TransMedics®
Organ Care System™ (OCS) Liver System

FDA Presentation for the July 14, 2021 Gastroenterology and Urology Devices Advisory Panel Meeting

Bridget Wildt, PhD
Materials Engineer/Lead Reviewer

Center for Devices and Radiological Health (CDRH)

FDA Review Team

Clinical	Arturo Hernandez, MD, FACS
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Post-approval Study	Lauren J. Min, PhD
GMP	Jordana Gilbert Honick, PhD
BIMO	Cynthia Bushee

FDA Presentations

Bridget Wildt, PhD

- Indications for Use, Device Description, Summary of Non-Clinical Information, OCS Principle of Operation, Clinical/Regulatory History, Panel Discussion Questions

Diane Cordray, VMD

- Ex Vivo Animal Studies conducted for IDE approval and device design changes

Min Min, PhD

- Trial Design, Trial Course, Donor Liver & Recipient Disposition

Arturo Hernandez, MD, FACS

- Clinical and Benefit/Risk Analysis

Lauren J. Min, PhD

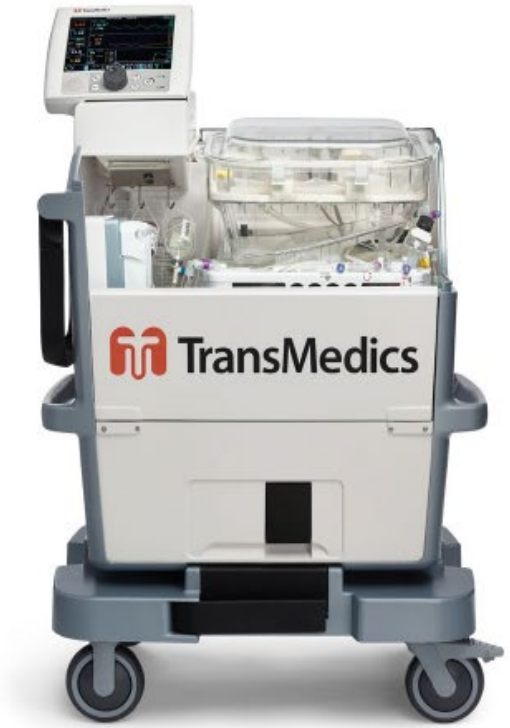
- Post Approval Considerations for the Panel Discussion

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 liver allografts from donors after circulatory death (DCD) ≤ 55 years old in a near-physiologic, normothermic and functioning state intended for a potential transplant recipient."

Device Description

- Console
  - Wireless Monitor
- Liver Perfusion Set
  - Perfusion solution is prepared by Hospital pharmacy
- Liver Bile Salt

OCS Liver Console	OCS Liver Perfusion Set	OCS Liver Bile Salts
		

Non-Clinical Testing

- System Operation & Component Testing
- Mechanical Design Verification
- Shock, Vibrational, and Altitude Testing
- Electrical Safety
- Electromagnetic Compatibility
- Sterilization/Shelf-life
- Packaging/Packaging Integrity
- Biocompatibility
- Battery Testing
- Software/Cybersecurity

OCS Principle of Operation

1. Liver accepted & flushed
2. OCS assembled & primed
3. Hepatic Artery (HA), Portal Vein (PV), Inferior Vena Cava (IVC) and common bile duct are cannulated
4. Perfusion clock starts
5. Pump flow rates adjusted*
6. Sample → Lactate, pH and Arterial Blood Gas (ABG)
7. Stable parameters & bile production
8. ABG & lactate every hour until lactate was trending down, then collected every 2 hours or after an adjustment in HA Flow or HA Pressure
9. Liver enzymes before cooling for reimplantation
10. Liver assessed at recipient site (stable or trending down lactate levels and bile production rate)

* For OCS Machine Parameter Ranges, see Table 6 from FDA Executive Summary (page 18).

Discussion Question 8a

Clinical History – PROTECT Trial

- First in Human, staged study: Part A (n=20) & Part B (n=280)
- OCS randomized with static, cold storage Control
- Included both Donor after Brain Death (DBD) & Donor after Circulatory Death (DCD) ≤ 55 years old liver allografts
- January 2016 – October 2019: 6, 12-month follow-up complete, 41% completed 24-month follow-up
- Continued Access Protocol CAP (n=74) November 2019 - January 2021, follow-up on going.

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."*

FDA's Study Design Considerations for PROTECT

- Eliminate early randomization and randomize after livers were deemed acceptable for the trial.
- Capture all biliary complications as Serious Adverse events in the safety endpoint.
- Include secondary endpoints to evaluate the correlation between OCS machine parameters and clinical outcomes to support assessment of livers on the OCS.
- Clearly designate and document all screening failures and dry runs. Provide follow-up outcomes and reports on both intended recipient and indexed organ.
- Pre-specify an appropriate method for multiplicity adjustment to control the study overall type I error.
- Consistency in primary outcome using PP, mITT, ITT when testing non-inferiority and superiority.
- Include 1-year recipient and graft survival as secondary effectiveness endpoints. Include incidence of liver graft related serious adverse events within 6-months as safety endpoints.

Ex Vivo Animal Studies

Diane Cordray, VMD
Veterinary Medical Officer

Center for Devices and Radiological Health (CDRH)

Phase 3 *Ex Vivo* Safety Study- Supported Initiation of the PROTECT Trial

FDA

Design

- N=3 each *ex vivo* porcine livers, OCS and SOC
- 12 hours OCS/SOC, 24 hours *ex vivo* simulated transplant on a reperfusion circuit

Results

- Stable perfusion parameters
- Liver enzymes, lactate, histology support improvement hepatic parenchyma and metabolic status in OCS vs. SOC livers
- Bile production equivalent between OCS and SOC livers

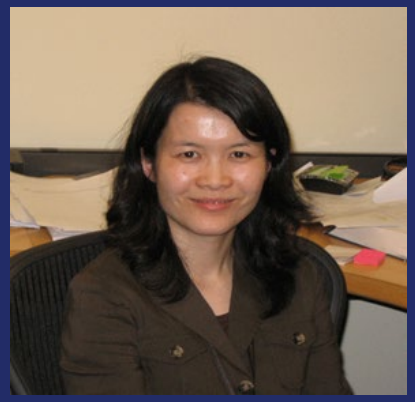
Other *Ex Vivo* Porcine Liver Studies

- Relied on to validate OCS design changes
- Early Developmental Studies (n=33 OCS)
- PMA Study to validate software/device updates (n=2 OCS)
  - OCS met pre-defined operational acceptance criteria
  - Not intended to generate safety data
- "Phase 2 Expanded" – (n=6 OCS, n=6 SOC)
  - Evaluated OCS and SOC followed by simulated transplant
  - Supported OCS maintains liver function and histologic integrity
  - Limits include minimal liver enzymes, histopathology data

Ex Vivo Porcine Testing Provided Safety Data for PROTECT Trial

- Early and Current PMA *ex vivo* studies - Device development and validation of design/software updates
- No *in vivo* transplant animal testing conducted
- Phase 3 *ex vivo* study - Provided safety data for approval of the PROTECT trial
  - Improved liver enzyme, lactate assessments, OCS vs. SOC
  - Bile production equivalent in OCS and SOC livers
  - Histology improved with OCS vs. SOC

Trial Design, Trial Course, Donor Liver & Recipient Disposition



Min Min, PhD
Statistical Reviewer

Center for Devices and Radiological Health (CDRH)

PROTECT

- Prospective, multicenter, open-label,1:1 randomized, controlled trial
- OCS-Liver System (OCS: test group) vs. standard of care cold storage (control group)
- Donors after brain death (DBD) and donors after circulatory death (DCD) ≤55 yrs donor livers
- Planned Sample Size: 300 recipients
- Sites: 20 US Sites
- The original PMA was submitted in June 2020

Primary Effectiveness Endpoint

Incidence of Early liver Allograft Dysfunction (EAD) Within the First 7 Postoperative Days:

- Defined as the presence of one or more of the following criteria:
  - ❑ 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 or
  - ❑ Primary non-functioning graft within the first 7 days
- Non-inferiority test hypothesis (superiority was planned to be tested if non-inferiority is met)

  H0: $\pi_{OCS} \geq \pi_{Control} + \delta$; H1: $\pi_{OCS} < \pi_{Control} + \delta$

  where δ = 0.075 is the non-inferiority margin, π_{OCS} and $\pi_{Control}$ are the respective EAD incidence rates
- Pre-Specified Statistical Analysis
  - Normal approximation test with one-sided alpha = 0.05

#1 Secondary Effectiveness Endpoint

OCS Donor Liver Assessment:

- Defined as the proportion of livers on which measurements of all of the following during perfusion were available on OCS device before transplant:
  - ❑ Lactate level (every two hours+ 20 mins. of time window)
  - ❑ Average bile production rate (based on total bile production volume and duration of OCS perfusion)
  - ❑ Hepatic Artery Pressure (continuously averaged every 30 minutes)
  - ❑ Portal Vein Pressure (continuously averaged every 30 minutes)

- Comparison with a performance goal

  H0: $\pi_{OCS} \leq 0.85$; H1: $\pi_{OCS} > 0.85$

- Pre-Specified Statistical Analysis
  - Exact test with one-sided alpha = 0.05

#2 and #3 Secondary Effectiveness Endpoints

#2: Survival at Day 30 Post Transplantation

#3: Survival at Initial Hospital Discharge Post Liver Transplantation

- Non-inferiority test hypothesis (superiority was planned to be tested if non-inferiority is met)

  H0: $\pi_{OCS} \leq \pi_{Control} - \delta$; H1: $\pi_{OCS} > \pi_{Control} - \delta$

  where $\delta = 0.075$ is the non-inferiority margin, π_{OCS} and $\pi_{Control}$ are proportions of recipient surviving to Day 30 post transplantation (#2) or at Initial Hospital Discharge Post Liver Transplantation (#3)

- Pre-Specified Statistical Analysis
  - Normal approximation test with one-sided alpha = 0.05

Safety Endpoint

Frequency of Liver Graft-Related Serious Adverse Events (LGRSAEs) up to 30 days following transplantation

- Non-inferiority test hypothesis (superiority was planned to be tested if non-inferiority is met)

  H0: $\mu_{OCS} \geq \mu_{Control} + \delta$; H1: $\mu_{OCS} < \mu_{Control} + \delta$

  where δ=1.0 is the non-inferiority margin, μ_{OCS} and $\mu_{Control}$ are the respective true mean numbers of liver graft-related SAEs up to the 30-day follow-up after transplantation per recipient

- Pre-specified Statistical Analysis
  - Two sample t-test with one-sided alpha = 0.05

Additional Endpoints / Exploratory Analyses

FDA recommended secondary effectiveness endpoints (2015/2016 IDE):

- 6- and 12-months survival post-transplantation
- 6- and 12-months graft survival post-transplantation

Sponsor's additional endpoints:

- Evidence of ischemic biliary complications through 6- and 12-months post-liver transplant
- Total ischemic and cross-clamp (out of body) times
- Length of ICU, hospital stay post-liver transplantation
- Recipient survival in DCD liver population
- EAD vs. no EAD: graft survival and pathology scoring, etc.

Multiplicity Adjustment Procedure

When a trial design involves multiple endpoints and/or multiple hypothesis tests, one way to avoid inflation of overall false positive rate (controlling overall trial-wise type 1 error) is to pre-specify a unique testing sequence.

