effectiveness Endpoint Results Clinically and Statistically Robust
OCS Demonstrated Superiority of Outcomes vs Control in Both PP and mITT Populations



Question 1b: EAD Criteria

EAD Definition in PROTECT Is Well Validated and Results Unequivocally Demonstrate Consistency with Prior Literature on Clinical Benefit of Reducing EAD

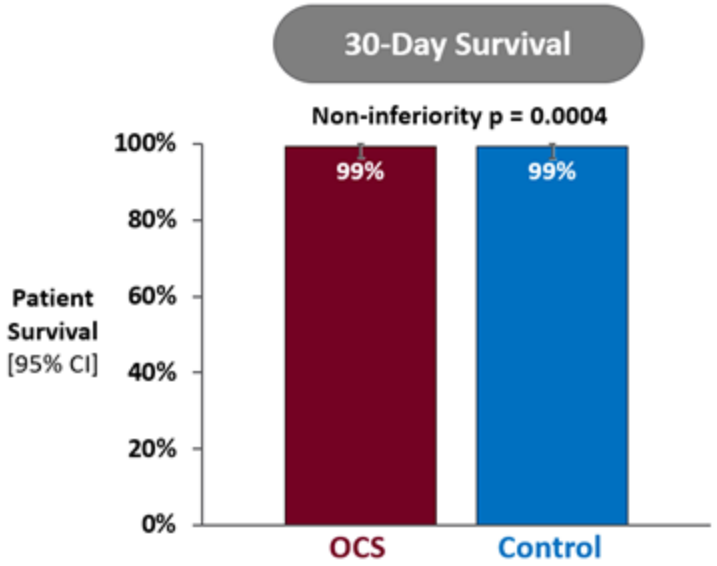
- EAD is validated and clinically accepted endpoint in liver transplantation[1]
- Published literature supports liver enzymes as reliable marker for donor liver injury[2-3]
- EAD results consistent with or without ALT
- Association between EAD and clinical outcomes replicated in PROTECT trial using Olthoff analysis
- PROTECT demonstrated mechanistic evidence of IR injury that correlated with EAD

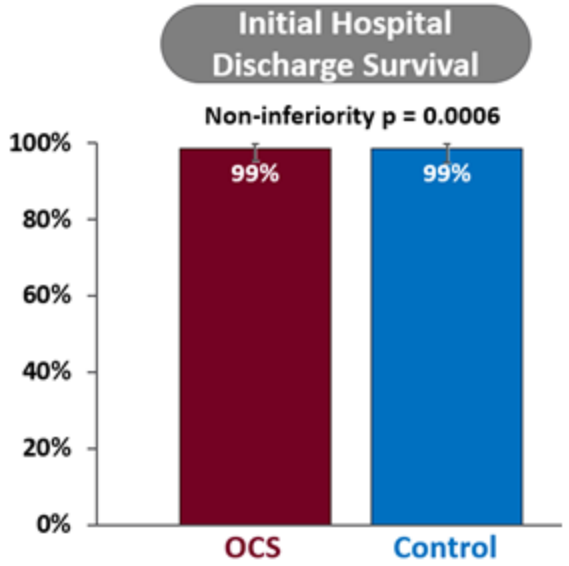
EAD Component(s) Met	Patients (% of total)	6-Month Outcomes	
		Mortality	Graft Failure
INR only	5 (7%)	40%	40%
Bilirubin only	28 (41%)	11%	14%
ALT/AST only	26 (38%)	19%	27%
INR + Bilirubin	4 (6%)	25%	50%
Bilirubin + AST/ALT	2 (3%)	0%	0%
INR + Bilirubin + AST/ALT	4 (6%)	50%	75%

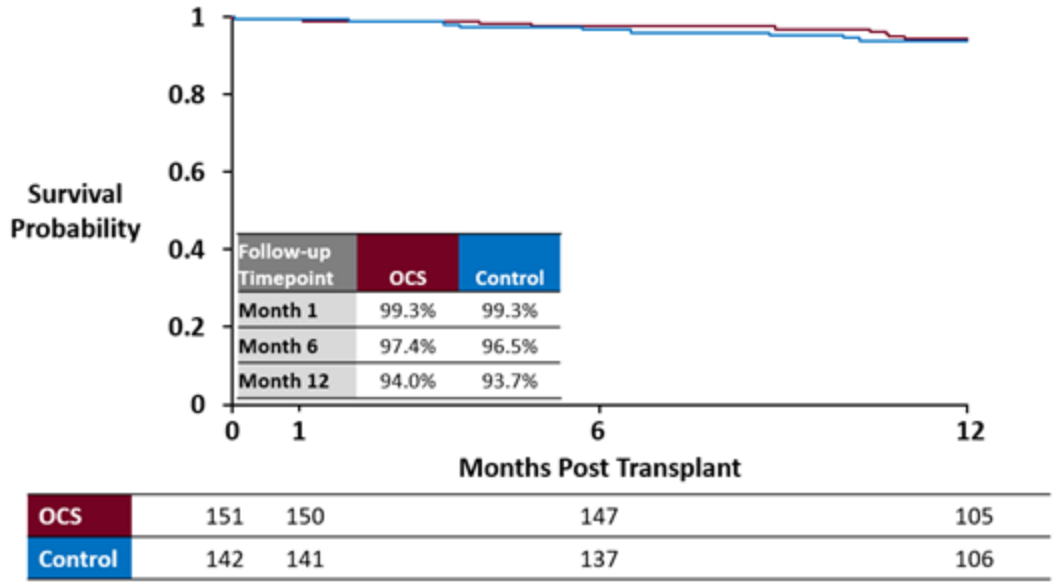
1. Olthoff et al, *Liver Transplant* 2010; 2. Nasralla et al, *Nature* 2018; 3. van Rijn et al., *N Engl J Med* 2021.

Question 2: Secondary Effectiveness Endpoints (Survival)

Survival Results Provide Further Support that OCS Liver System is Safe and Effective
Limited Follow-up Beyond 12 Months Makes Later Survival Estimates Unreliable







Follow-up Timepoint	OCS	Control
Month 1	99.3%	99.3%
Month 6	97.4%	96.5%
Month 12	94.0%	93.7%

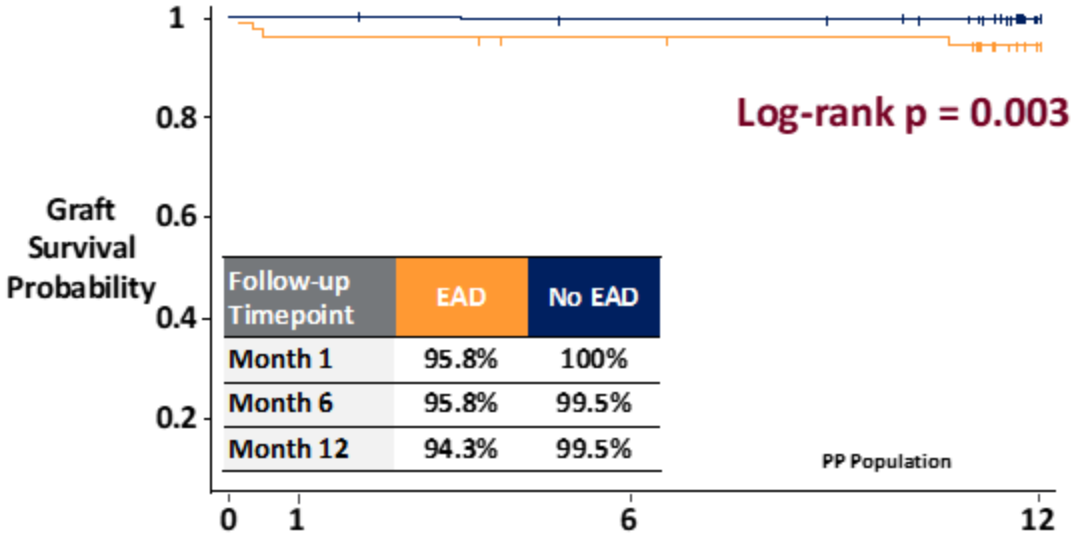
OCS	151	150	147	105
Control	142	141	137	106

PP Population

Question 3: EAD Is an Appropriate Surrogate Endpoint for Survival

PROTECT Demonstrated that EAD (Even Driven by AST) Is an Appropriate Surrogate for Graft Survival, Consistent with Prior Clinical Studies

- PROTECT powered to assess differences in EAD, not survival
- Trial of **~2,500** patients required to show survival differences between treatment arms based on observed EAD rates
- EAD as pre-specified in PROTECT was associated with significant risk of graft loss
- Further validates Olthoff et al.'s finding that EAD is a surrogate for graft loss, mortality, and other negative outcomes

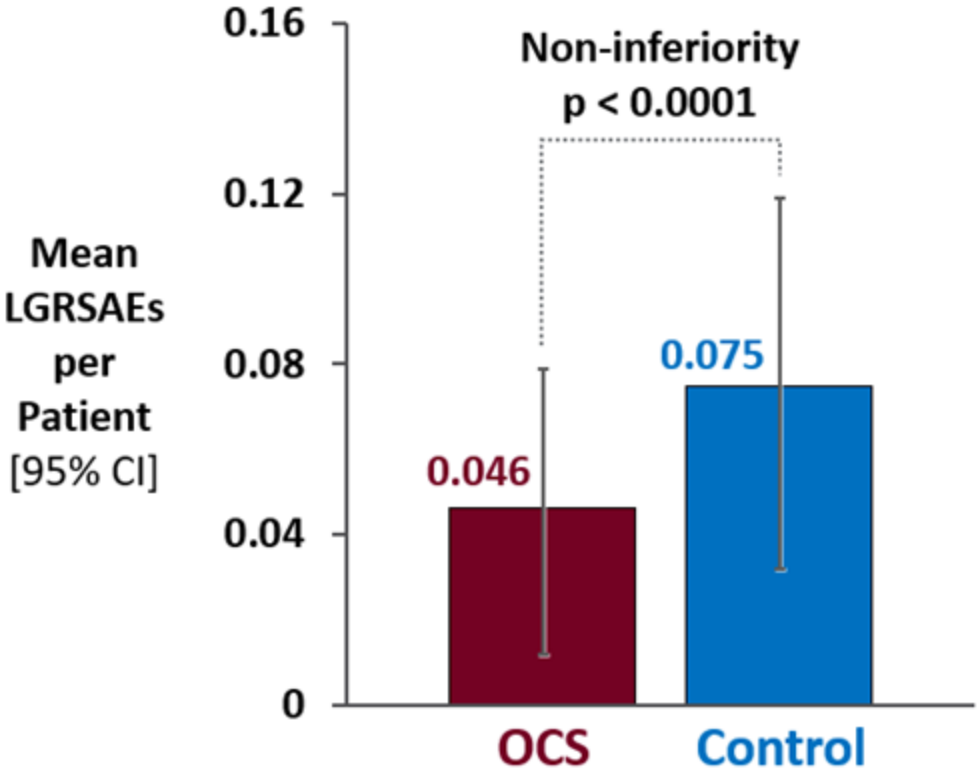


EAD	71	68	66	43
No EAD	220	220	215	166

Question 4: Safety Assessment

PROTECT Met the Pre-Specified Safety Endpoint Analysis

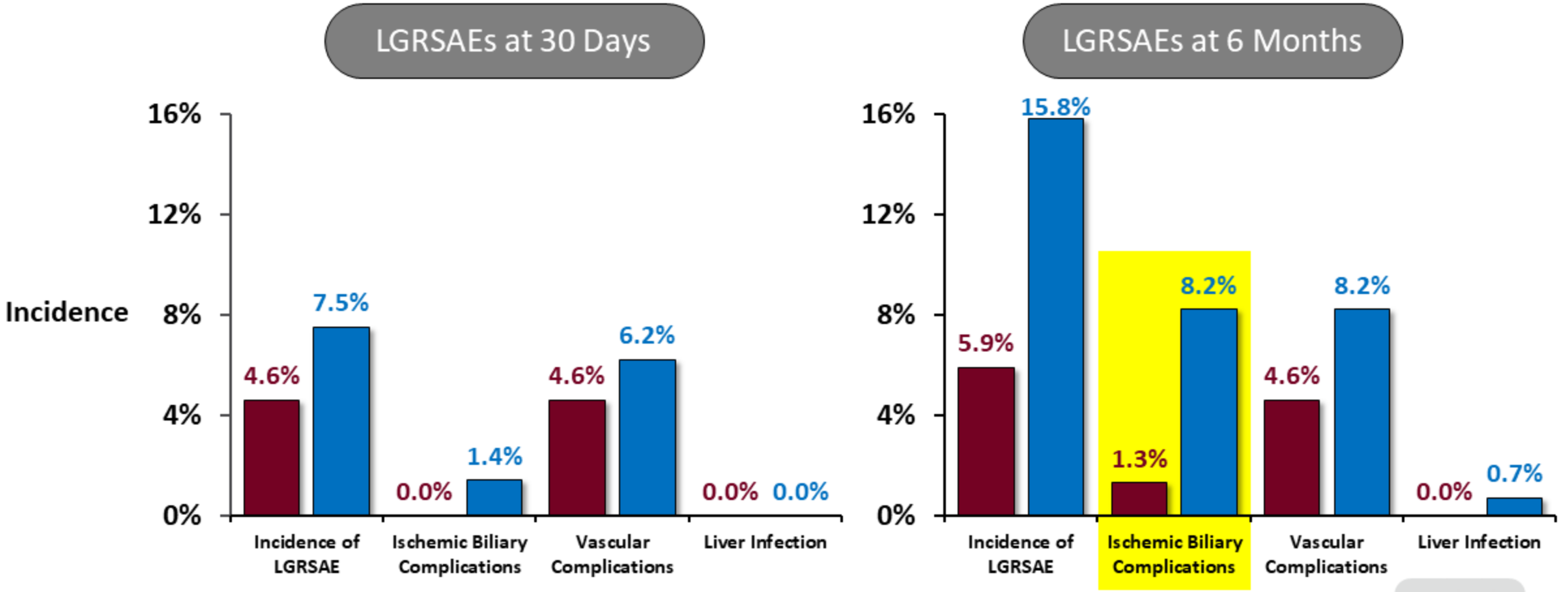
- Safety endpoint: average number of LGRSAEs per patient in the first 30 days post-transplant
- LGRSAEs also collected through 6 months
- PROTECT met the pre-specified safety endpoint analysis



AT Population. Non-inferiority margin = 1.0

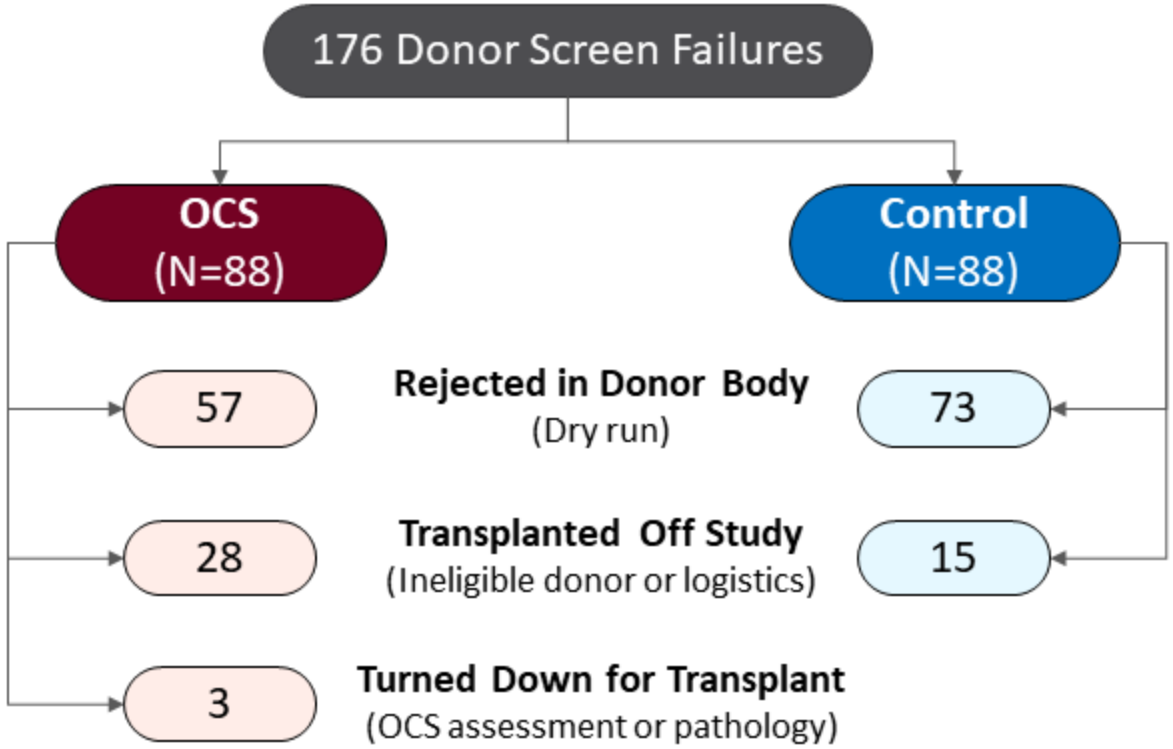
Question 4: Safety Assessment

Lower Incidence of LGRSAEs with OCS in All Pre-Specified Categories



Question 5a: Donor Screen Failures

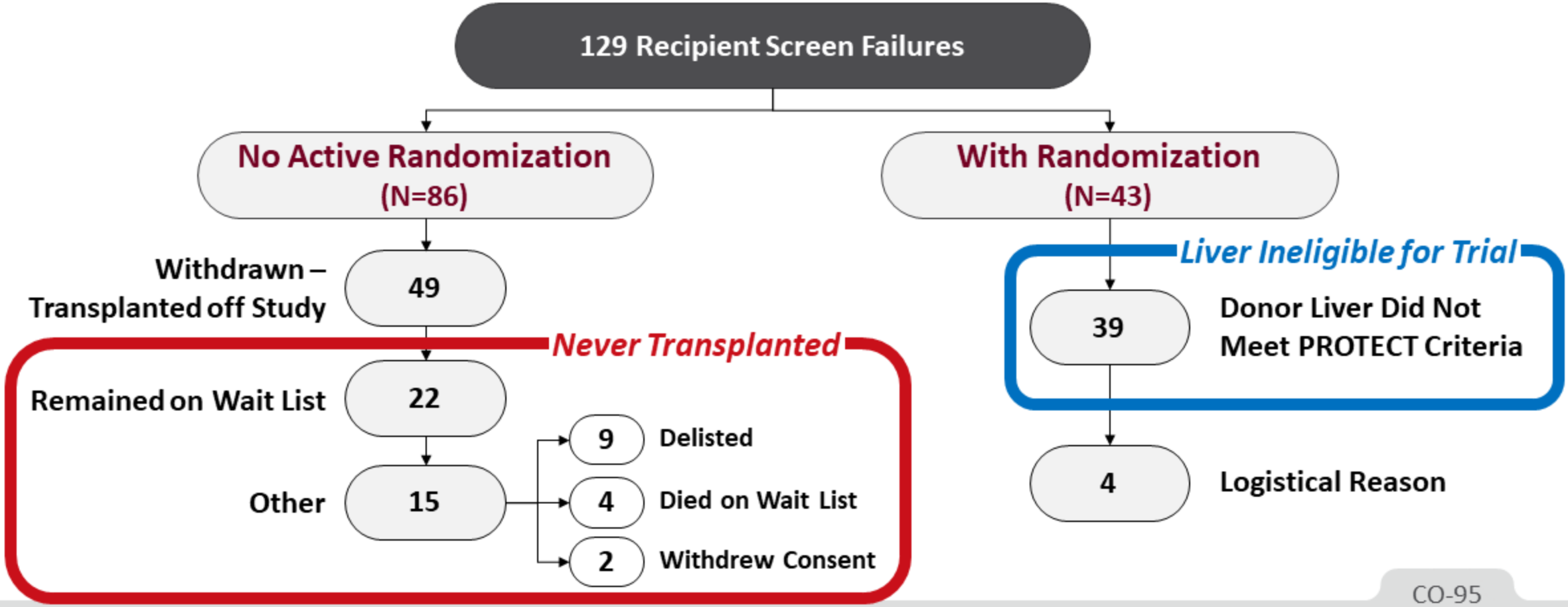
No Evidence of Uncertainty in PROTECT Results Due to Donor Screen Failures – They were Identical Between Groups
No Differences in Baseline Donor Liver Histological Assessment



- **130/176 (74%)** clinically rejected at physical examination (dry runs)
  - Dry runs common in liver transplant due to the complex, multi-step process of donor screening
- **43/176 (24%)** failed to meet eligibility on physical examination or due to logistical reasons, and transplanted off study
- **3/176 (2%)** turned down based on pathological findings or OCS assessment
- **No differences in baseline histopathology**

Question 5b: Recipient Screen Failures

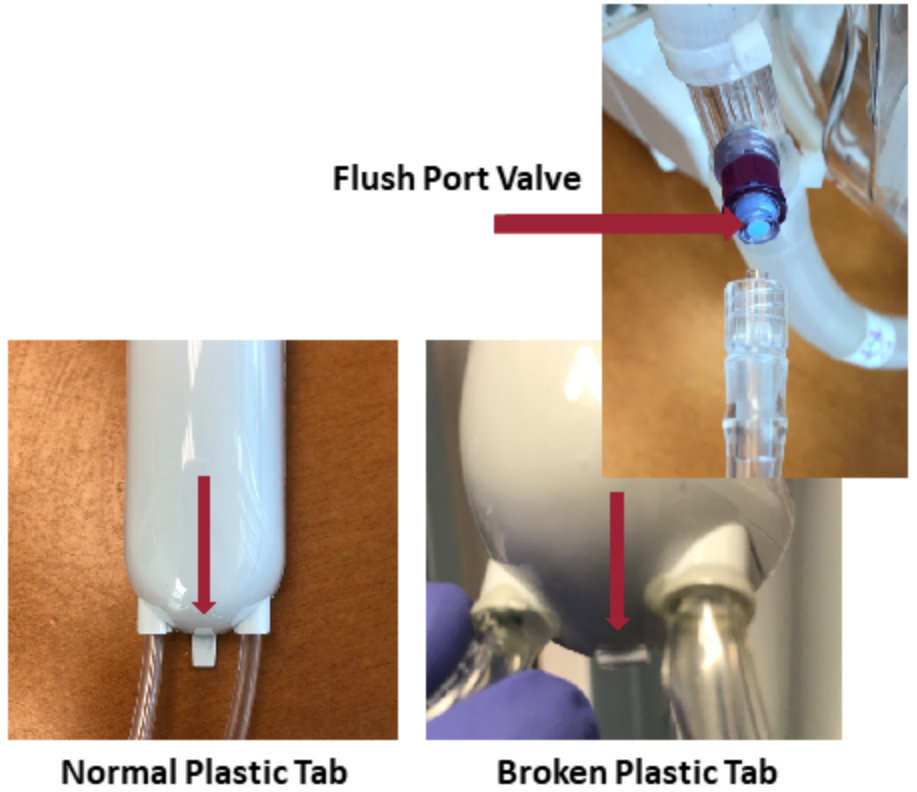
PROTECT Was Appropriately Designed and Analyzed
Recipient Screen Failures Common in Transplant Trials and Did Not Impact Results



Question 6: Significance of Device Malfunctions

Low Rate of Device Malfunctions with No Negative Impact to the Liver Allograft or the Recipient

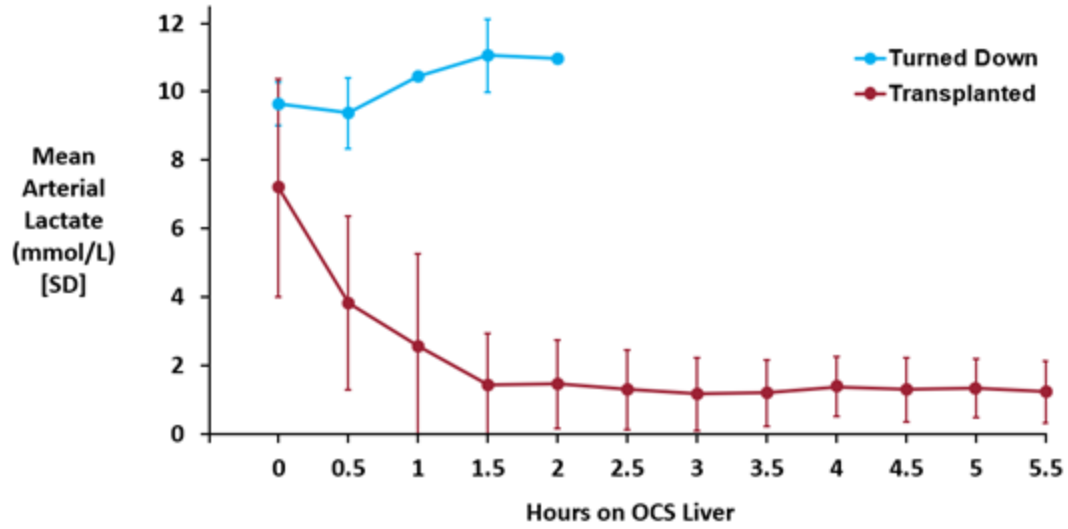
- Device malfunctions are a fact of medical technology use
- **3/155 (1.9%)** rate reported in PROTECT is an acceptable low rate of malfunction
  - 2 malfunctions did NOT alter the OCS function, livers were preserved on OCS, and transplanted successfully
  - 1 malfunction occurred before surgical retrieval and the donor liver was preserved on cold storage and transplanted successfully
- **NO harm occurred to recipients and NO organs were lost**



Question 7: Donor Liver Turndowns on OCS

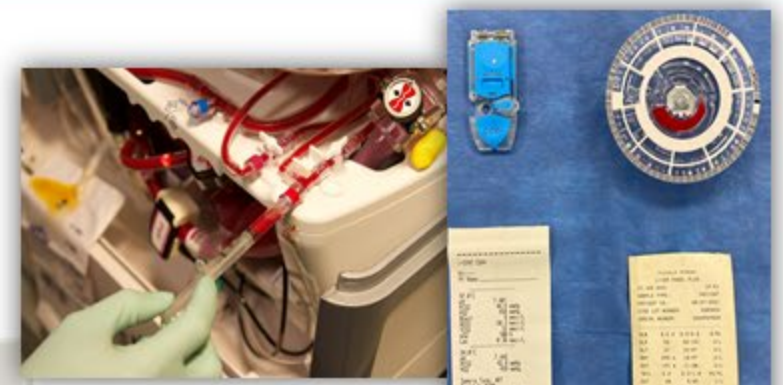
OCS Assessment Capabilities Enabled Higher Utilization of DCD Livers
Ability to Detect Livers Unsuitable for Transplant is a Clinical Benefit of OCS

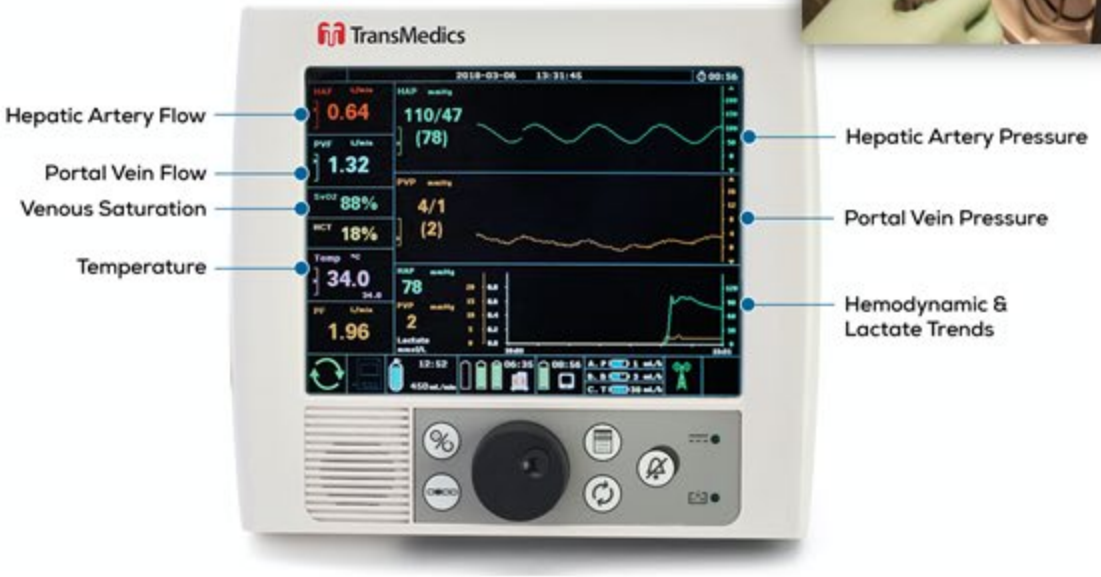
- **3 DCD donor livers** were turned down on OCS Liver System
  - 1 clinically rejected for transplant and **unrelated to OCS assessment**
  - 2 due to rising lactate trend on OCS
- **2** patients later **transplanted and analyzed in PROTECT**
- **1** patient **remained on waiting list**
- OCS enabled parameters are helpful to gain more confidence in accepting or declining DCD donor livers for transplantation