PROTECT trial had

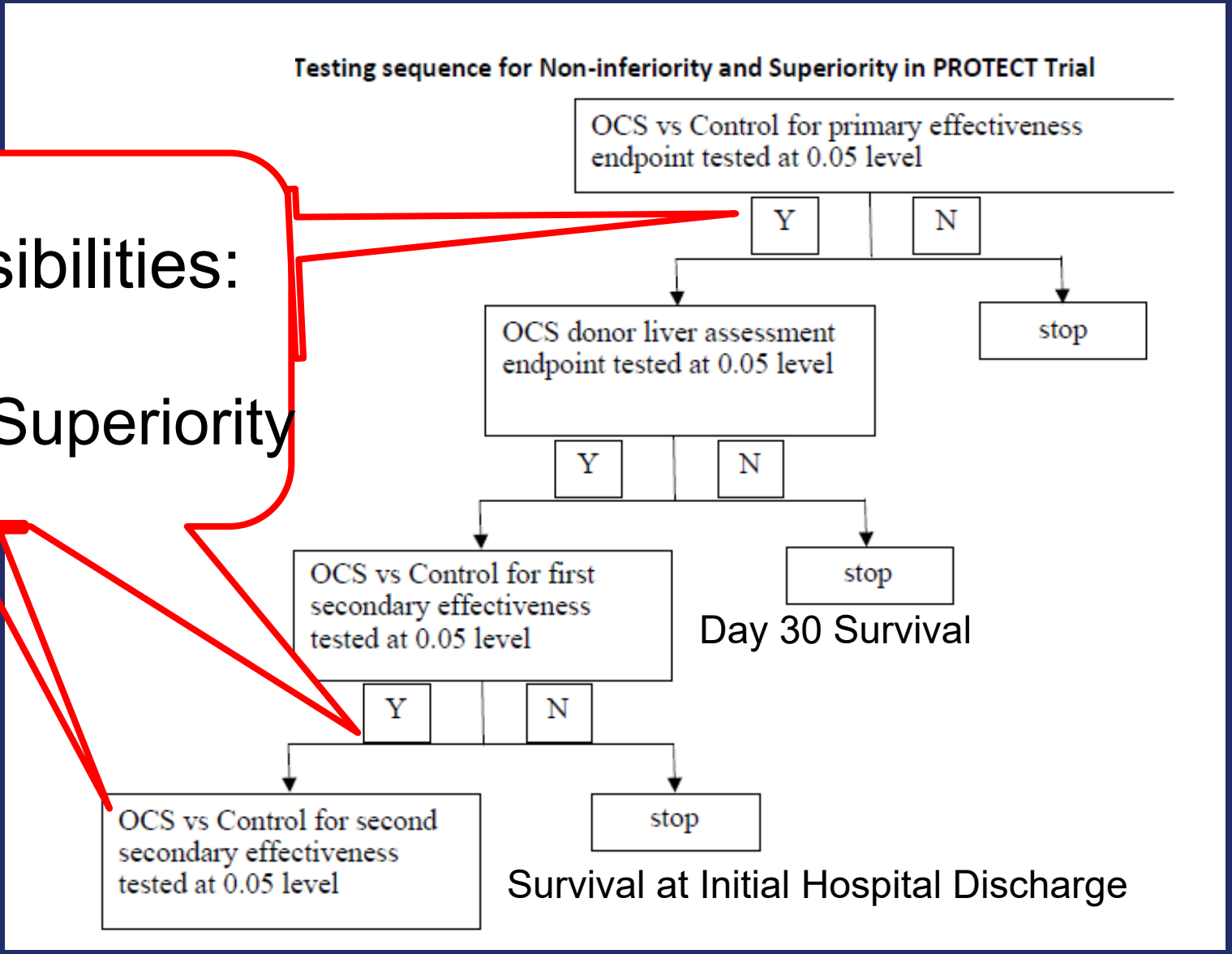
- One primary and three secondary endpoints as well as a safety endpoint
- non-inferiority and superiority testing for primary and 2 secondary endpoints as well as the safety endpoint

Statistical conclusions cannot be drawn based on p-values if they come from unadjusted or inappropriately adjusted test procedures, exploratory analyses, or post hoc analyses.

Sponsor's Proposed Testing Sequence

Two Possibilities:

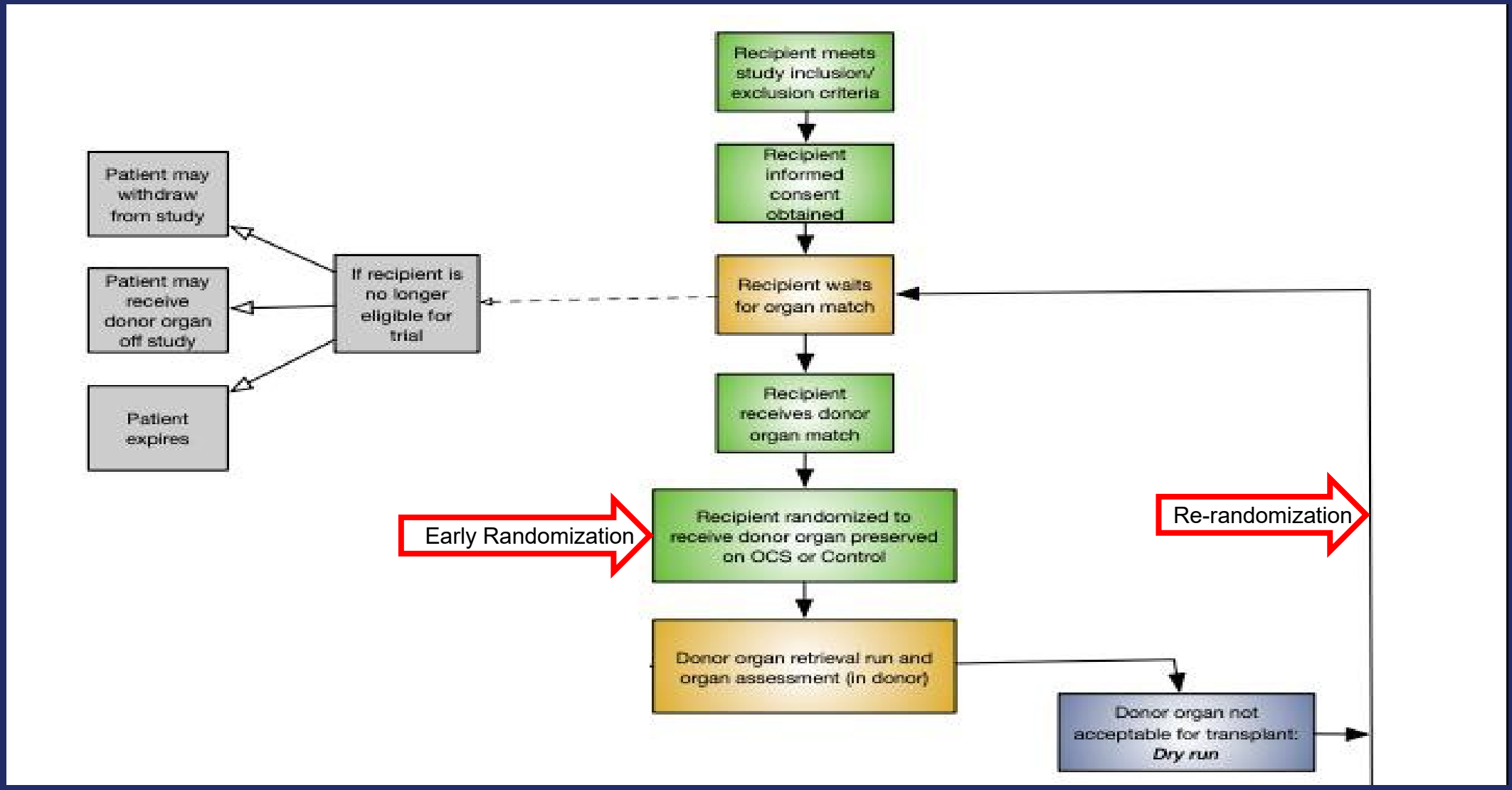
- NI, or
- NI and Superiority



The safety endpoint was not included in the testing sequence

Statistical inferences for the safety and secondary endpoints should be interpreted with caution.

PROTECT Trial Course



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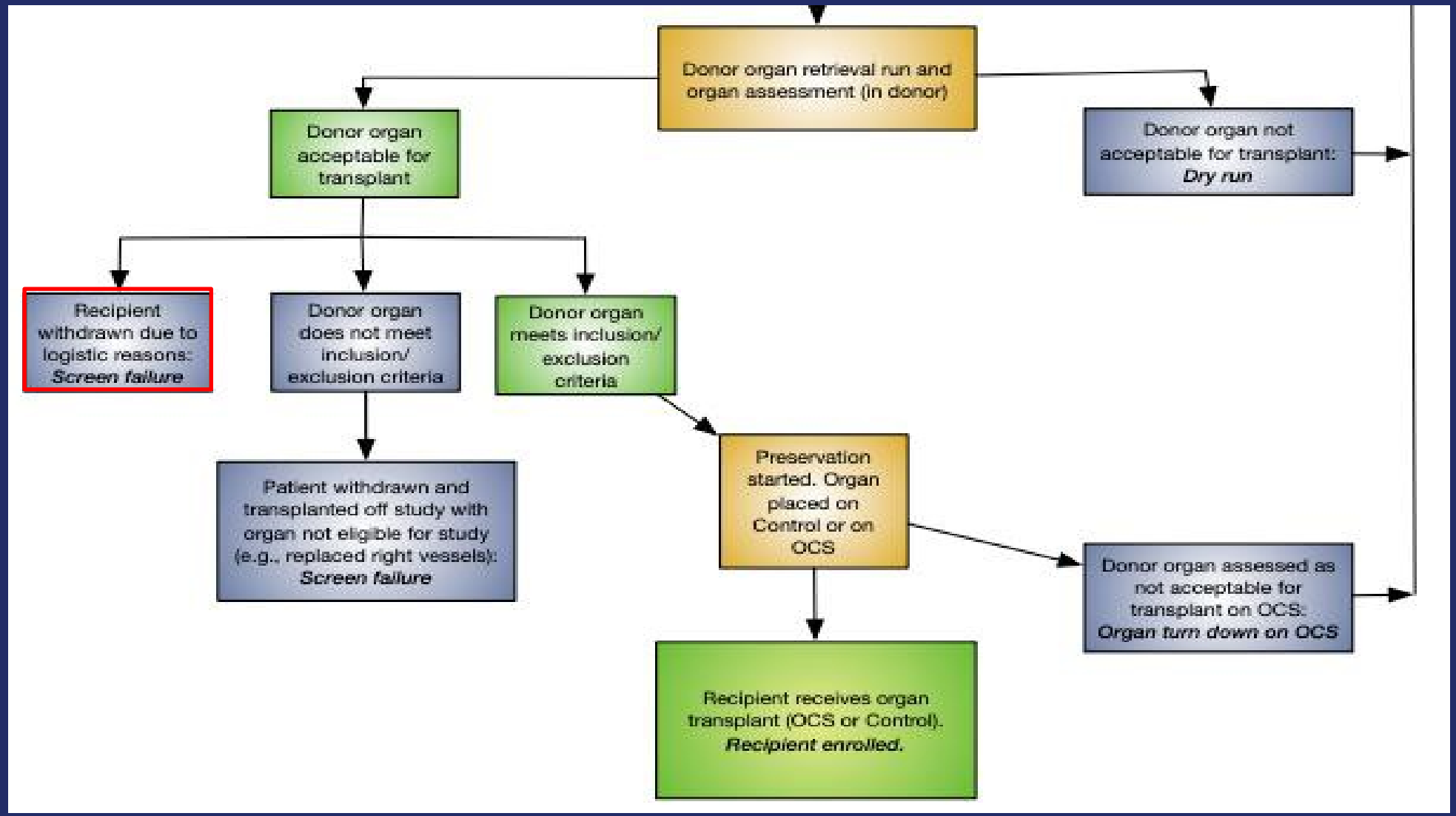