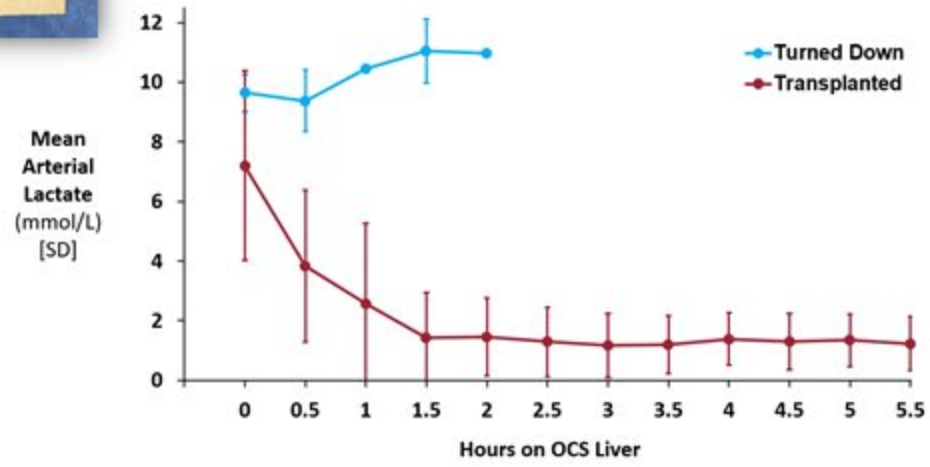


Question 8a: Labeling/Claims – *Ex-Vivo* Assessment

OCS *Ex-Vivo* Assessment of Donor Livers Based on Perfusion Hemodynamics, Lactate Trend, Liver Enzymes, and Bile Production Useful Tools in Clinical Decision-Making

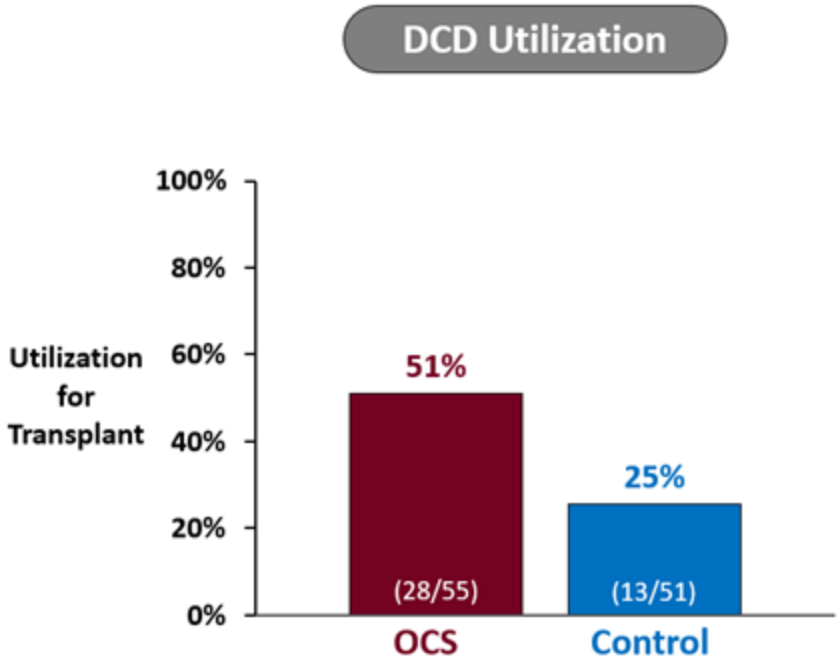


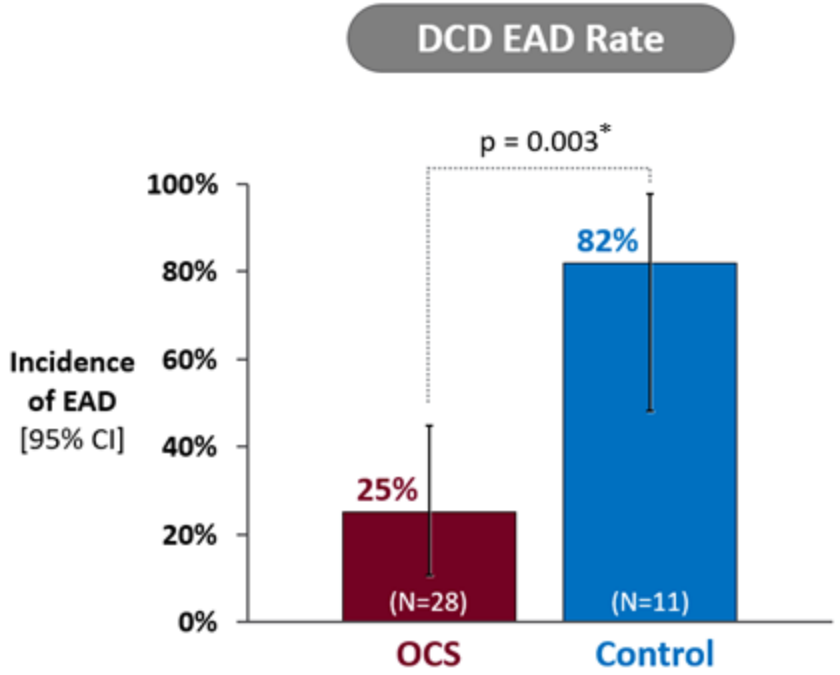




Question 8b: Liver Allografts from DCD Donors ≤ 55 Years Old

OCS Demonstrated Favorable Benefit-Risk for DCD Liver Allografts: Significantly Improved Utilization and Reduction in EAD with No Liver Graft-Related Mortality





- All deaths in OCS group among patients with DCD livers not liver graft related
  - 2 metastatic recurrent cancer
  - 1 sepsis due to perforated duodenal ulcer
  - 1 unknown cause

* Unadjusted p-value

Question 8b: Liver Allografts from DCD Donors ≤ 55 Years Old

British Transplant Society Guidelines Cited By FDA

Ideal DCD Donor Criteria	OCS DCD Livers (N=28) Number of Donors n/N (%)	Control DCD Livers (N=13) Number of Donors n/N (%)
Donor age < 50	23/28 (82%)	12/13 (92%)
WIT < 20 min	6/25 (24%)	4/12 (33%)
CIT < 8 hours	20/28 (71%)	12/13 (92%)
Macrosteatosis < 15%	27/28 (96%)	9/11 (82%)
Weight < 100 Kg	21/28 (75%)	9/13 (69%)
Meet ALL Criteria (Ideal DCD Organ)	**2/27 (7%)**	**2/13 (15%)**

Question 8c: Ischemic Biliary Complications

Definitions Pre-Specified in Protocol

4.4. Safety Endpoint

Safety will be analyzed principally by examination of the frequency of liver graft-related serious adverse events (SAEs) up to the 30-day follow-up after transplantation. This endpoint is defined as the average number of liver graft-related serious adverse events through the 30 days post-liver transplantation per subject, consisting of the following serious adverse events (at most one per type per person):

- Primary non-function (defined as irreversible graft dysfunction requiring emergency liver re-transplantation or death with the first 10 days, in the absence of immunologic or surgical causes)
- Ischemic biliary complications (ischemic biliary strictures, and non-anastomotic bile duct leaks)

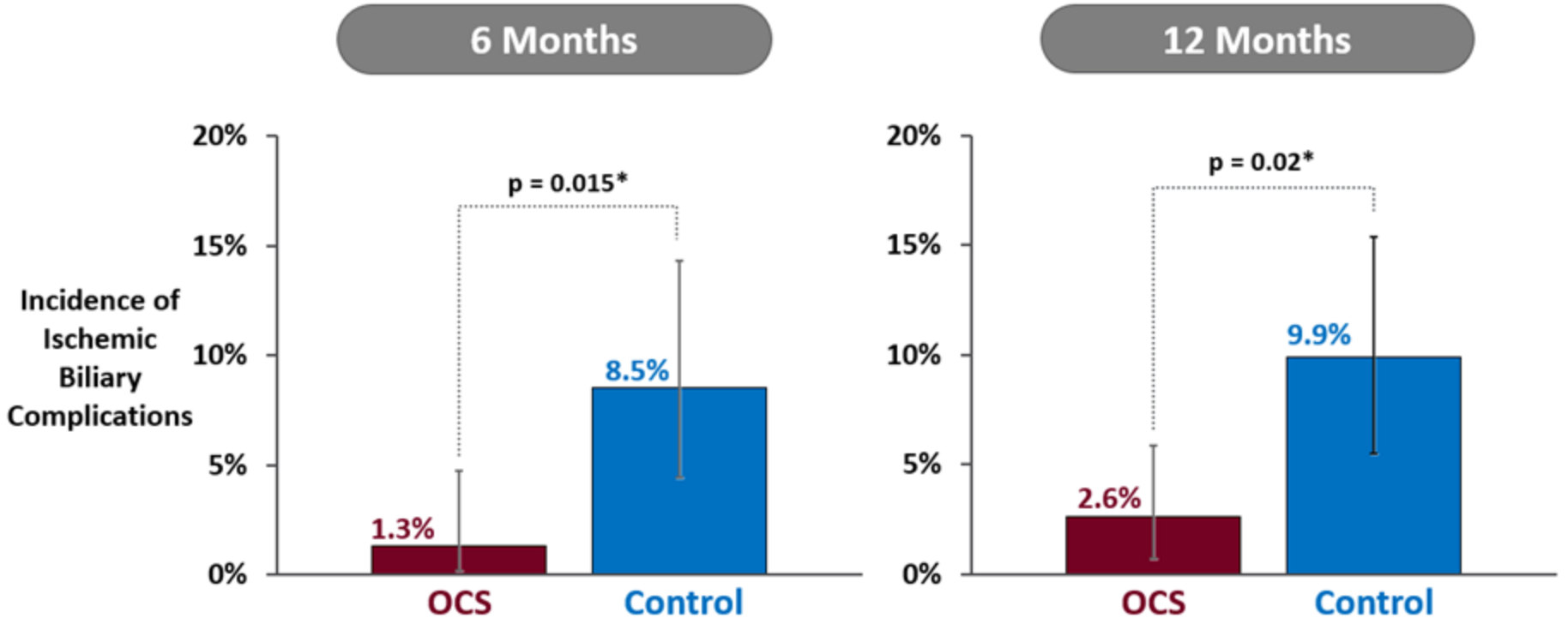
7.3.1. 6 and 12-Month Follow-up

At approximately 6 and 12 months post-transplant, the patient will be evaluated at an office visit if this is the institution's standard of care, and, if not, by phone contact by the site. The patient's medical record may be reviewed to confirm patient's answers. This follow up will collect information on:

- Patient and graft survival;
- Liver graft related SAEs (6 months only);
- Liver graft related re-hospitalized after initial discharge, and, if yes, the primary reason/diagnosis for the hospitalization and the length of stay;
- Information will also be collected on any diagnosis of ischemic biliary complications and, if so, the method of diagnosis and treatment.

Question 8c: Ischemic Biliary Complications

OCS Demonstrated Clinically and Statistically Significant Reductions in Ischemic Biliary Complications at 6- and 12-Months Post Transplantation



- All Biliary Complications were Diagnosed Based on ERCP or MRCP
- All Biliary Complications were Blindly Reviewed and Adjudicated by the CEC

* Unadjusted p-values

Question 9: Post-Approval Program

- **Two-part post-approval study** to evaluate long-term safety and effectiveness
  1. Continued follow-up of PROTECT OCS and Control patients for 2 years
  2. Continued follow-up of PROTECT CAP patients for 2 years
- Will provide 2-year data on up to 374 patients
- TransMedics contends that long-term follow-up of PROTECT and CAP patients meets the regulatory standard for the intent of a post-approval study

Question 9: Post-Approval Program

Post Approval Study

9. If the OCS Liver System is approved, TransMedics proposes to continue following participants in the OCS Liver PROTECT trial and in the OCS Liver CAP study up to 2 years post-transplant. FDA agrees with the PAS plan to continue follow-up of the pre-market cohorts, as this approach is the fastest way to collect longer-term data. However, a key limitation of this approach is that potential bias introduced in the design and conduct of the PROTECT trial would persist in the extended follow-up studies.

- NO evidence of bias in the conduct of the PROTECT trial
  - Donor screen failures balanced across groups
  - No difference in donor pre-preservation histopathology or risk factors
  - Reasons for recipient screen failures consistent with protocol and clinical practice (e.g., ineligible donor livers or patient never transplanted)
- PROTECT is a randomized trial, which is less subject to bias than a single-arm PAS

Question 9: Post-Approval Program

and device malfunctions. FDA also recommends a longer-term evaluation of clinically meaningful outcomes, such as patient and/or graft survival post-transplant. For this post-market evaluation, FDA recommends leveraging the existing TOP Registry, which is an all-comers registry designed to collect real-world use data on OCS-perfused lungs and the patients who receive them.

- 2 years is adequate for long-term follow-up of a preservation technology
- **TOP Registry not appropriate & will limit access to OCS Liver System**
  - All-comers design has had substantial negative impact on enrollment
  - Overly burdensome data collection of outcomes not routinely collected by UNOS/SRTR data has been challenging for transplant programs
  - Not warranted given the superiority in outcomes vs Cold Storage in PROTECT

Summary of OCS Liver Training Program

TRAINING

Initial hands-on clinical training and certification of every new clinical center starting OCS Liver program

SUPPORT

TransMedics provides 24/7 retrieval support via phone, messaging and email

TECHNOLOGY

Dedicated OCS Liver iPad® training and support application

TransMedics®

Clinical Perspective and Benefit-Risk Assessment

Parsia A. Vagefi, MD, FACS

Chief of Division of Surgical Transplantation
Ernest Poulos Distinguished Chair in Surgery
UT Southwestern Medical Center

Ischemia-Reperfusion (IR) Injury Is the Cause of Most Severe Clinical Issues Post Liver Transplantation

- Primary cause of liver transplant failure and post-transplant complications
- Unavoidable pathological process
  - Warm IR injury during transplant procedure
  - Cold IR injury during transport on cold storage
- Challenge of addressing demand for transplant with current donor pool

Overall quality of donor pool has declined

Increased utilization of higher-risk donors (older, steatosis, DCD)

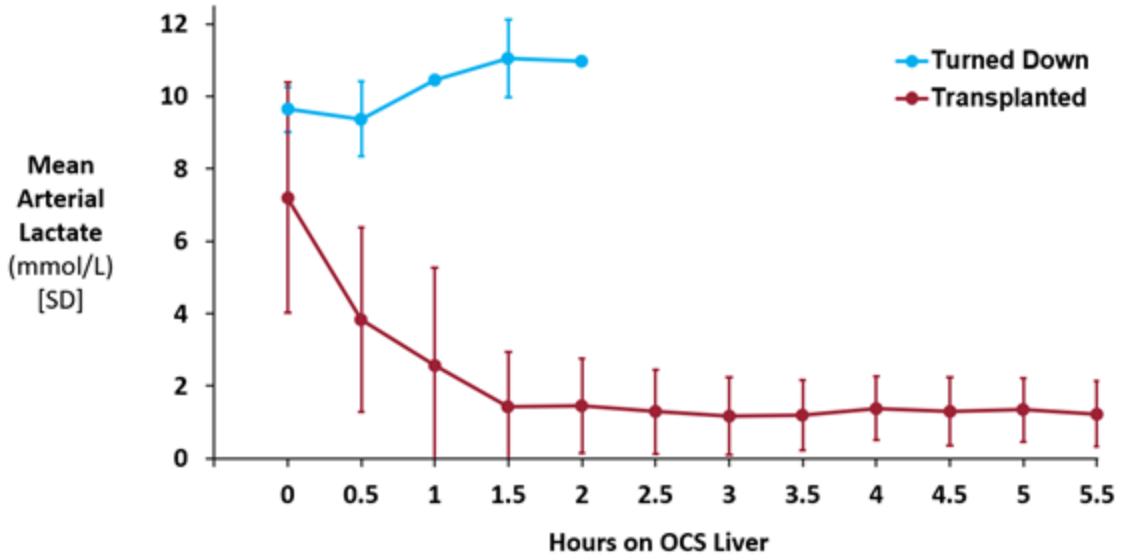
OCS Liver Significantly Attenuates IR Injury

- Significant reduction in early allograft dysfunction (EAD)
  - Lower risk of graft failure and mortality
  - Lower use of hospital resources
- Significant reduction in ischemic biliary complications through 1 year
- Reduction in lobular inflammation by histopathological assessment
- Reduction in post-transplant reperfusion syndrome

OCS Liver System Substantially Reduces the Pathological Process that Leads to Most Severe Complications after Transplant

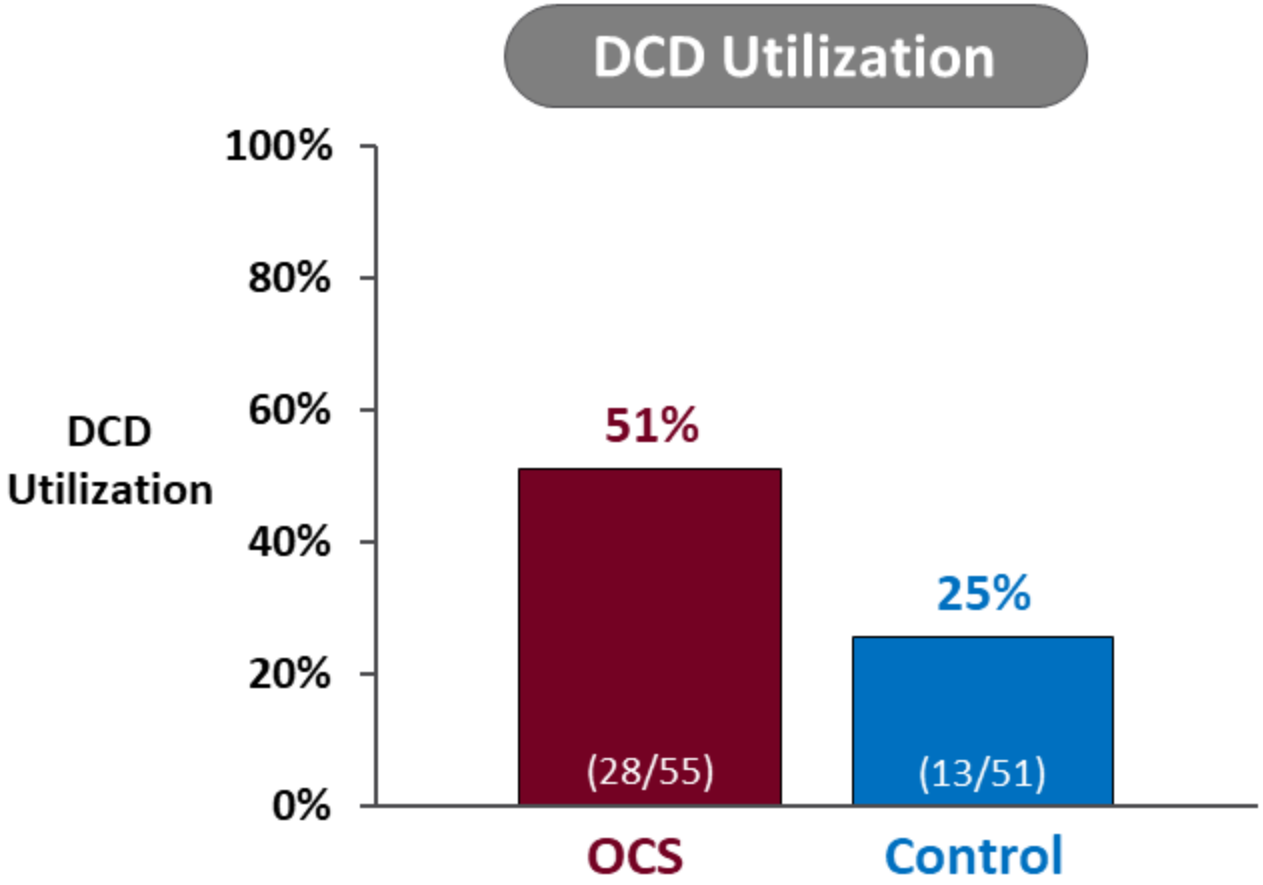
OCS Liver System Reduces Ischemic Damage to Donor Livers

- High lactate levels indicate hypoperfusion and liver damage after transplant
- Extent of IR injury unknown with cold storage until after transplantation
- OCS reperfuses donor livers *ex vivo*



OCS Liver System Allows for Optimization and Assessment *Ex Vivo* to Ensure Better Clinical Outcomes for Recipients

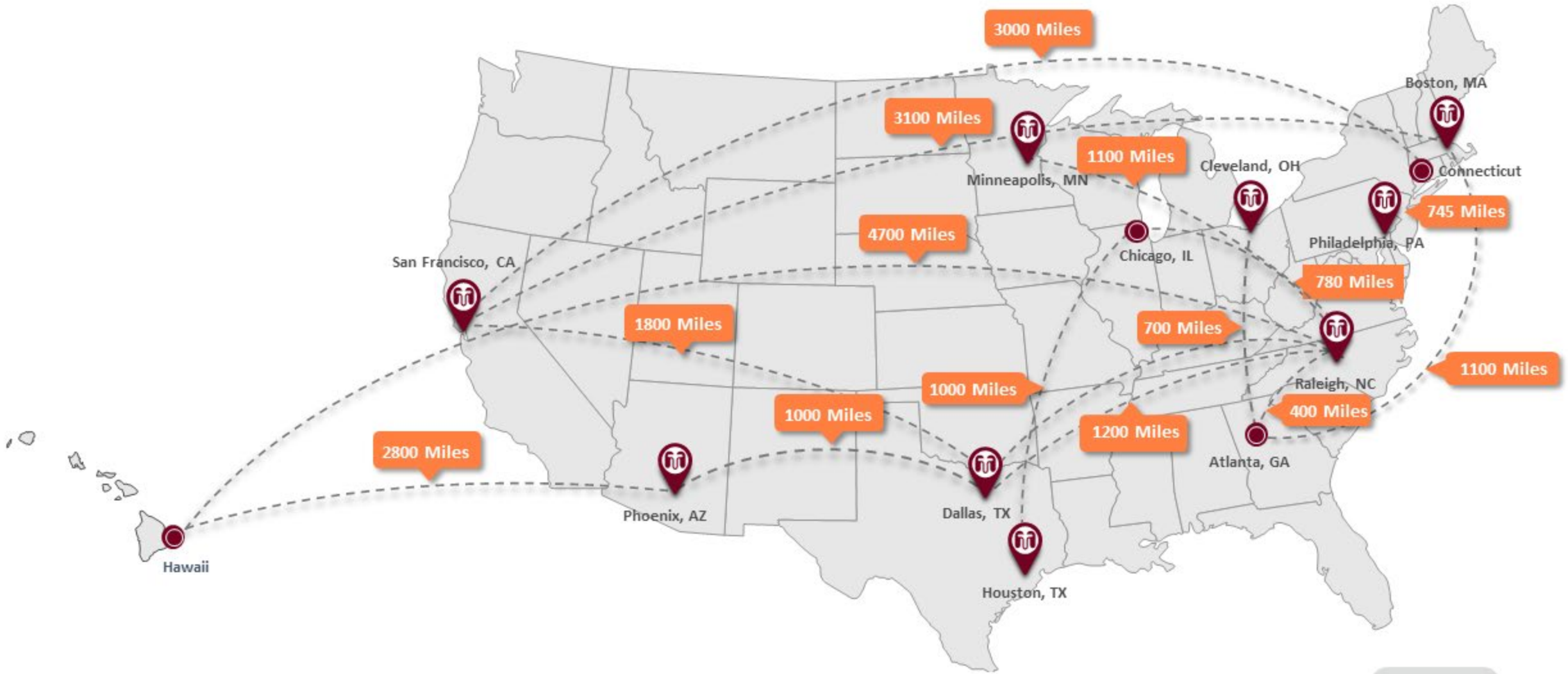
OCS Liver System Optimization and Assessment Capabilities Will Facilitate More DCD Liver Transplants



- Doubling of DCD utilization will provide meaningful expansion in donor pool
- **~3 of 4** DCD livers currently discarded
- OCS is an important advancement to address scarcity of donor livers
  - More transplants in safest possible fashion

Long-Distance Retrieval in PROTECT Trial

OCS Lung Highlights Potential of Long-Distance Retrieval



OCS Liver System is Safe for Proposed Indications for Use

- OCS Liver System non-inferior to cold storage on all safety endpoints
- No adverse safety signals observed
- Long-term mortality through 12 months similar across groups
- Low rate of device malfunction that did not impact recipient/graft safety
- Significantly fewer ischemic biliary complications
- Histopathologic evidence of less IR injury

What Approval of OCS Liver System Would Mean for Liver Transplant

Post-Transplant Outcomes

- Significant reduction in ischemic damage to donor livers
- Superior clinical outcomes
  - Reduced rates of EAD
  - Reduced rates of ischemic biliary complications
- No adverse safety signals

Donor Organ Utilization

- Enable optimization and assessment capabilities
  - Increase in DCD liver utilization
  - Identify damaged liver allografts
- Increase flexibility in challenging clinical situations where more time is needed
- Expand utilization
  - Reduce waiting list mortality

OCS™ Liver System for the Resuscitation, Preservation, and Assessment of Donor Livers