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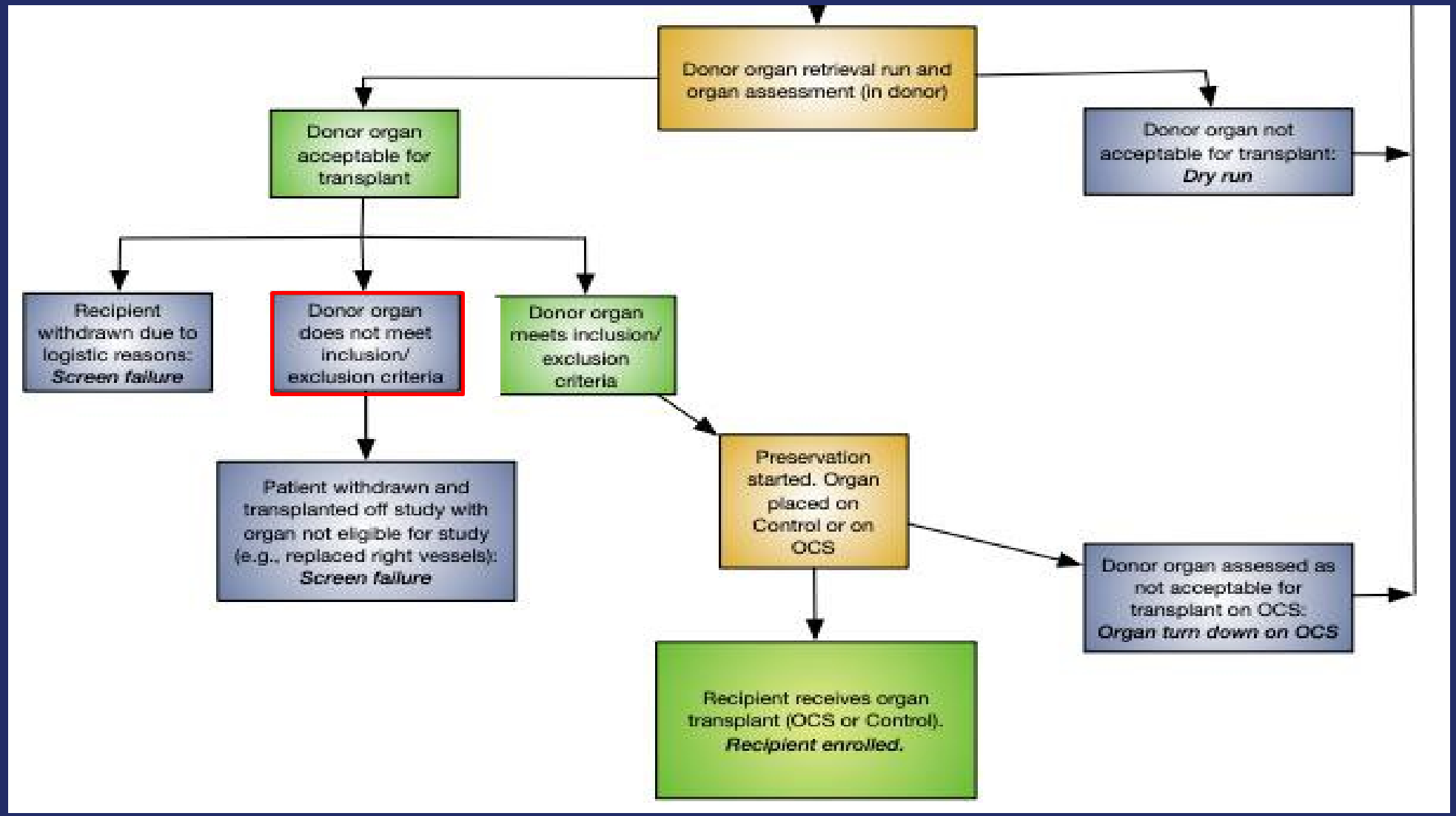

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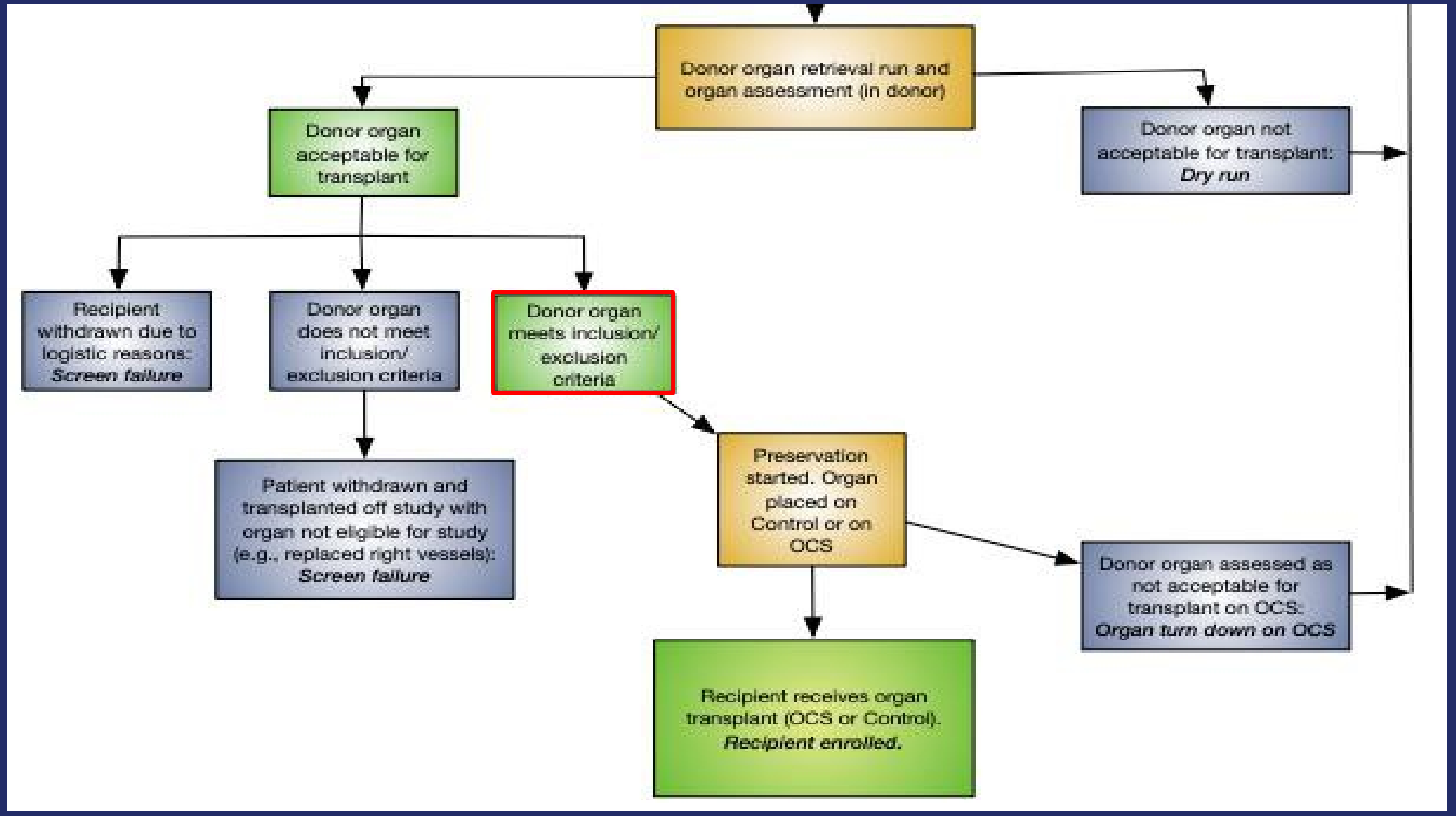

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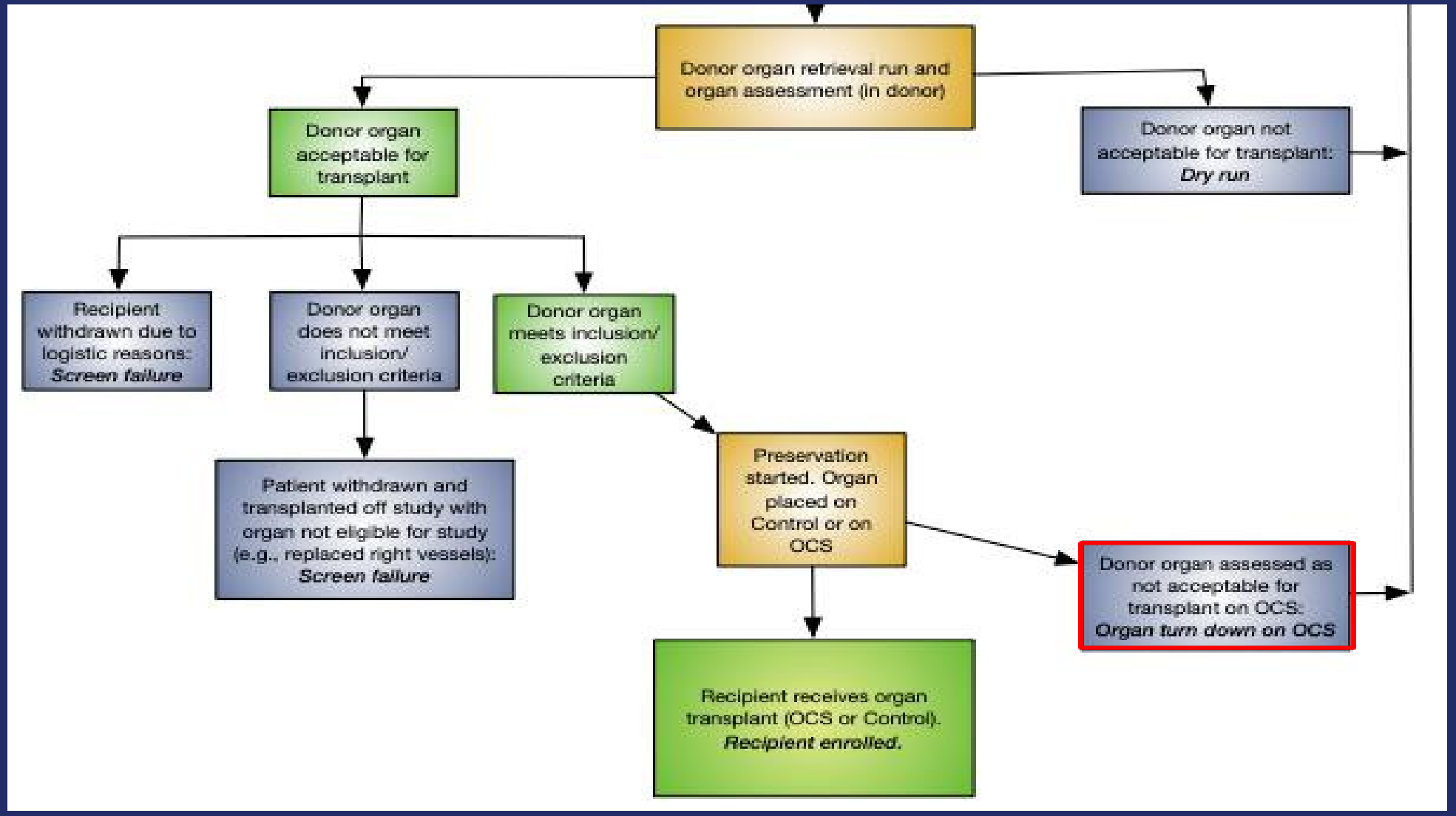

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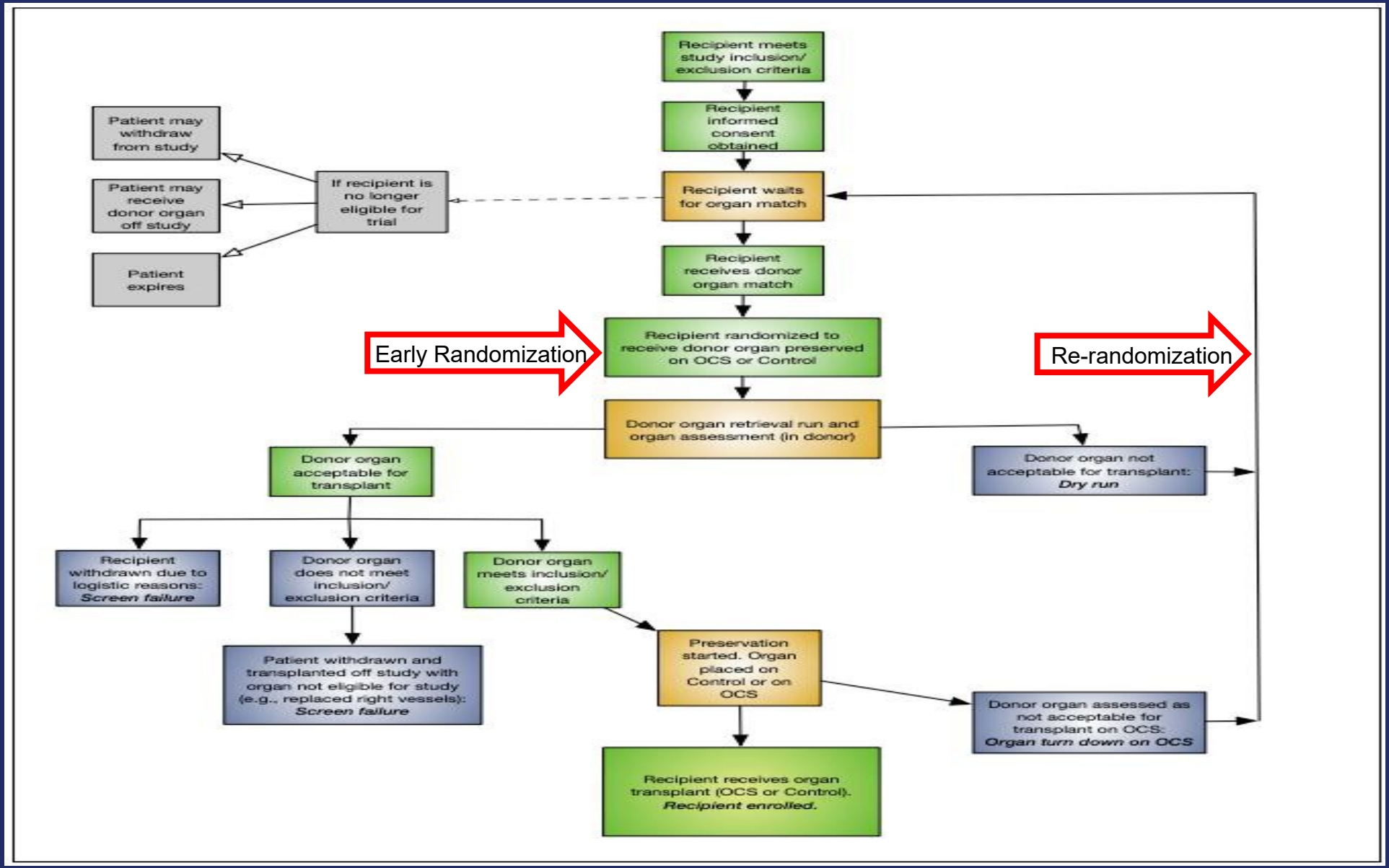


Early Randomization and Re-randomization

"Early randomization": randomization took place when the donor liver was matched to a Waitlist (WL) consented recipient, before final assessment of the donor liver.

Re-randomization: if the matched donor liver was not acceptable for transplant, the recipient who was not transplanted was put back on the waiting list for another donor liver match and was treated as a new recipient. The recipient would be re-randomized if matched again.

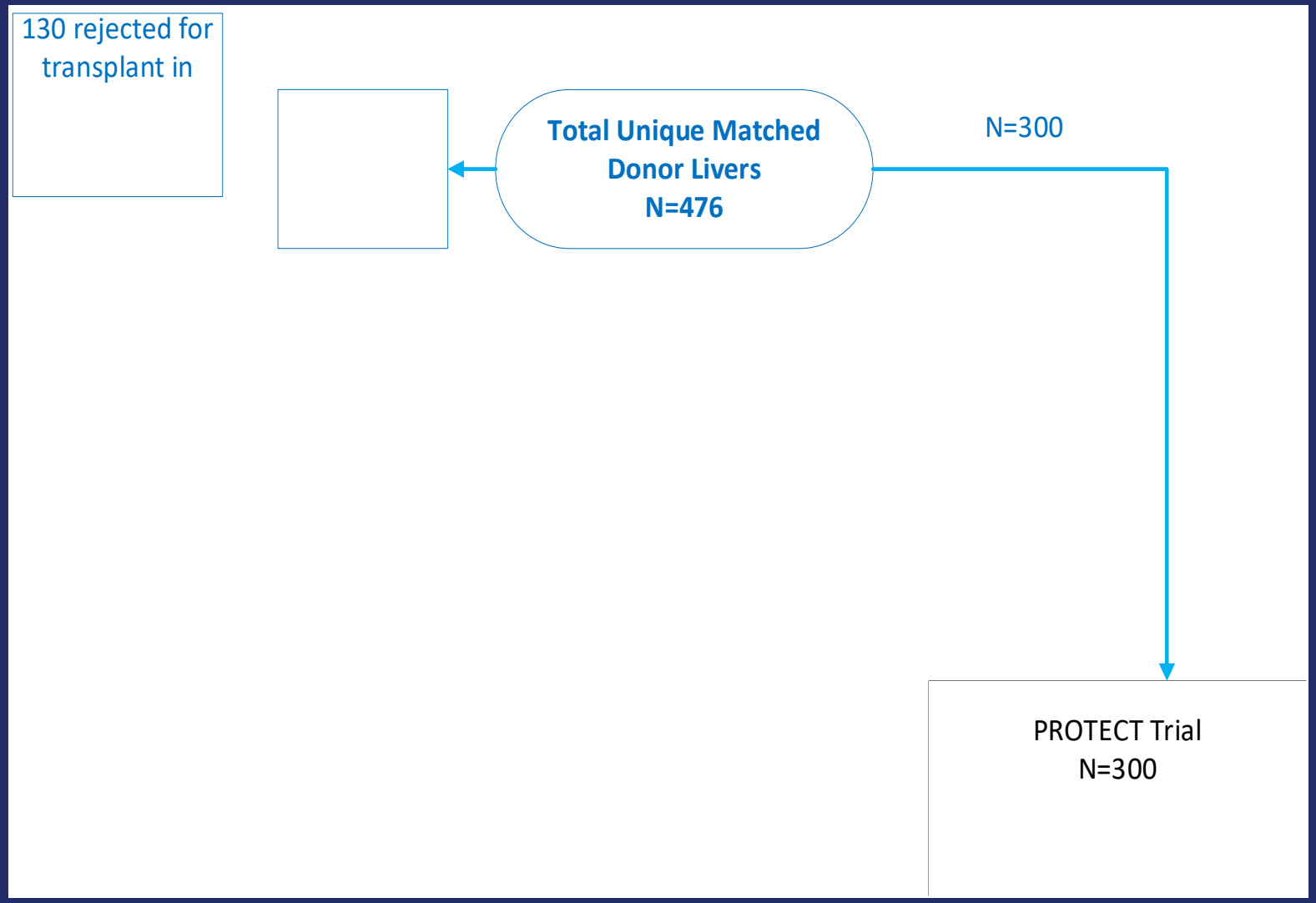
Early randomization and Re-randomization could increase the potential for bias and the complexities in data interpretation.