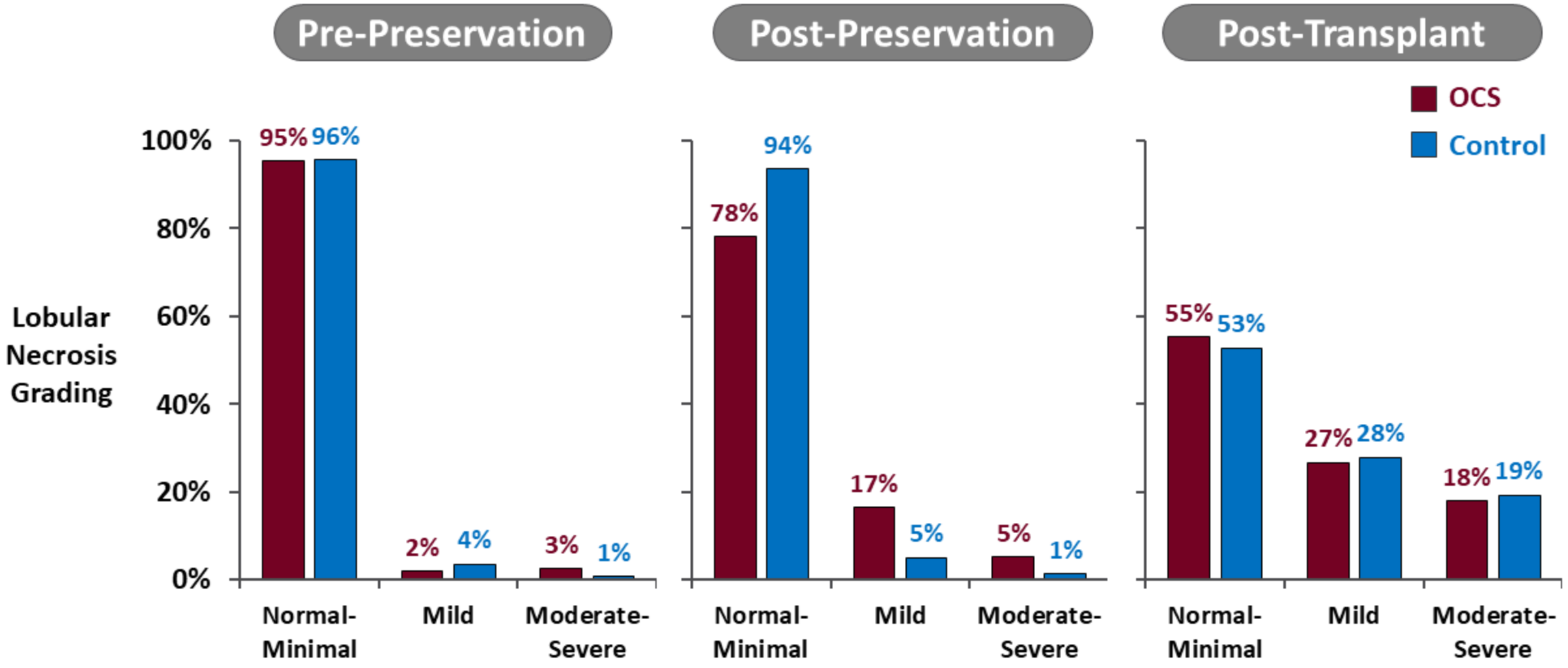
July 14, 2021

Gastroenterology and Urology Devices Panel

TransMedics®

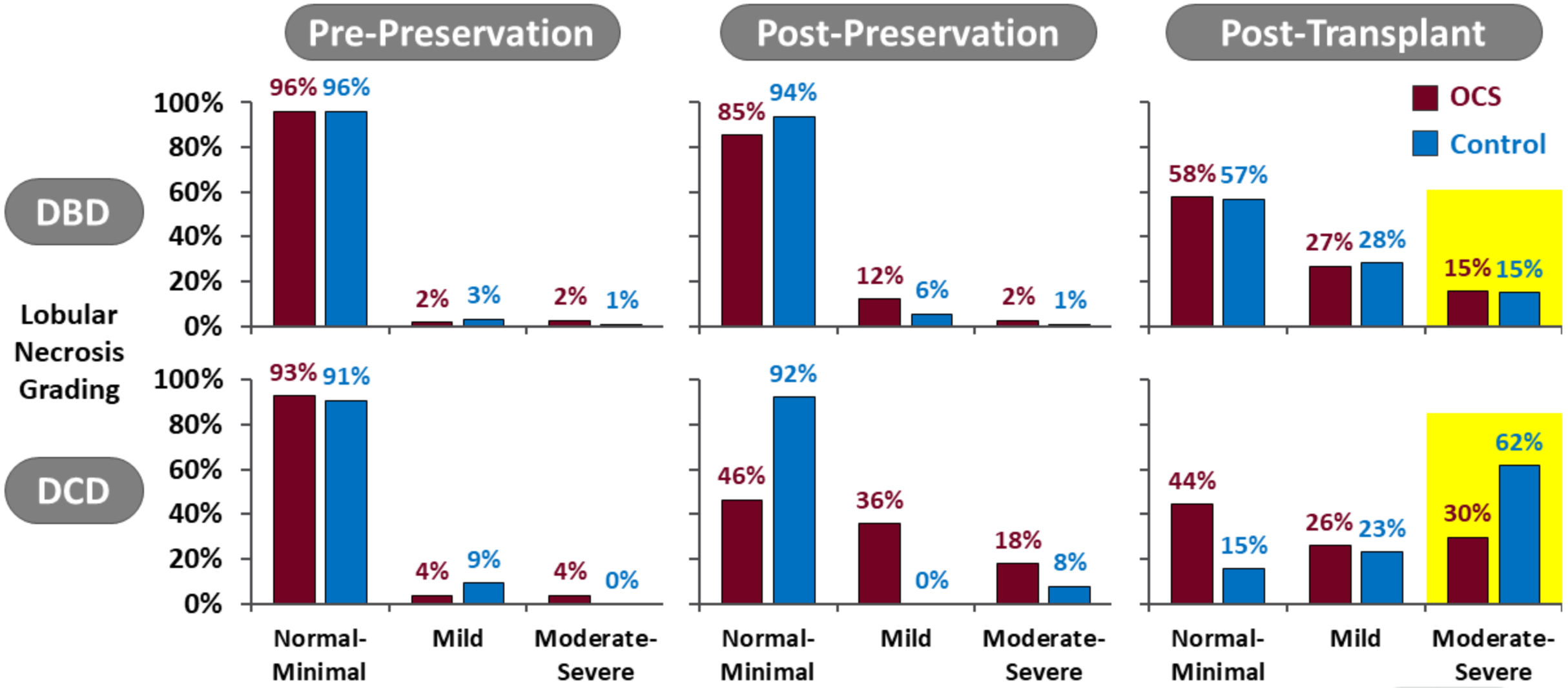
Back-up Q&A Slides Shown

Lobular Necrosis Over Time



mITT Population

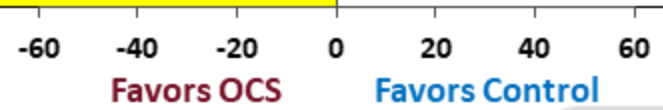
Lobular Necrosis Over Time: DBD & DCD



mITT Population

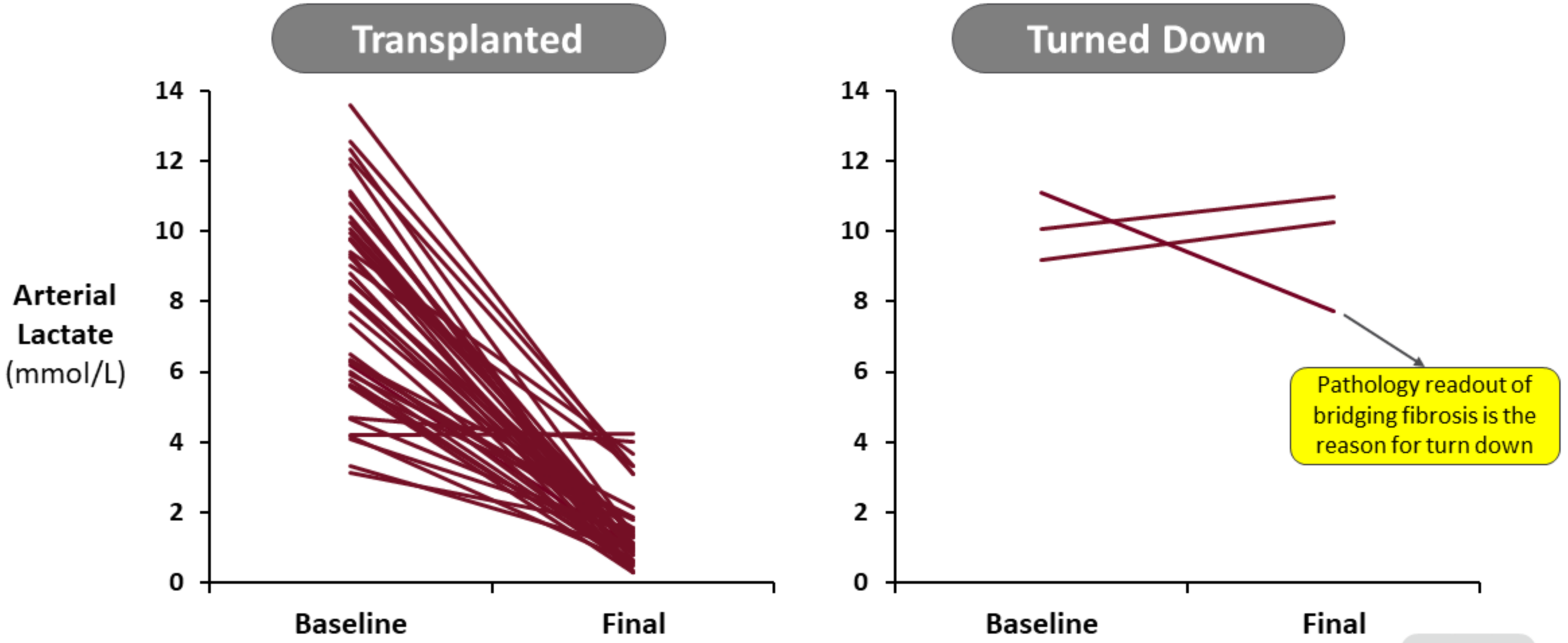
OCS Associated with Lower EAD Rate in All Subgroups

Factor	Criteria	OCS		Control		Difference (Percentage Points)
Macrosteatosis	≤ 20%	147	16%	134	28%	-12
	> 20%	4	50%	4	100%	-50
Donor Age	≤ 50 yrs	82	21%	82	38%	-17
	> 50 yrs	69	13%	63	24%	-11
MELD Score	≤ 25	45	18%	39	36%	-18
	>25	106	17%	106	30%	-13
DBD Cross-Clamp Time	< 6 hrs	34	6%	82	22%	-16
	≥ 6 hrs	89	19%	50	34%	-15
Donor Inclusion criteria	Age ≥ 40 yrs	102	16%	91	22%	-6
	Cross-clamp ≥ 6 hrs	47	23%	56	36%	-12
	DCD & Age ≤ 55 yrs	28	25%	13	85%	-60
	Steatotic liver	93	19%	87	30%	-11
Donor Type	DCD	28	25%	13	85%	-60
	DBD	123	15%	132	27%	-11

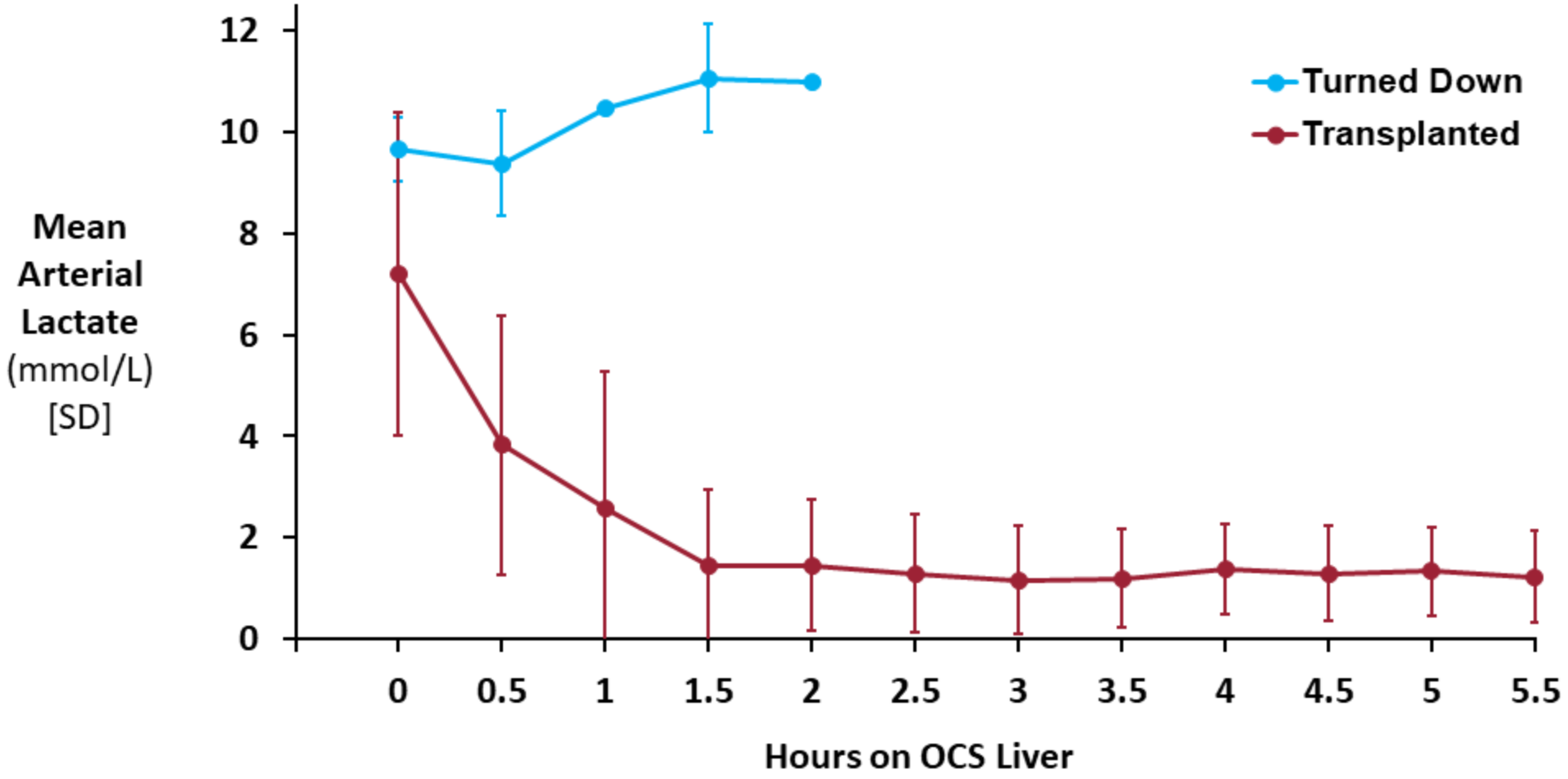


mITT Population

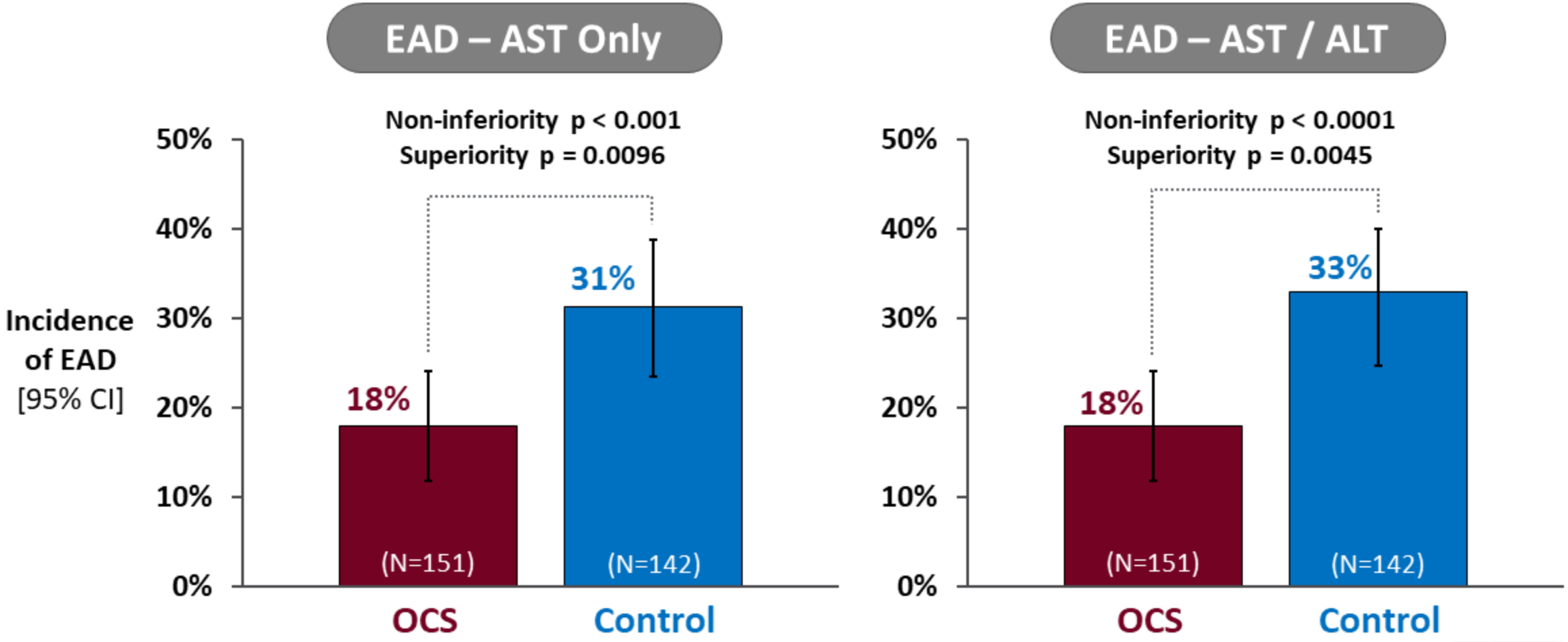
Baseline and Final Arterial Lactate Levels for Transplanted and Turned Down Livers in OCS Group