Donor Liver Disposition

PROTECT Trial
N=300

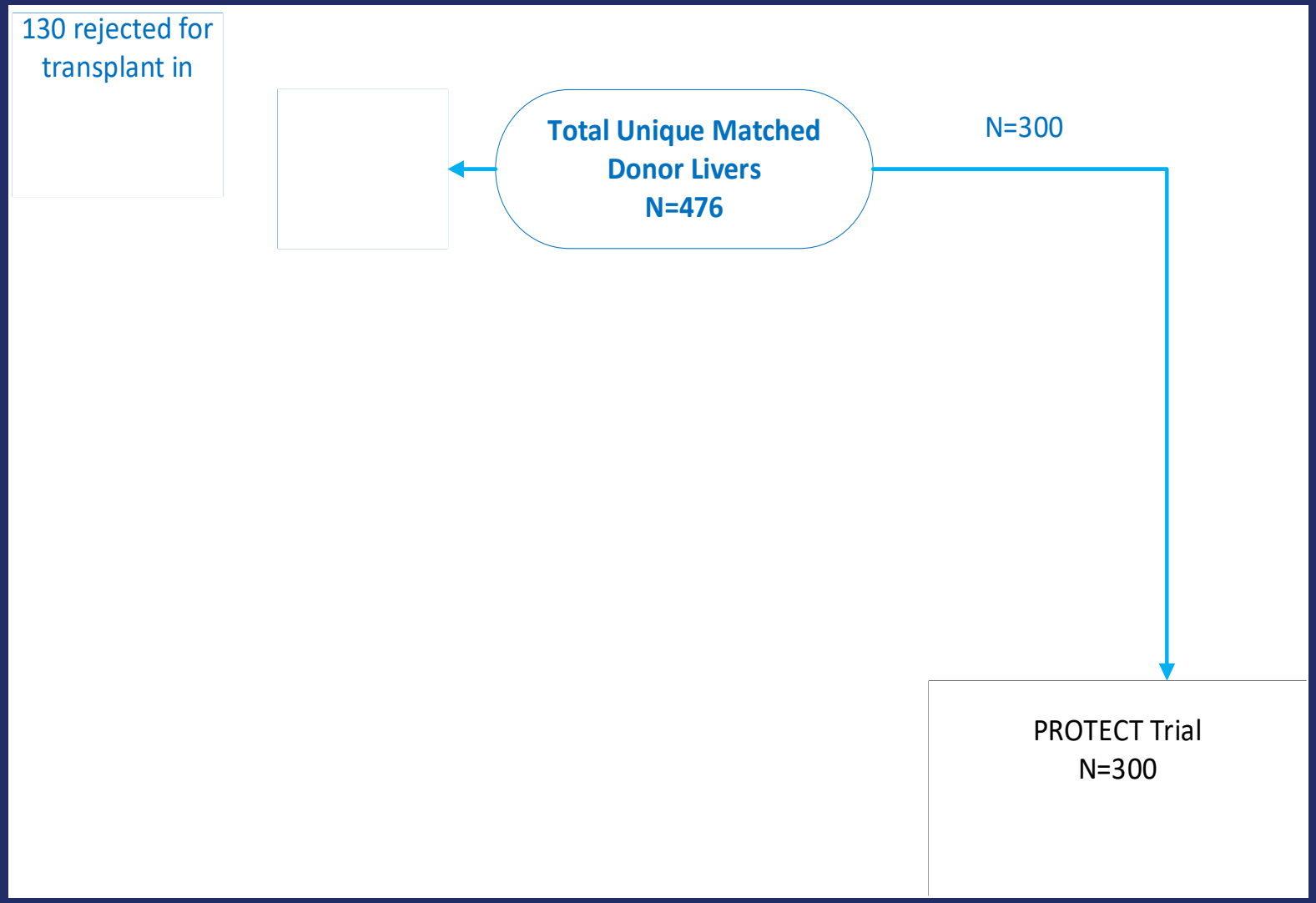
Discussion Question 5a

Donor Liver Disposition



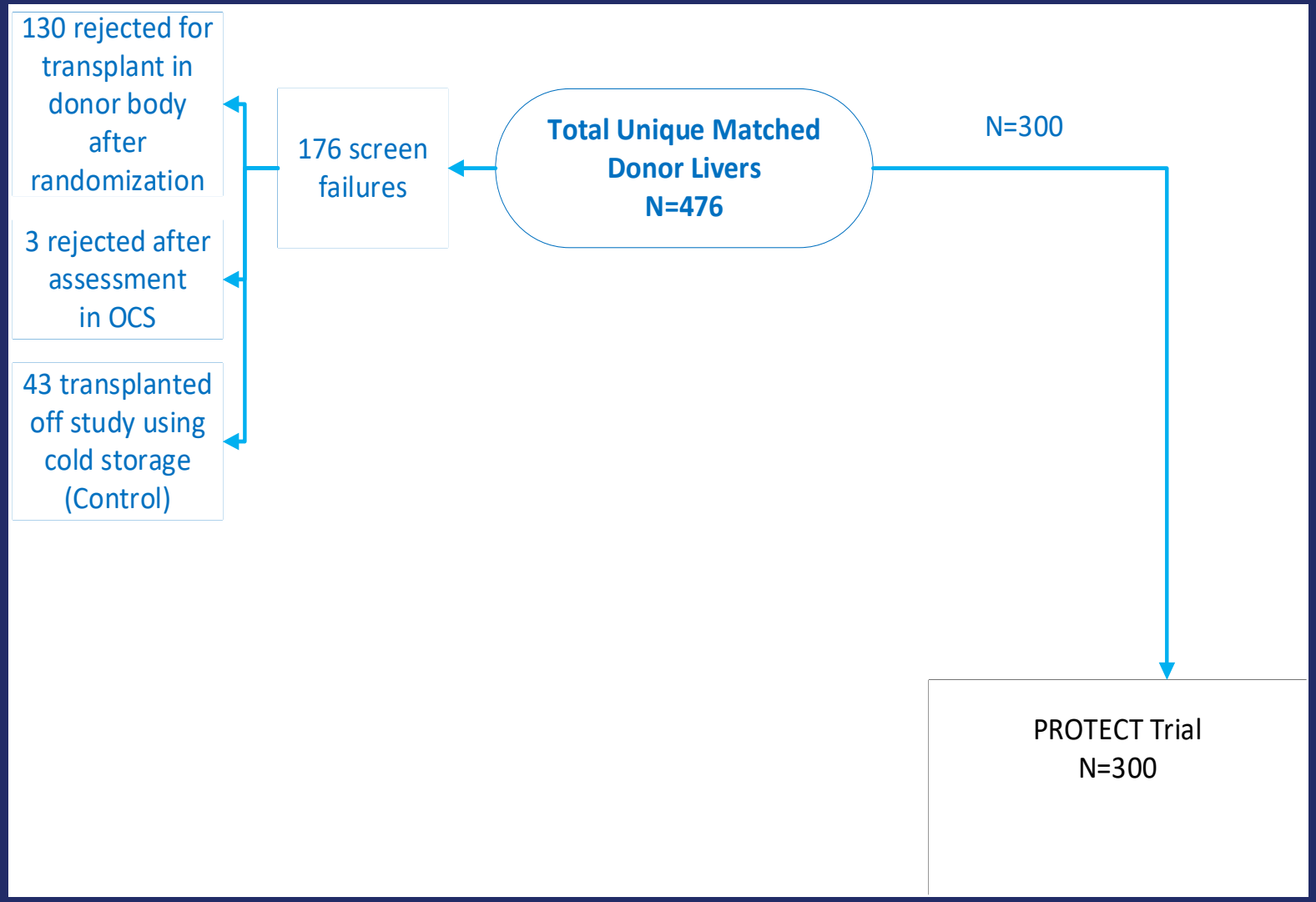
Discussion Question 5a

Donor Liver Disposition



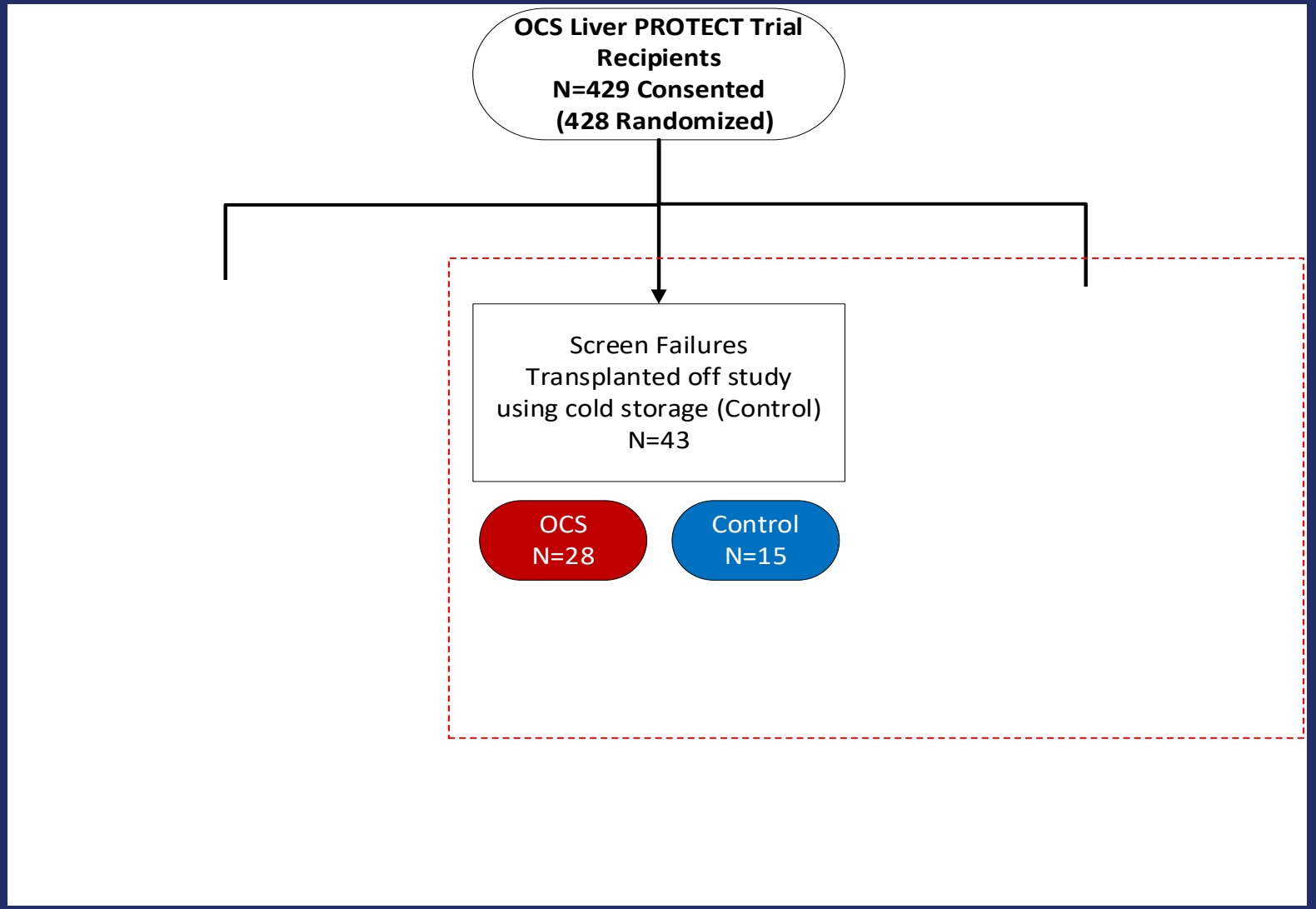
Discussion Question 5a

Donor Liver Disposition



Discussion Question 5a

Recipient Disposition



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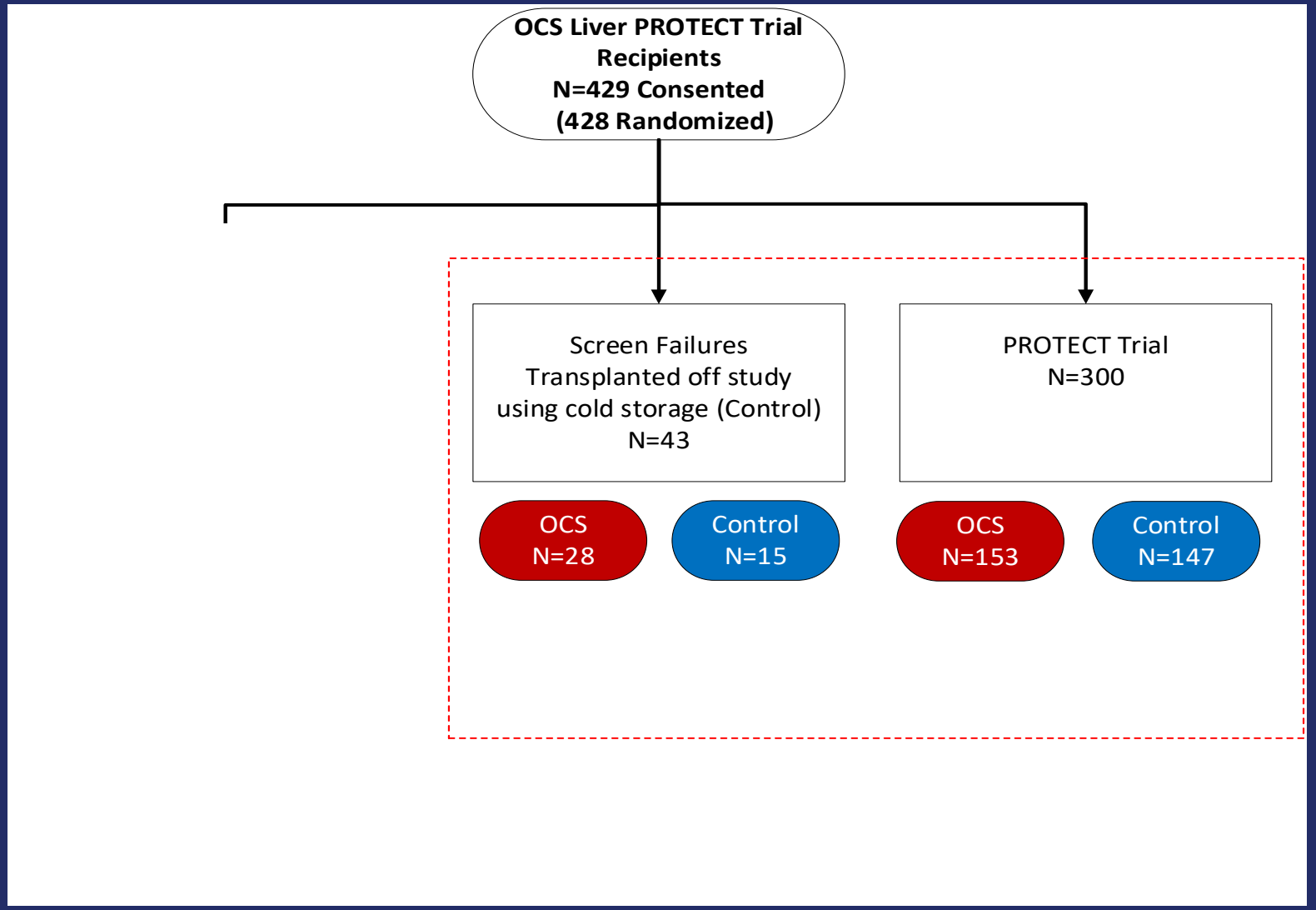

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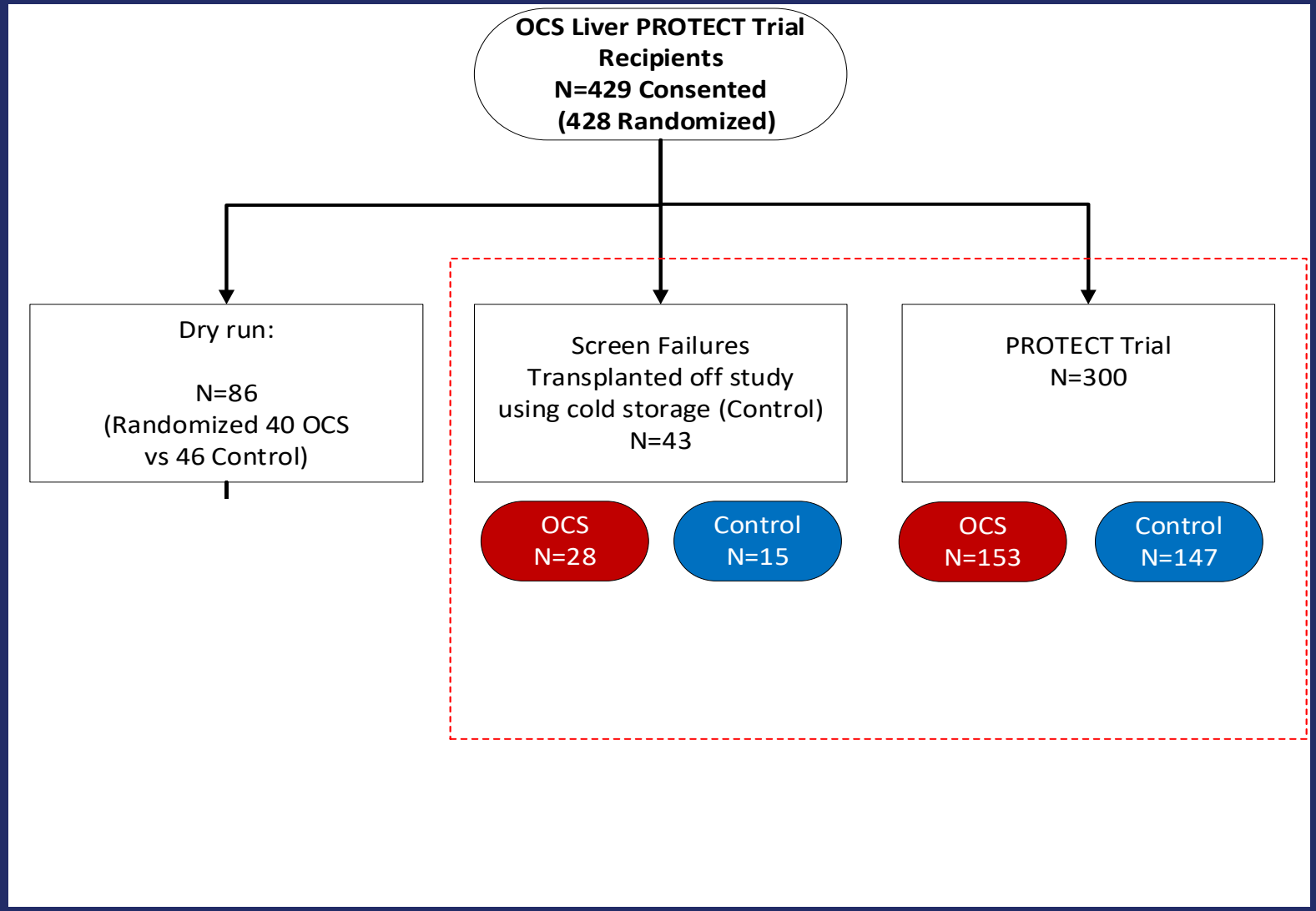