PROTECT Trial – Lactate Trends



Primary Effectiveness Endpoint by AST Only or AST / ALT

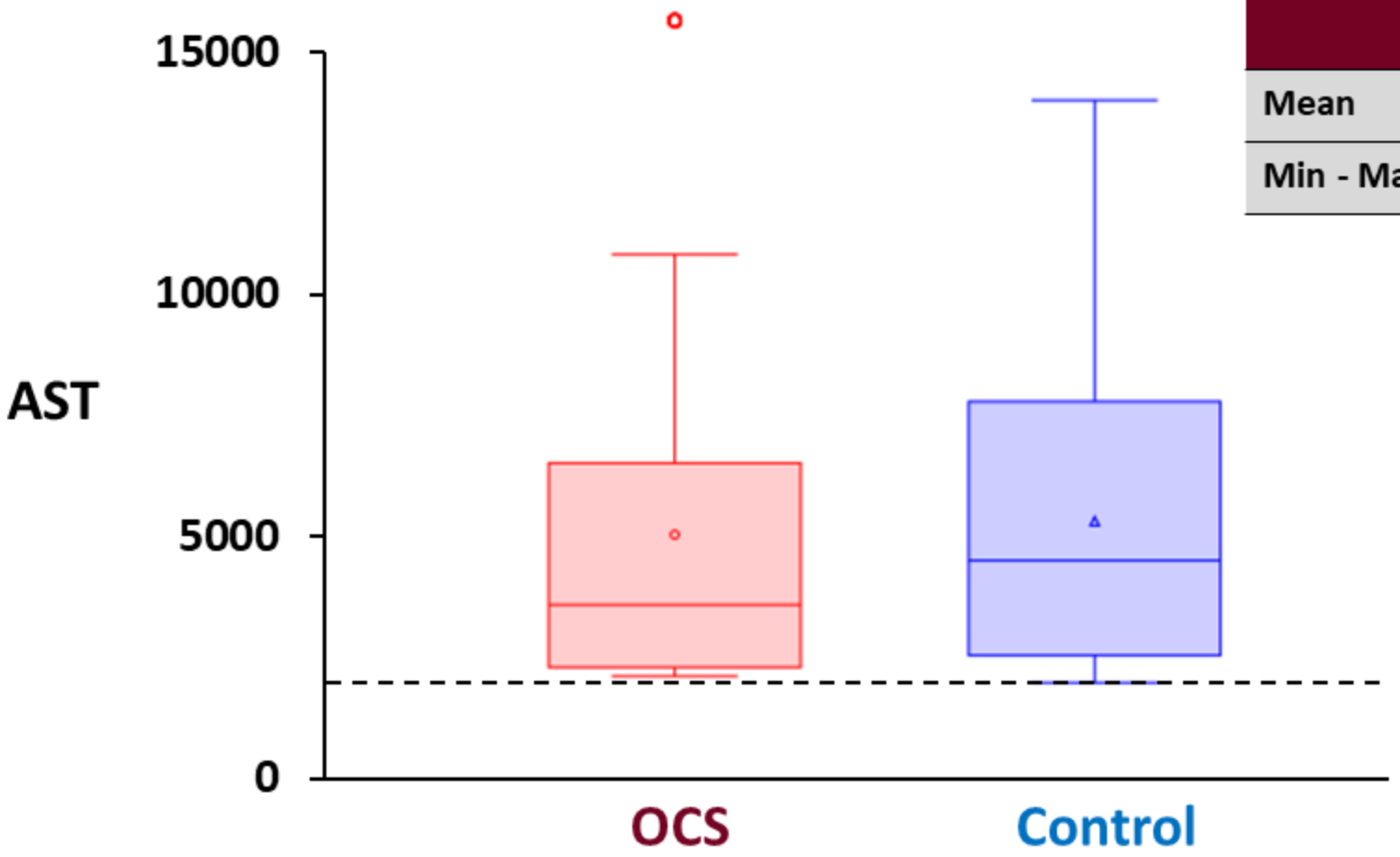


PP Population

PROTECT Trial – DCD Donor Dry Runs Clinical Reasons

Clinical Reasons for Donor Dry Runs (N=65)	OCS (N=27)	Control (N=38)
DCD Did Not Expire Within 30 Mins.	18 (67%)	25 (66%)
Clinical Judgement of Retrieval Surgeon on Quality of Donor Liver	2 (7%)	9 (24%)
Steatosis	4 (15%)	3 (8%)
Donor Family Refused Donation	1 (4%)	1 (3%)
Enrollment Error (age > 55 years)	1 (4%)	0
Pre-Retrieval Biopsy – Fibrosis	1 (4%)	0

Peak AST



	OCS (N=20)	SOC (N=43)
Mean	5074.0	5354.3
Min - Max	2146.0 – 15,723.0	2008.0 – 14,072.0

PROTECT Trial Design

- Prospective, randomized trial of 300 recipients at 20 US liver transplant sites
- 1:1 randomization to OCS Liver or Control (cold storage)
- Designed to compare safety and effectiveness of preservation techniques among donor livers with at least one of the following characteristics
  - Donor age ≥ 40 years
  - Expected total cross-clamp/cold ischemic time ≥ 6 hours
  - DCD donor with age ≤ 55 years
  - Steatotic liver > 0% and ≤ 40% macrosteatosis at time of retrieval*

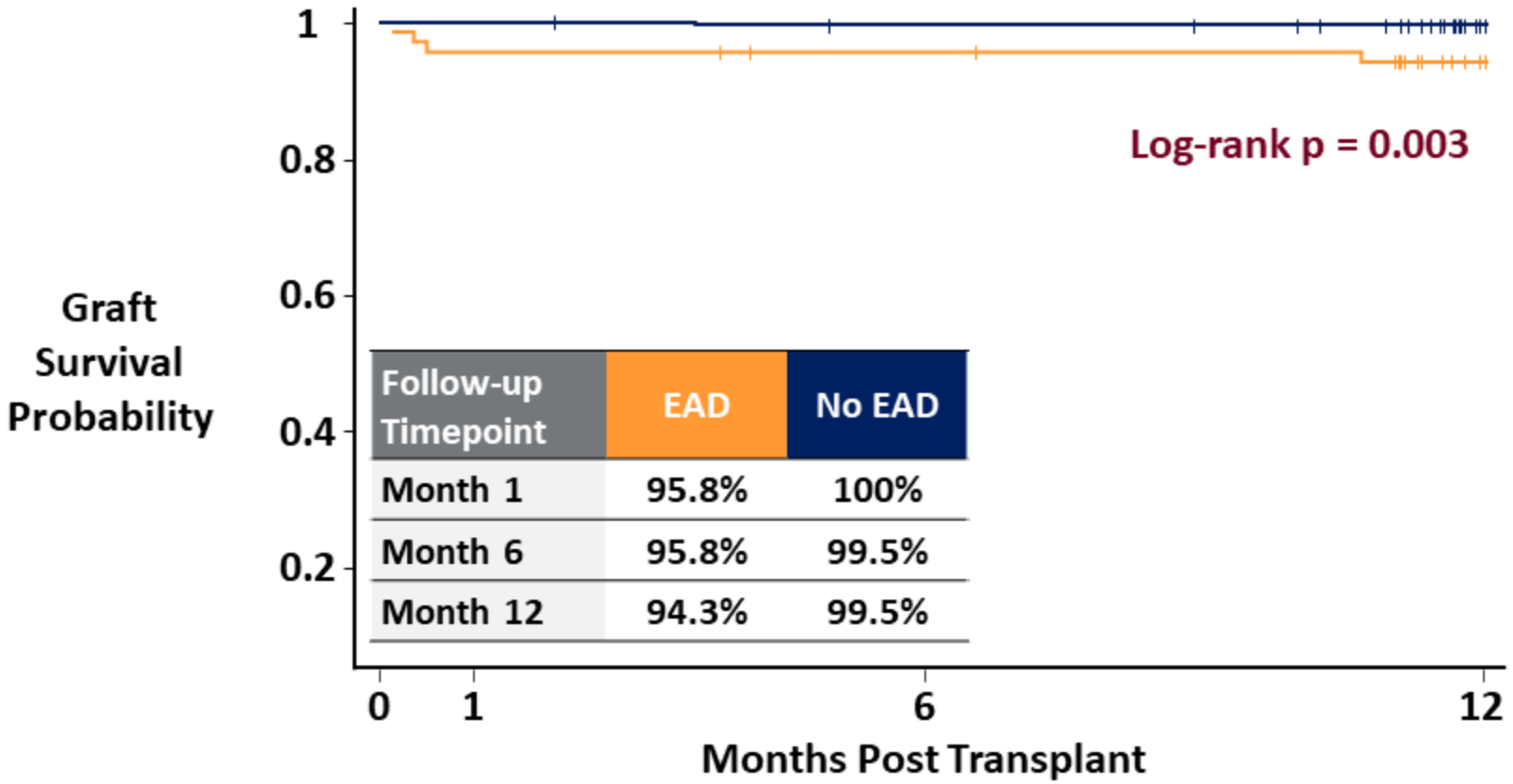
PROTECT Evaluated Donor Livers that Are Challenging to Preserve on Cold Storage

* Based on retrieval biopsy readout only if the donor liver was suspected to be fatty at time of retrieval

Donor Age

	OCS (N=152)	SOC (N=146)
Max age	83.7	80.6
> 70 years old	6 (4%)	7 (4%)

Absence of EAD Associated with Lower Risk of Graft Failure



Follow-up Timepoint	EAD	No EAD
Month 1	95.8%	100%
Month 6	95.8%	99.5%
Month 12	94.3%	99.5%

EAD	71	68	66	43
No EAD	220	220	215	166

PP Population

Ischemic Biliary Complications

Definitions Pre-Specified in Protocol

4.4. Safety Endpoint

Safety will be analyzed principally by examination of the frequency of liver graft-related serious adverse events (SAEs) up to the 30-day follow-up after transplantation. This endpoint is defined as the average number of liver graft-related serious adverse events through the 30 days post-liver transplantation per subject, consisting of the following serious adverse events (at most one per type per person):

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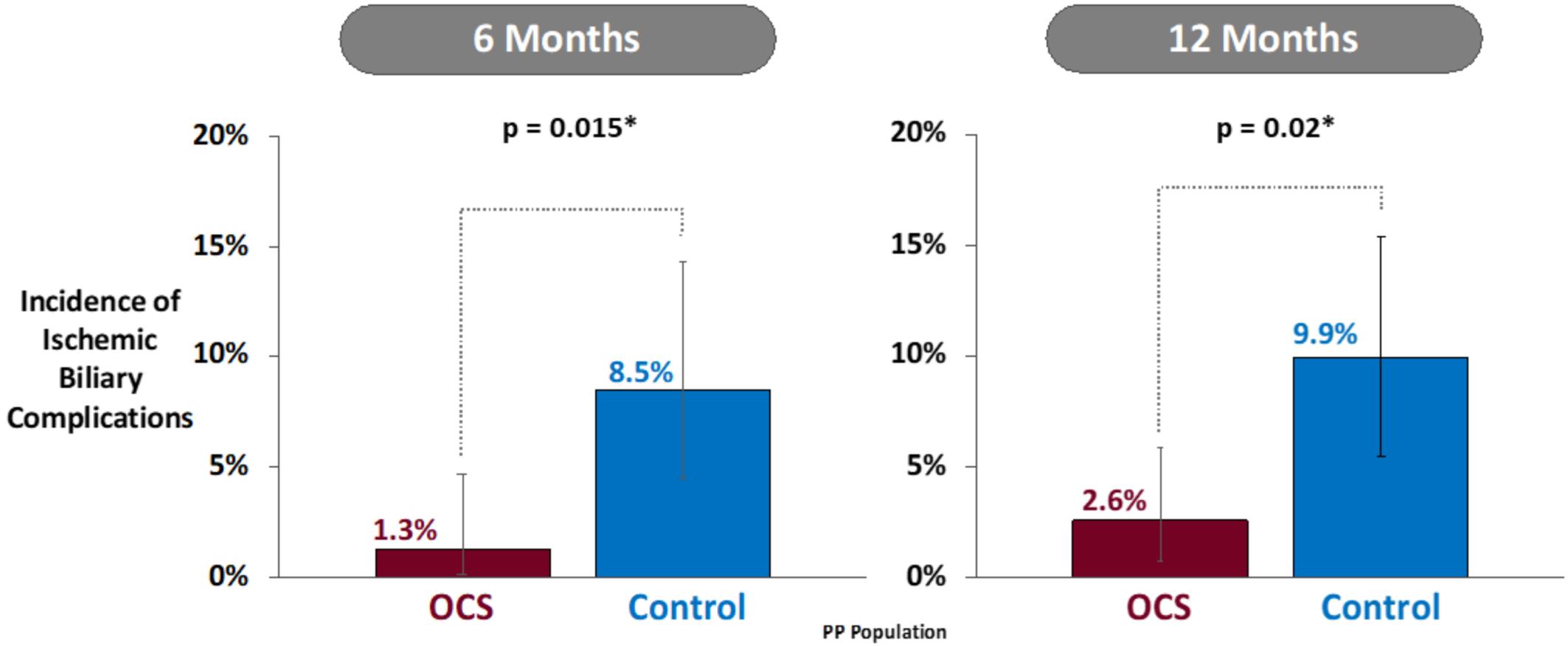
- Ischemic biliary complications (ischemic biliary strictures, and non-anastomotic bile duct leaks)

7.3.1. 6 and 12-Month Follow-up

At approximately 6 and 12 months post-transplant, the patient will be evaluated at an office visit if this is the institution's standard of care, and, if not, by phone contact by the site. The patient's medical record may be reviewed to confirm patient's answers. This follow up will collect information on:

- Patient and graft survival;
- Liver graft related SAEs (6 months only);
- Liver graft related re-hospitalized after initial discharge, and, if yes, the primary reason/diagnosis for the hospitalization and the length of stay;
- Information will also be collected on any diagnosis of ischemic biliary complications and, if so, the method of diagnosis and treatment.