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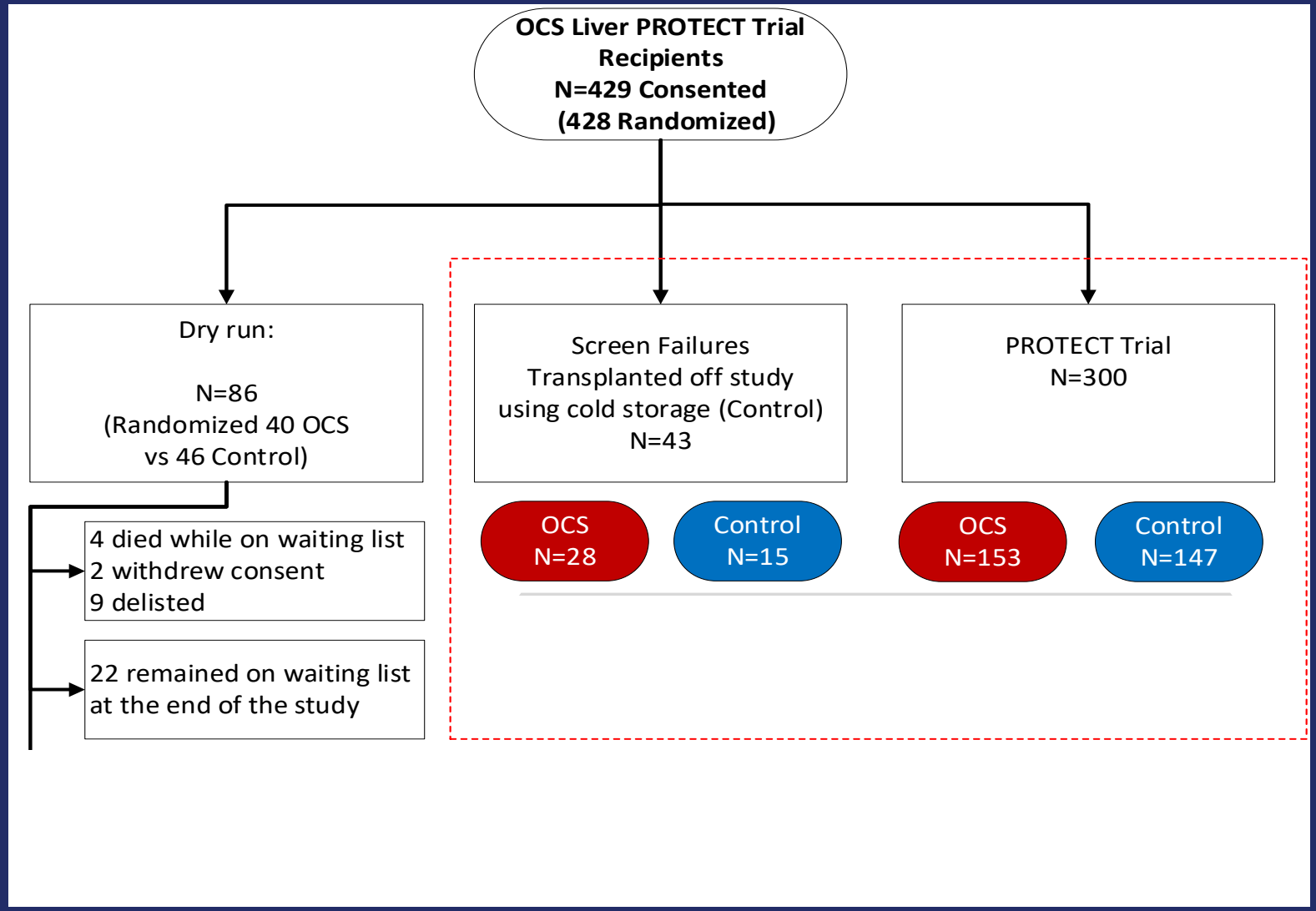

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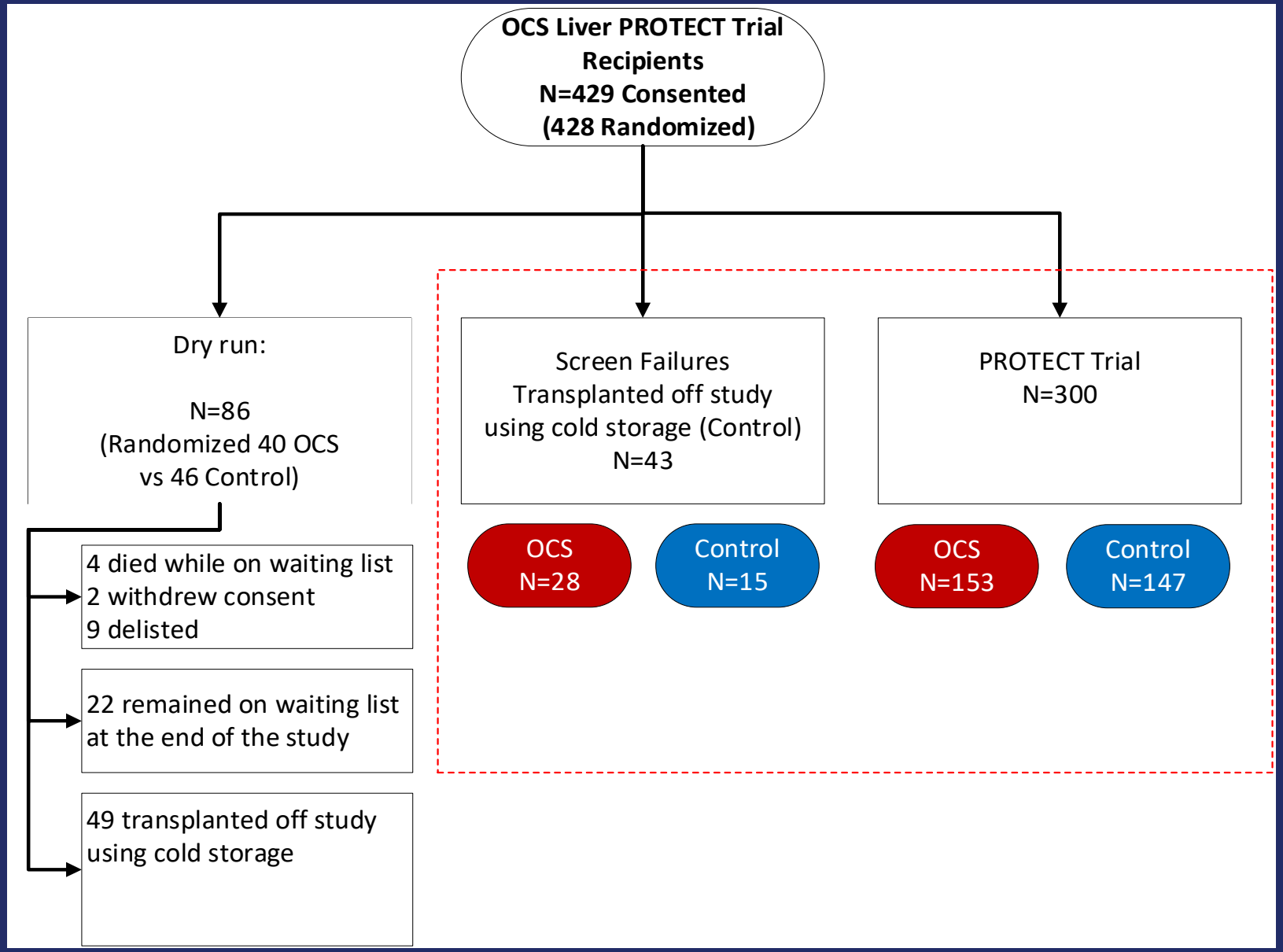
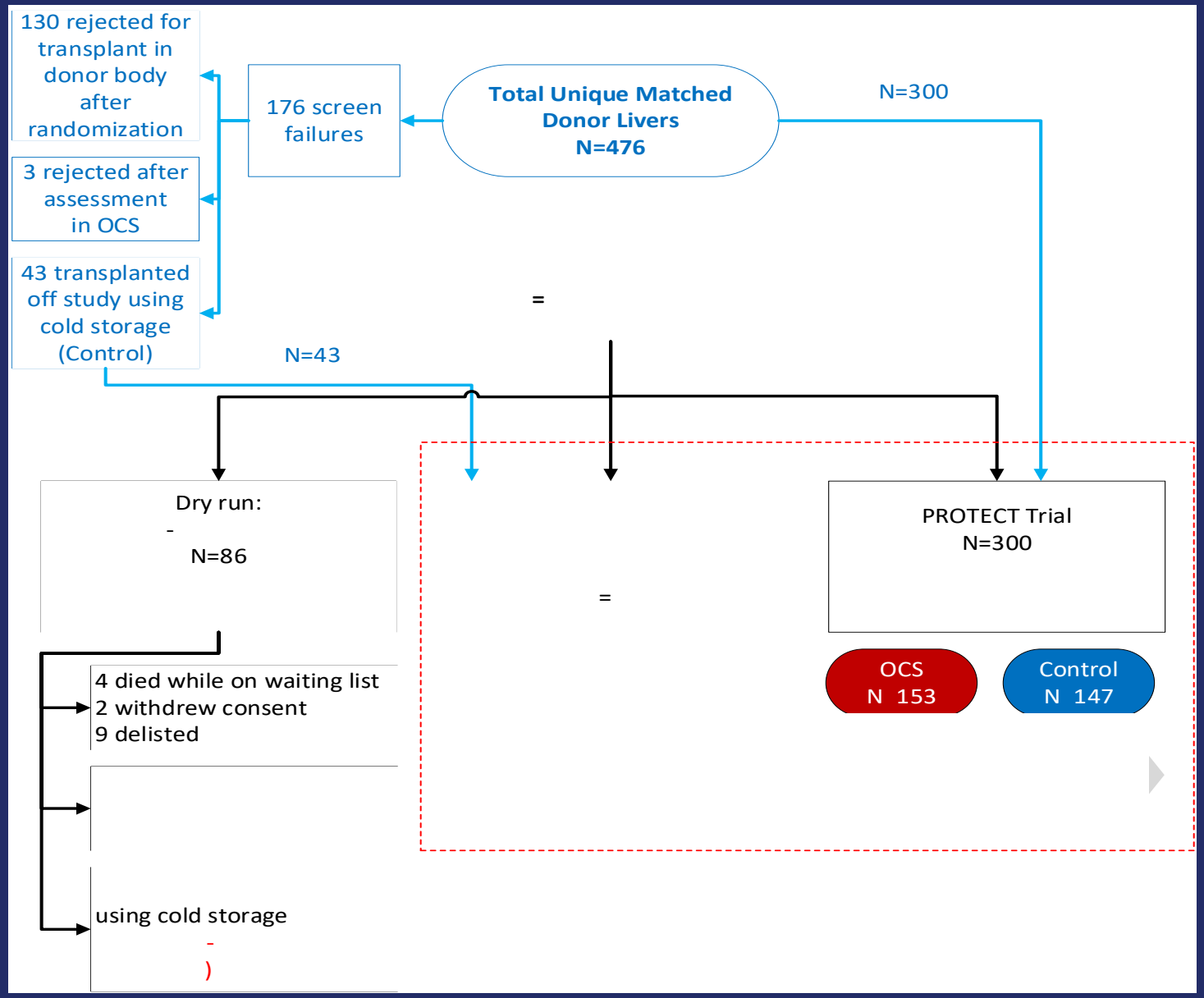


Donor Liver and Recipient Disposition



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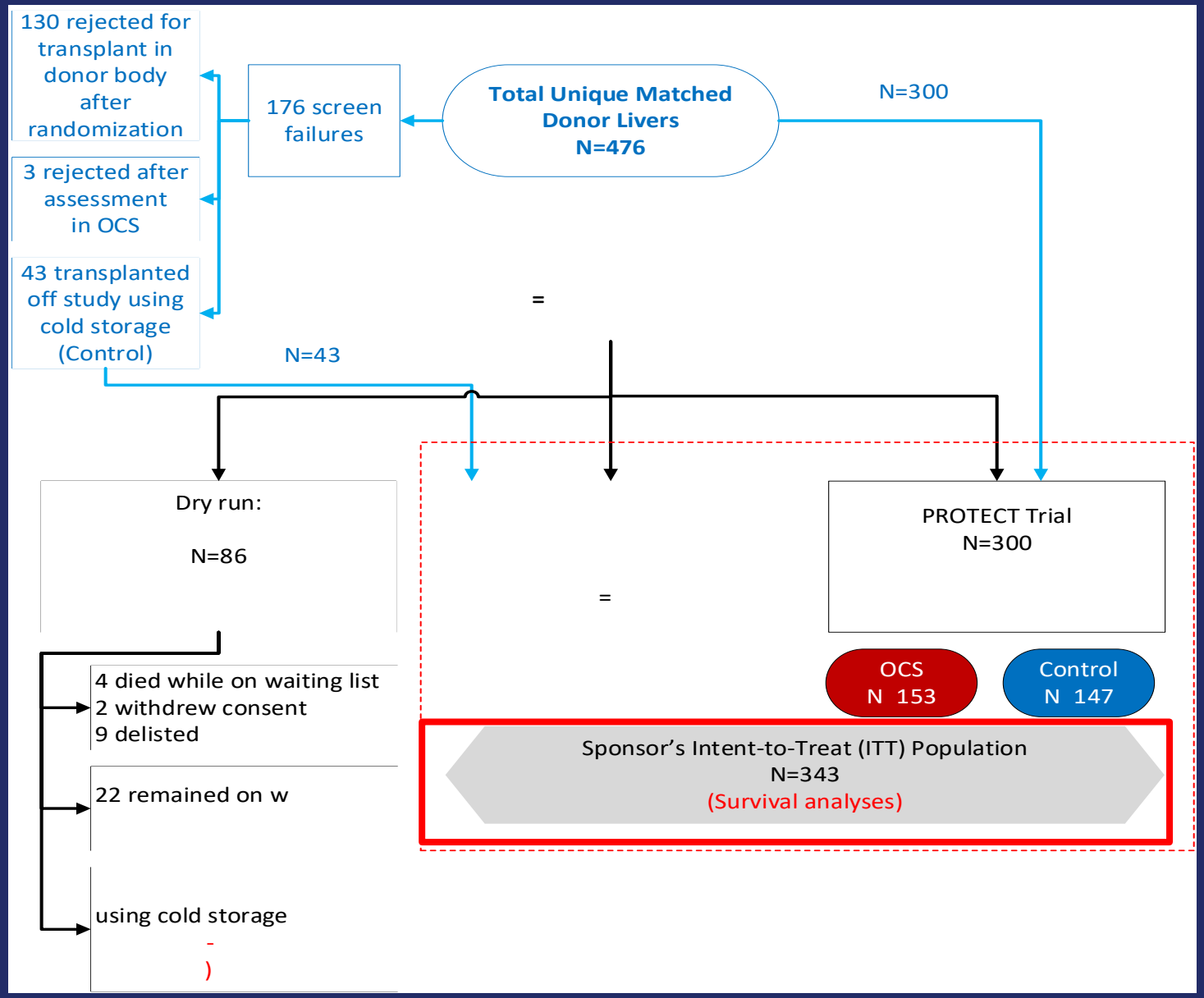