PROTECT Trial – Incidence of Ischemic Biliary Complications



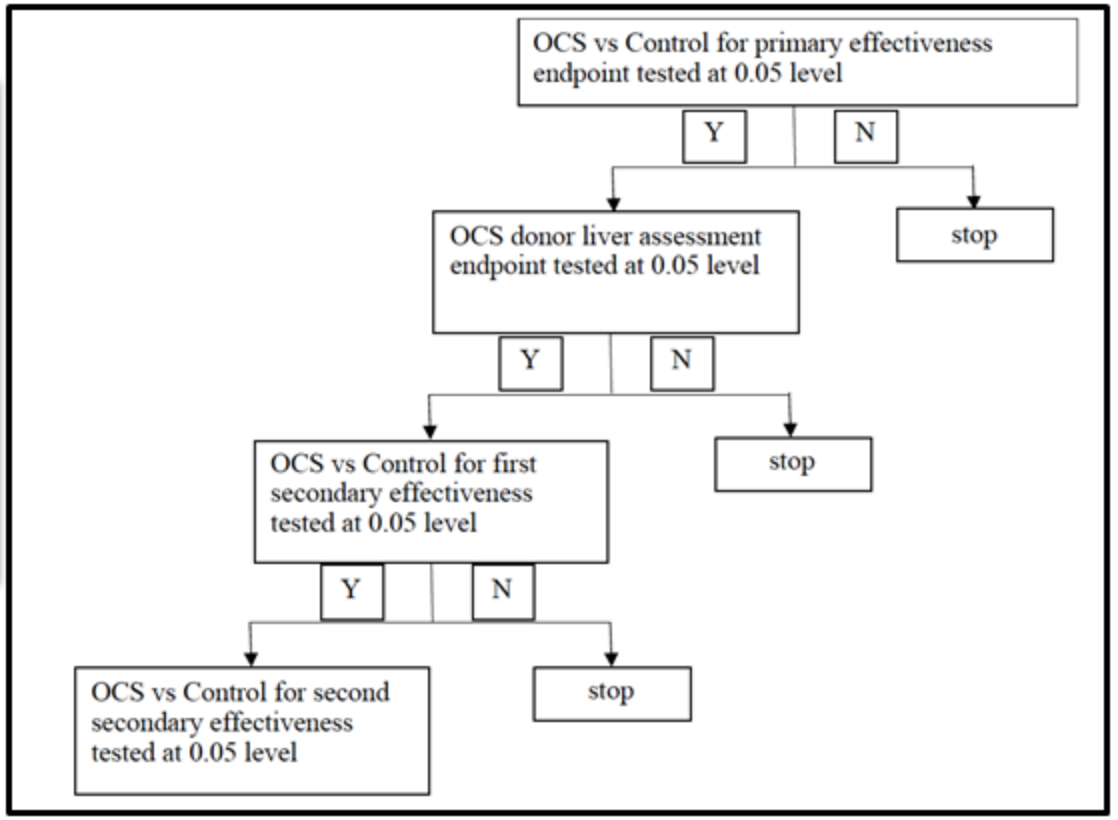
- All Biliary Complications were Diagnosed Based on ERCP or MRCP
- All Biliary Complications were Blindly Reviewed and Adjudicated by the CEC

* Unadjusted p-values

PROTECT Prespecified Appropriate Type-I Error Control

Because fixed sequence testing will be used for the secondary endpoints, no adjustment for the multiplicity of these endpoints needs to be made. The endpoints will be tested in the order listed above. The test for non-inferiority for the first secondary effectiveness endpoint will be performed only if the null hypothesis has been rejected for the OCS donor liver assessment endpoint. The test for non-inferiority for the second secondary effectiveness endpoint will be performed only if the null hypothesis has been rejected in favor of the alternative hypothesis of non-inferiority of the OCS treatment to the Control treatment for the first secondary effectiveness endpoints. Similarly, the test for superiority for the second secondary effectiveness endpoint will be performed only if the null hypothesis of equality has been rejected in favor of superiority of the OCS treatment to the Control treatment for the first secondary effectiveness endpoints (and non-inferiority has been demonstrated for the given secondary effectiveness endpoint). Due to statistical power limitations, it is not expected that non-inferiority will be demonstrated for patient survival at day 30 or at initial hospital discharge.

Page 44 of PROTECT Protocol
Pages 31-32 of PROTECT SAP



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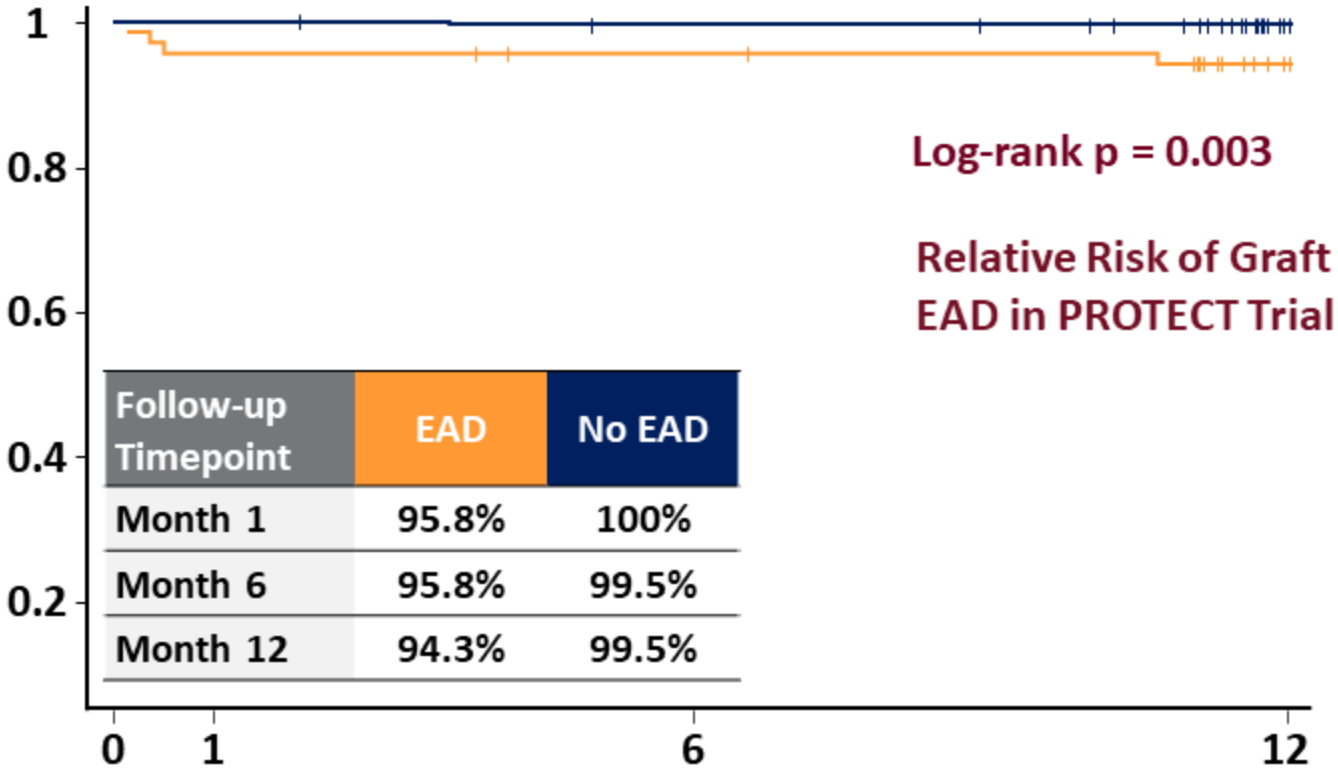
Absence of EAD Associated with Lower Risk of Graft Failure



Log-rank p = 0.003

Relative Risk of Graft Failure for EAD in PROTECT Trial: 11.4

Follow-up Timepoint	EAD	No EAD
Month 1	95.8%	100%
Month 6	95.8%	99.5%
Month 12	94.3%	99.5%

EAD	71	68	66	43
No EAD	220	220	215	166

PP Population

Exclusion Criteria in Olthoff (2010) and PROTECT Trial

Olthoff (2010) Inclusion Criteria

- None

- Patient cohort 2004-5
- 100 consecutive patients at 3 centers
- High incidence of HCV

PROTECT Exclusion Criteria

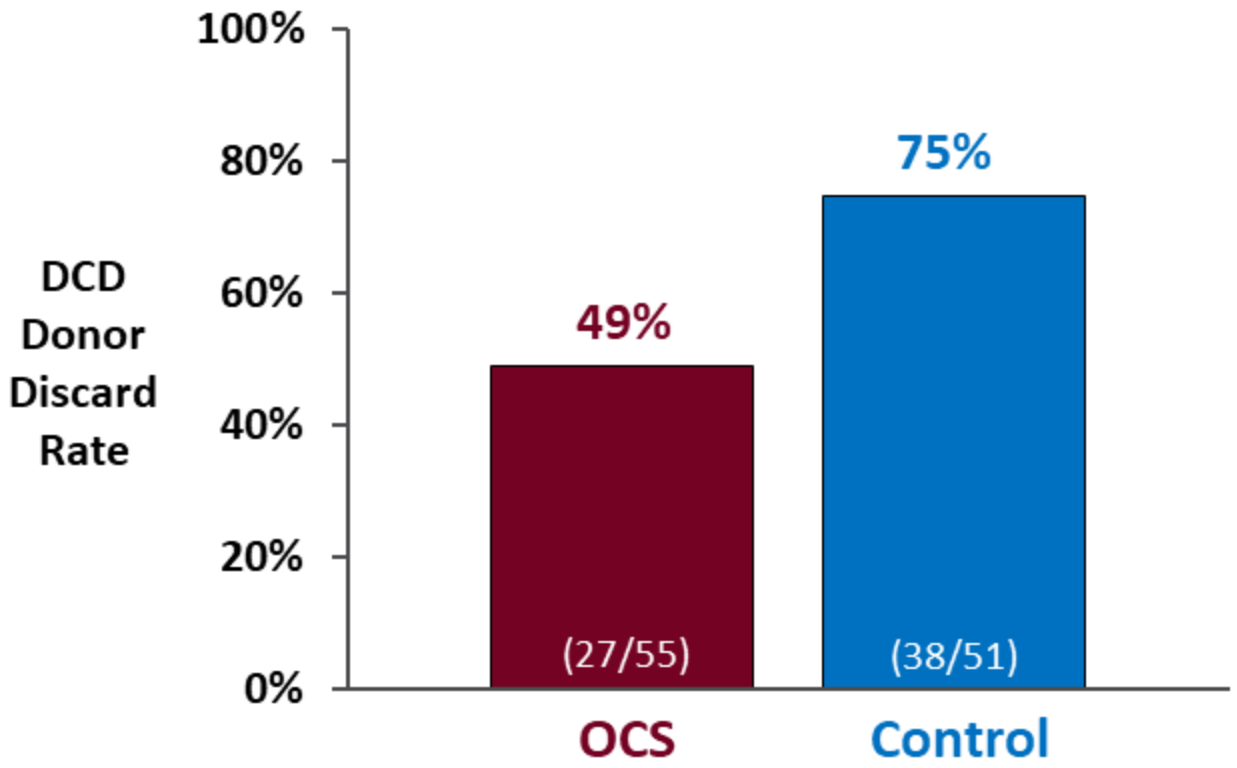
- Acute, fulminant liver failure
- Prior solid organ or bone marrow transplant
- Chronic use of hemodialysis or diagnosis of chronic renal failure
- Multi-organ transplant required
- Ventilator dependent
- Dependent on > 1 IV inotrope to maintain hemodynamics

EAD and AST Used as Surrogate Endpoints in Contemporary Randomized Liver Transplant Trials in Normothermic Machine Perfusion

Publication	Biochemical Endpoints
Ravikumar et al, *Am J Transpl* 2016	▪ Peak AST with 7 days ▪ EAD
Nasralla et al, *Nature 2018*	▪ Peak AST within 7 days (primary) ▪ EAD
Ghinolfi et al, *Liver Transpl* 2019	▪ Peak AST and ALT within 7 days ▪ EAD
Bral et al, *Am J Transpl*, 2017	▪ Peak AST within 7 days ▪ EAD

11 Ongoing Clinical Trials of Machine Perfusion with EAD/Peak AST as a Surrogate Endpoint		
NCT03929523	NCT03456284	NCT04023773
NCT03837197	NCT03930459	NCT03089840
NCT03098043	NCT03376074	NCT02515708
NCT03484455		NCT02775162

DCD Donor Discard Rate



Characteristics of Screened DCD Livers Similar Between Groups

DCD Donor Liver Characteristics	OCS (N=58)	Control (N=51)
Age – mean ± SD	**37 ± 11**	**41 ± 10**
Female	**33%**	**31%**
BMI – mean ± SD	**29 ± 7**	**29 ± 5**
Active Infection	**43%**	**25%**
Abdominal Trauma	**7%**	**4%**
Donor Experienced Cardiac Arrest Prior to Donation	**72%**	**51%**

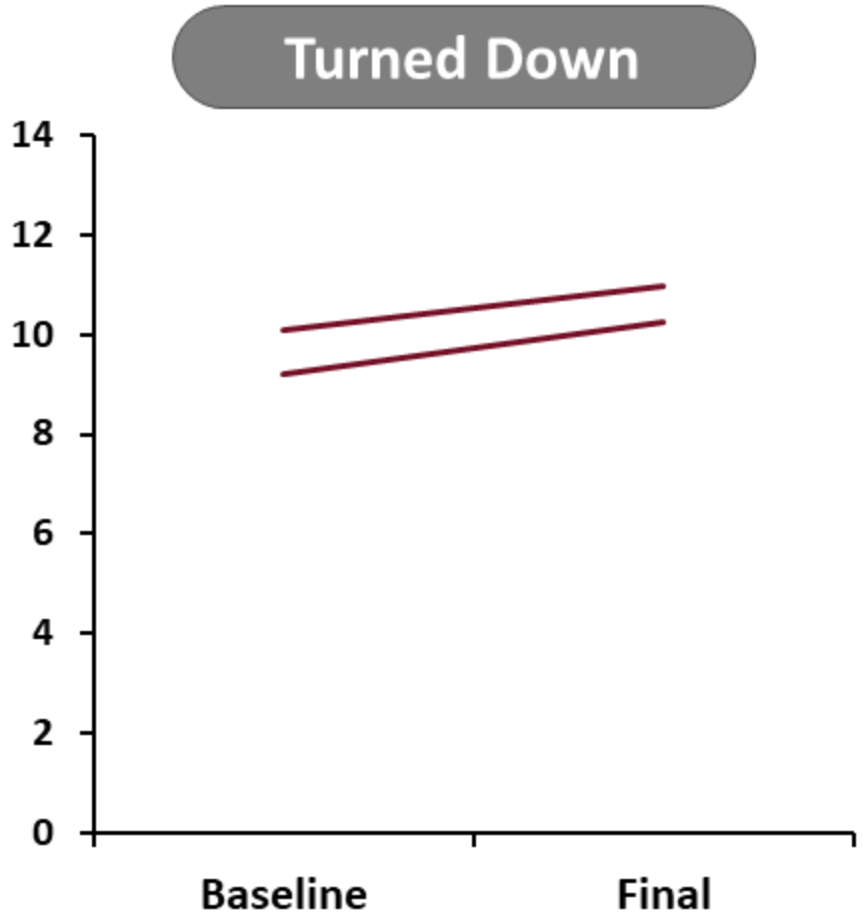
Recipient Demographic and Baseline Characteristics (DCD)

Recipient Baseline Characteristics	OCS (N=28)	Control (N=13)
Age (years), mean ± SD	61 ± 7.8	63 ± 5.1
Male	19 (68%)	7 (54%)
BMI (kg/m^2), mean ± SD	30.2 ± 4.97	33.8 ± 3.73
MELD score, mean ± SD	23.8 ± 5.8	24.3 ± 4.3
History of diabetes	12 (43%)	4 (31%)
History of liver cancer	12 (43%)	6 (46%)
Primary diagnosis		
Cholestatic diseases	2 (7%)	0 (0%)
Chronic hepatitis	5 (18%)	3 (23%)
Alcoholic cirrhosis	12 (43%)	4 (31%)
Primary hepatic tumors	2 (7%)	0 (0%)
Other	7 (35%)	6 (46%)

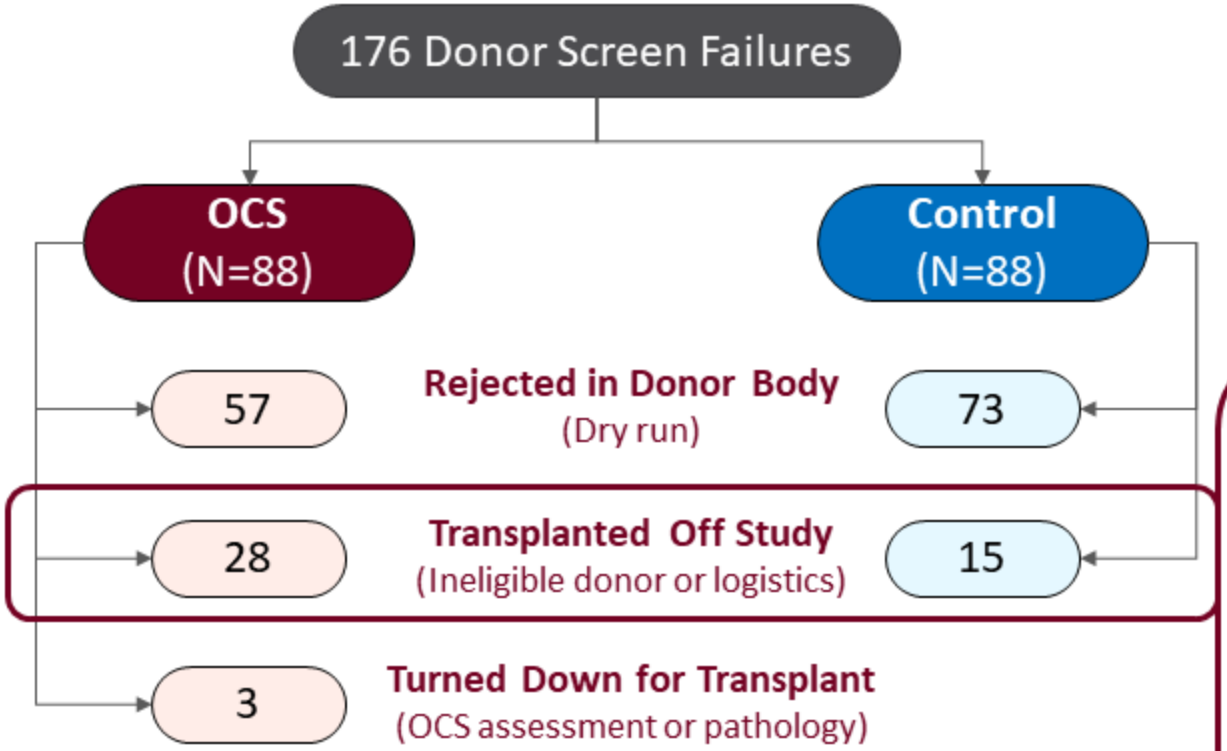
AT Population

Turn-Down Cases Based on Lactate – OCS Perfusion Parameters

OCS PROTECT Trial (Mean ± SD)	Transplanted Liver Allografts (N=152)	Turned Down Liver Allografts (N=2)
Hepatic Artery Pressure (mmHg)	70.6 ± 16.2	82 ± 8.9
Hepatic Artery Flow (L/min)	0.7 ± 0.2	0.8 ± 0.07
Portal Vein Pressure (mmHg)	5.4 ± 2.3	7.8 ± 0.5
Portal Vein Flow (L/min)	1.3 ± 0.1	1.38 ± 0.07
Starting Lactate (mmol/L)	7.2 ± 3.2	9.64 ± 0.63
Ending Lactate (mmol/L)	1.2 ± 1.0	10.62 ± 0.52

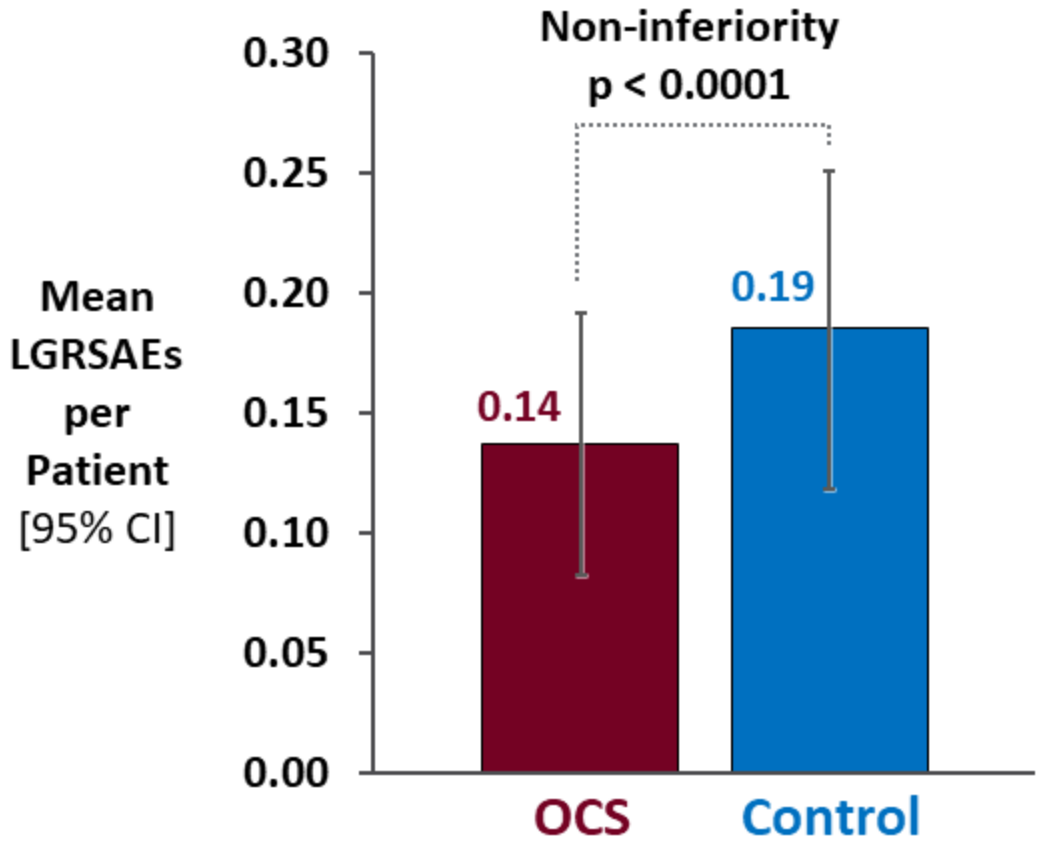


PROTECT Trial – Donor Screen Failures



- **Accessory vessels:** OCS 24 Control 15
- **Logistics** – OCS 4
  - Donor family refused consent
  - Lack of path. Read-out
  - Donor OR time changed
  - PI withdrew the recipient out of trial

Post-Hoc Safety Endpoint Analysis Including All Biliary Complications: OCS Non-Inferior to Control in LGRSAEs



LGRSAE within 30 Days Post Transplant	OCS (N=153)		Control (N=146)	
	Patients	Events	Patients	Events
Any LGRSAE	21 (14%)	25	26 (18%)	30
Non-functioning graft	0	0	0	0
Ischemic biliary complication	0	0	2 (1%)	2
Biliary anastomosis complication	13 (8%)	13	6 (4%)	6
Post-transplant bile leak	4 (2%)	4	11 (8%)	11
Vascular complication	7 (5%)	8	9 (6%)	11
Liver allograft infection	0	0	0	0

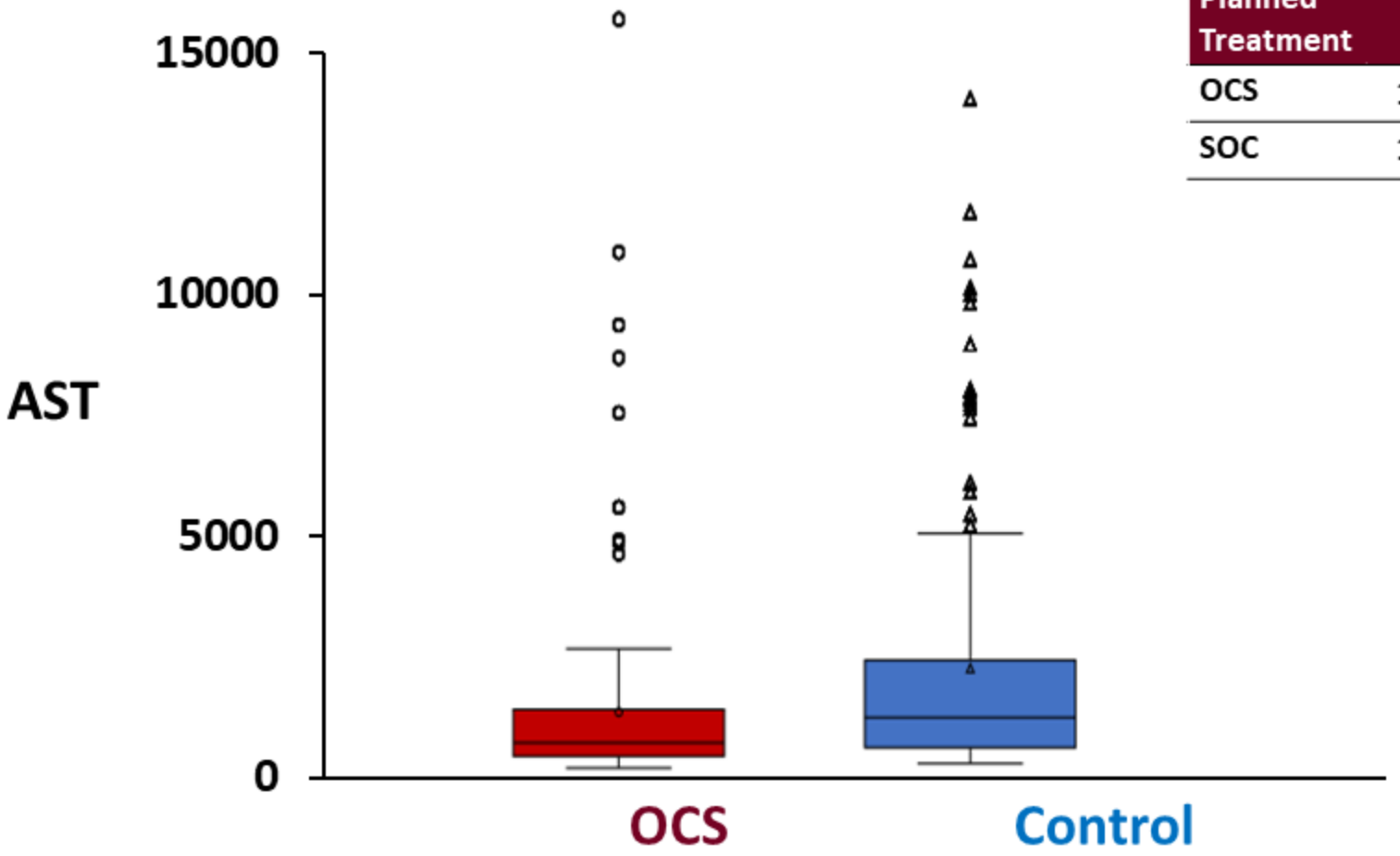
AT Population. Non-inferiority margin = 1.0

Post-Hoc Safety Analyses Requested by the FDA

AE within 30 Days Post Transplant	OCS (N=153)	Control (N=146)
Anastomotic biliary complication	13 (8.5%)	6 (4.1%)
Post-transplant bile leak	4 (2.6%)	11 (7.5%)

AT Population

Analysis Variable : AST for Entire PROTECT Trial Population



Planned Treatment	N	Mean	STD	Min	Max
OCS	151	1315.46	2017.71	150	15723.00
SOC	145	2228.50	2683.30	245	14072.00