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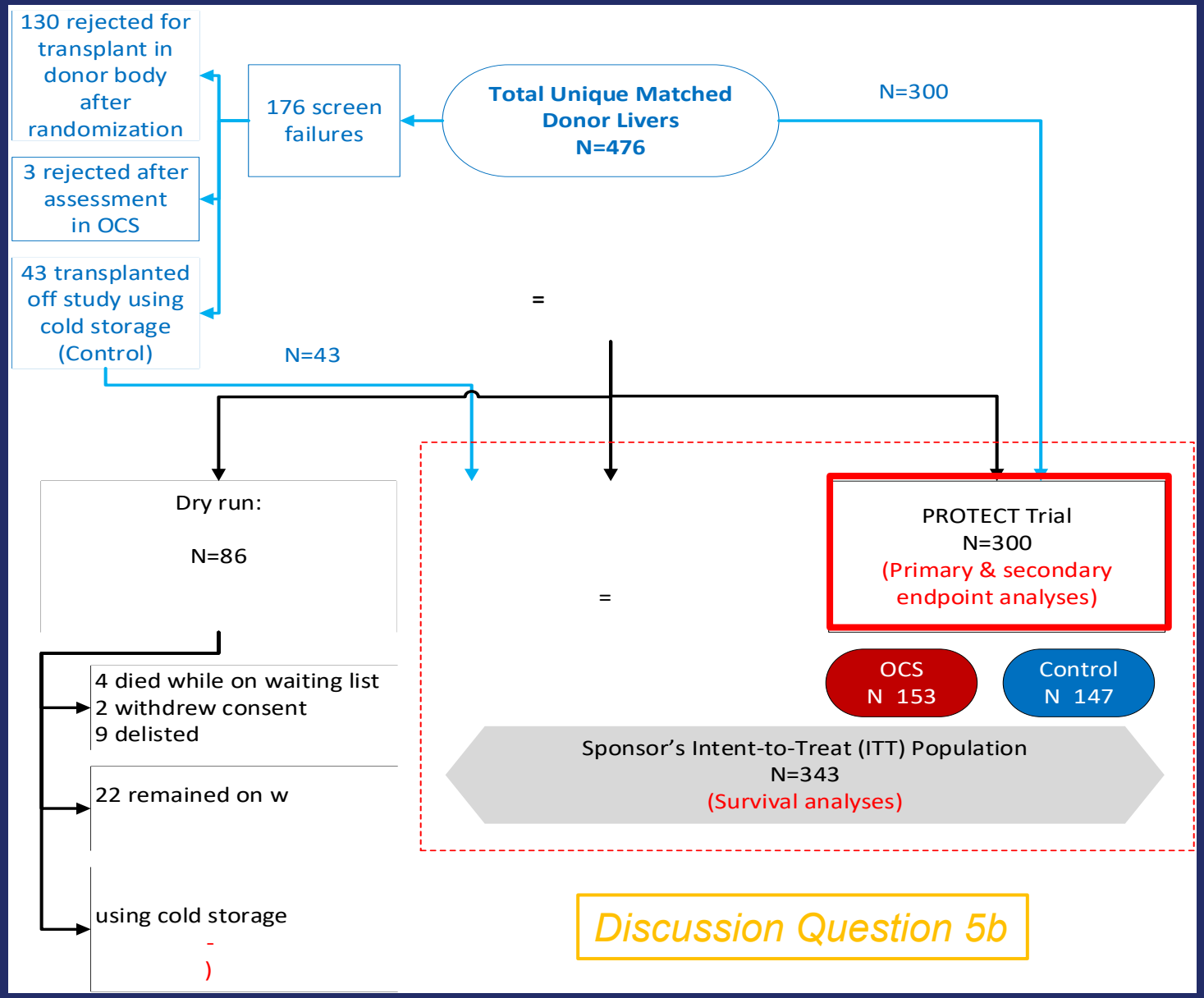

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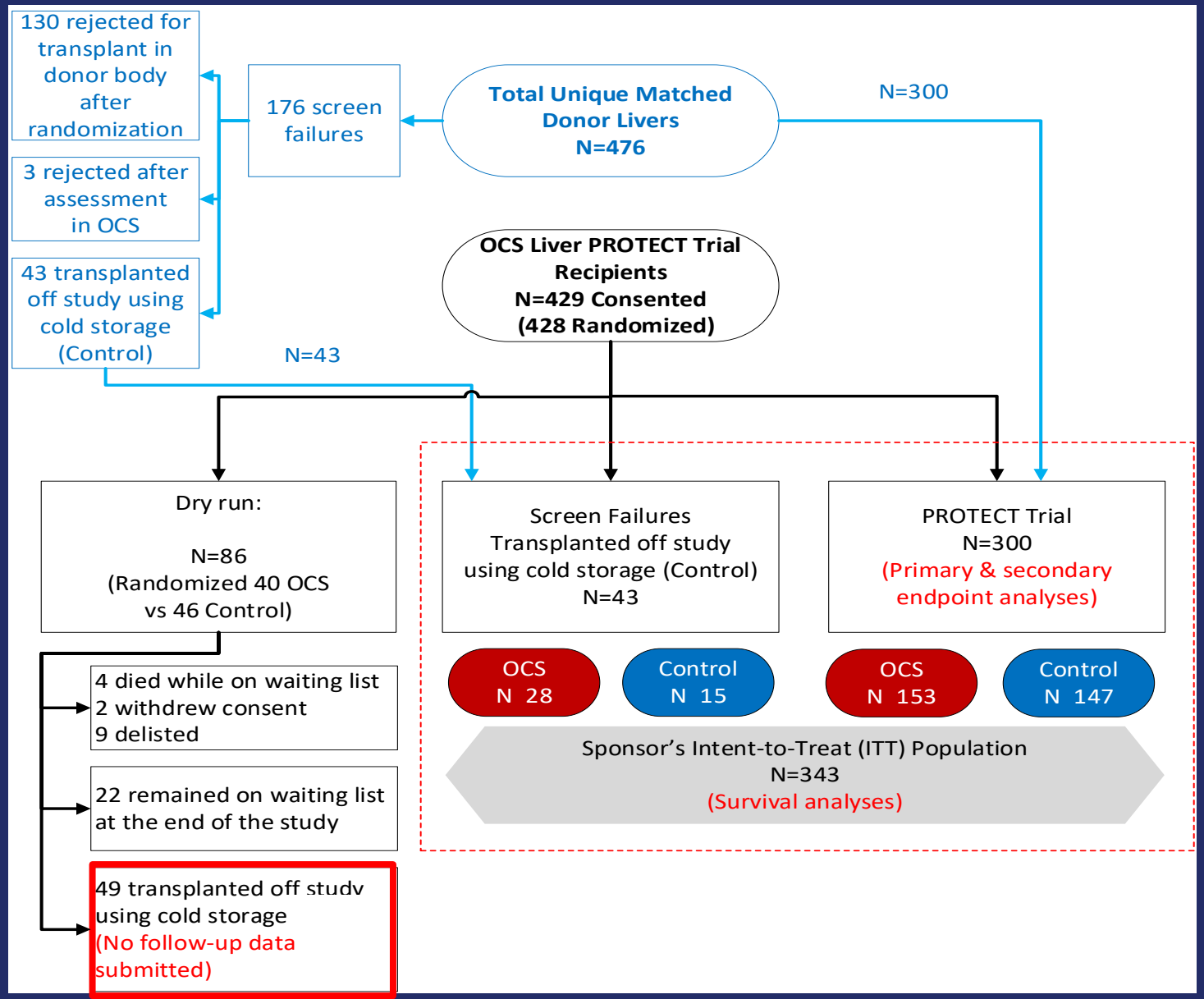

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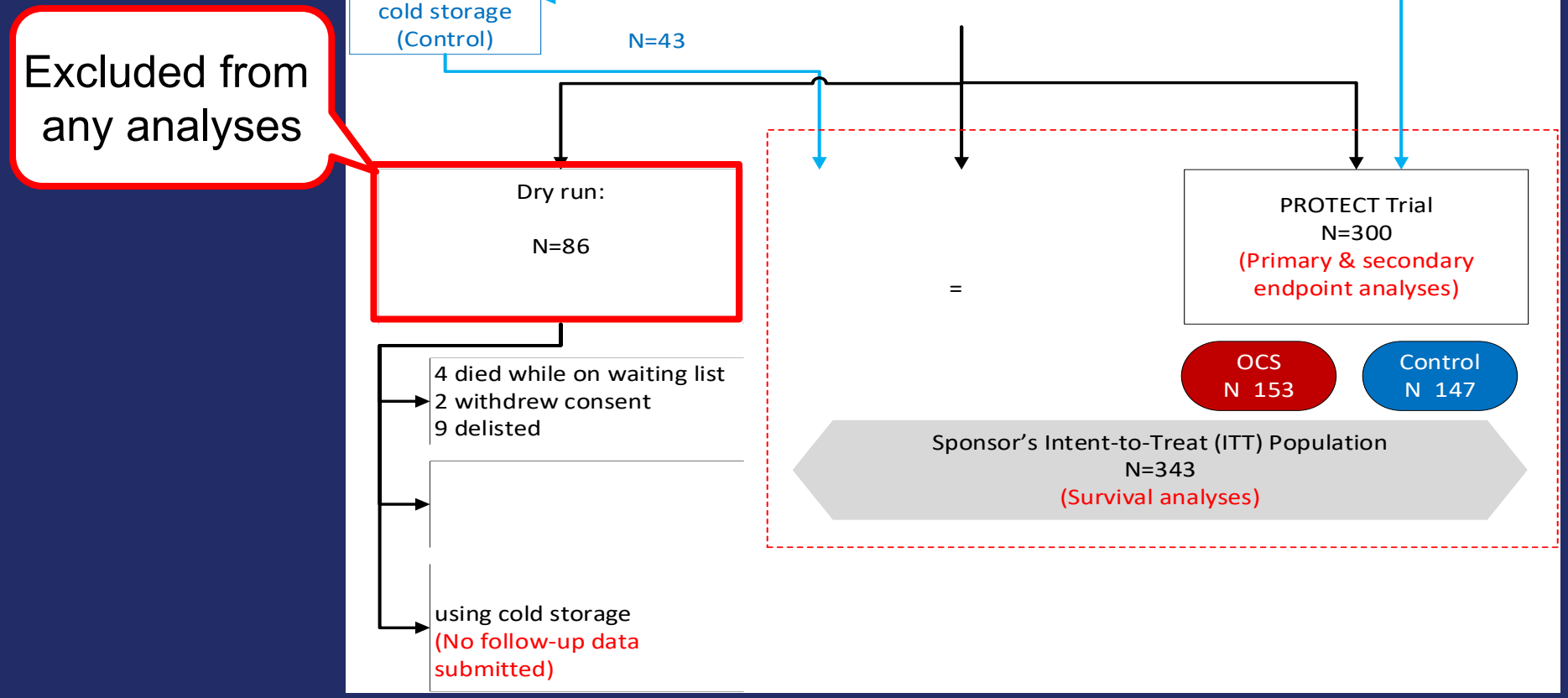
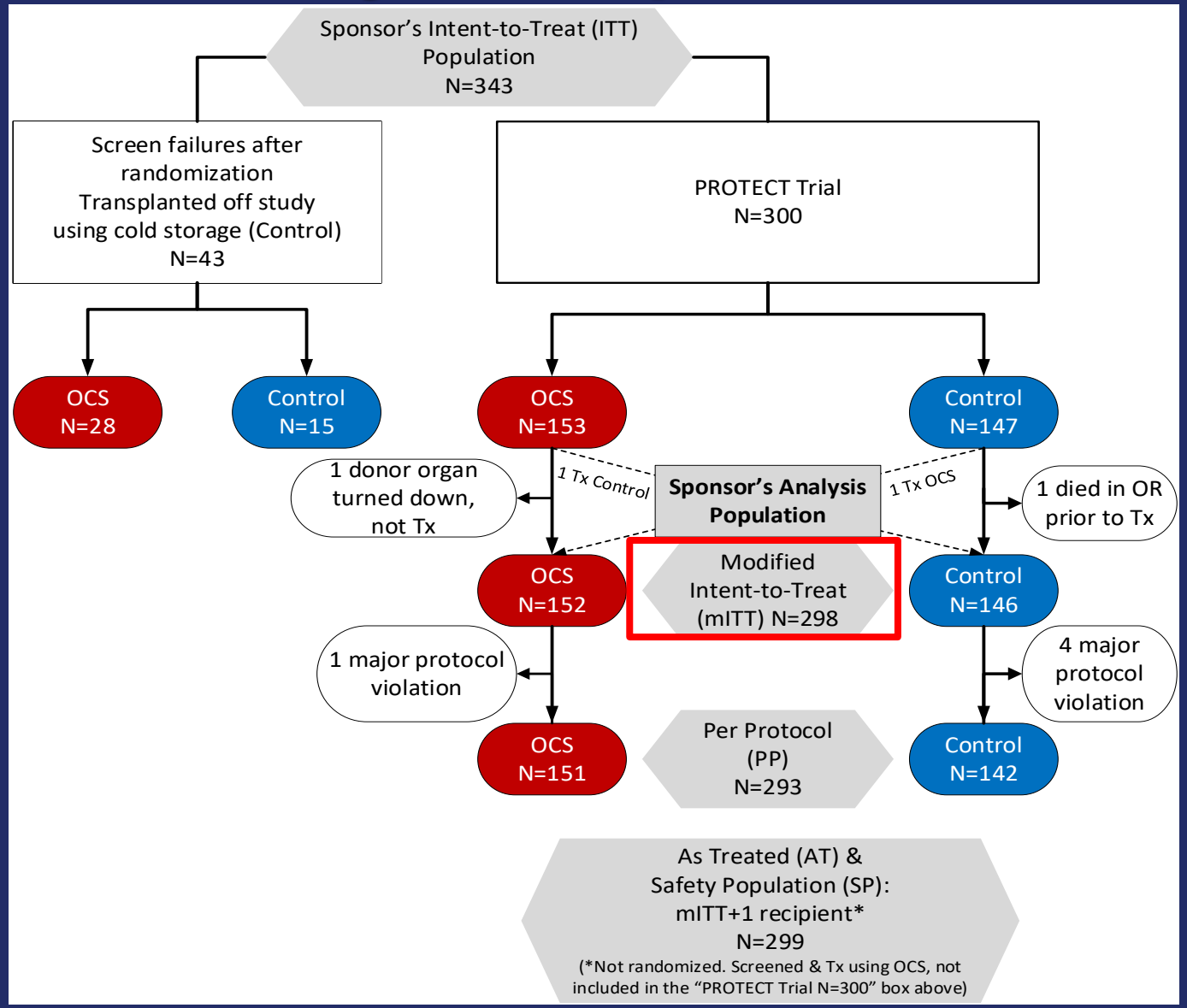


Recipient Disposition and the Sponsor's Analysis Populations



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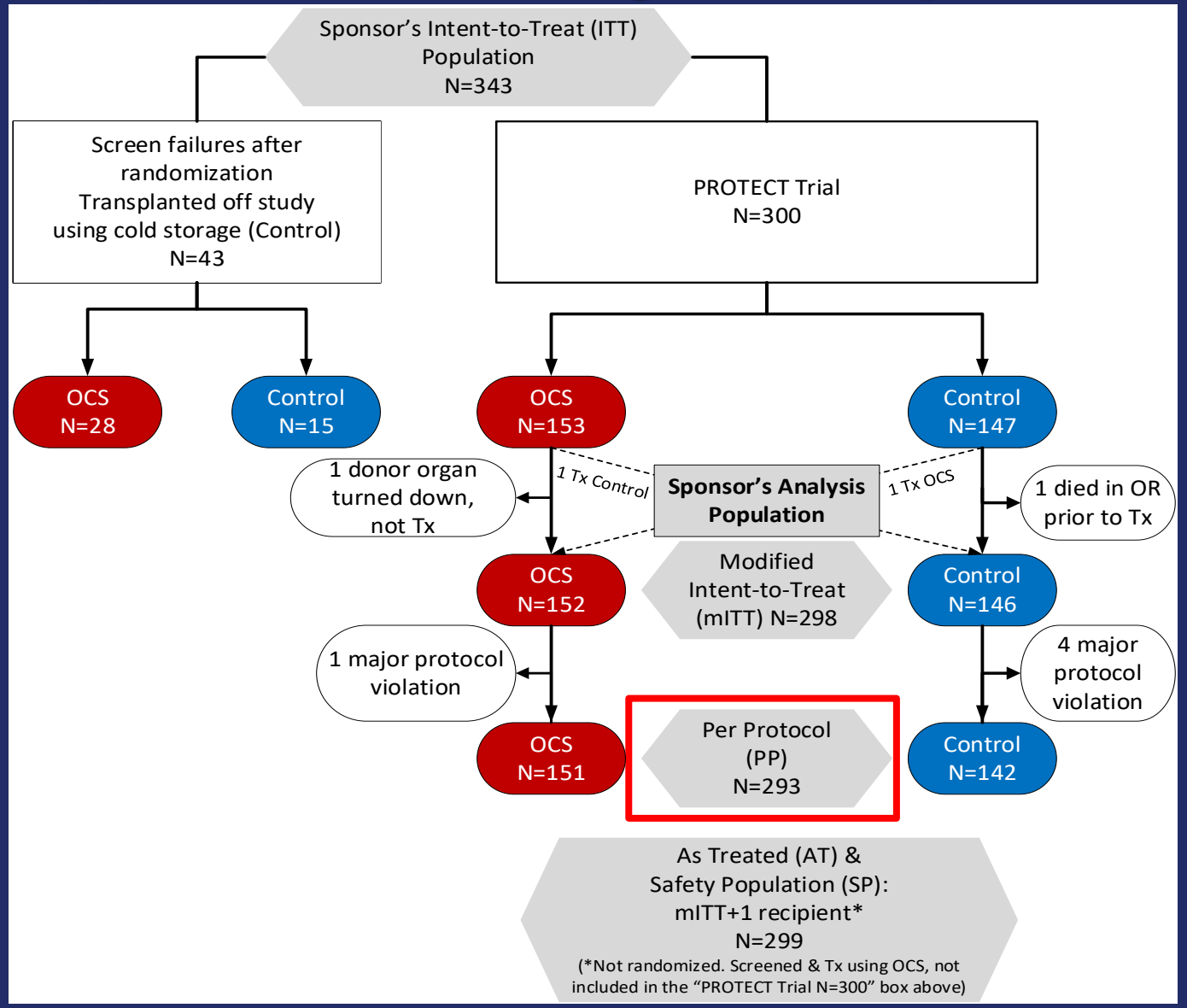

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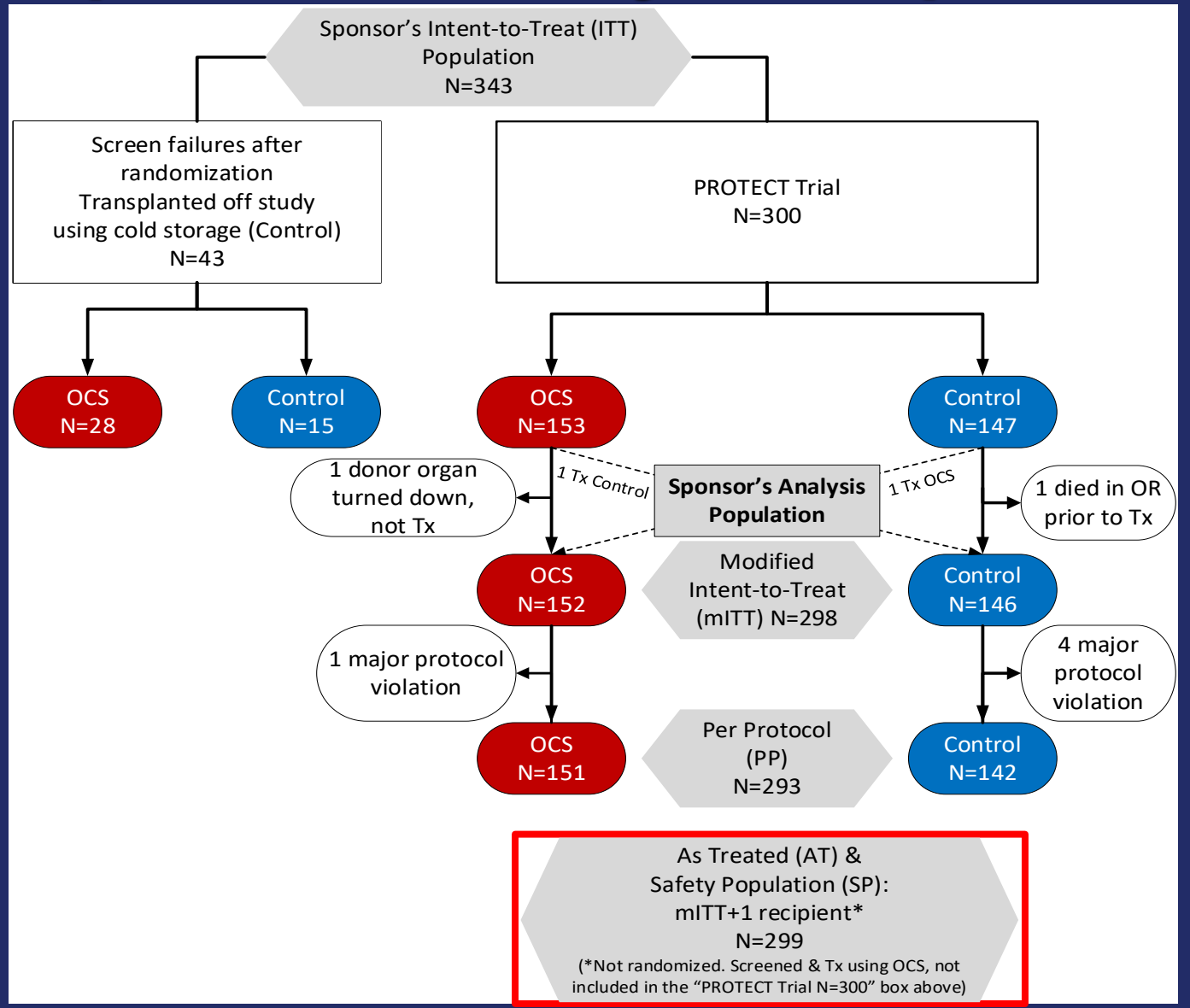


TransMedics®
Organ Care System™ (OCS) Liver System

FDA Presentation for the July 14, 2021 Gastroenterology and Urology Devices Advisory Panel Meeting

Arturo Hernandez, MD, FACS
Medical Officer

Center for Devices and Radiological Health

Today's Plan

- Trial Objective
- Trial Conduct
  - Randomization and Screening Failures
  - Major Protocol Violations
  - Donor and Recipient Characteristics
- Study Results
  - Primary effectiveness endpoint
  - Secondary effectiveness endpoints, survival results
  - Safety results
  - CAP Study Results
- Device Operation
  - Assessment of Organs on OCS
  - Device Malfunctions
  - Livers turned down after OCS preservation
    - Pathology results
- DCD Livers
- Benefit-Risk Assessment

PROTECT Trial Objective

Clinical Objective - compare the safety and the effectiveness of the OCS Liver System vs. cold storage (Control) to preserve and assess donor livers meeting current standard donor liver transplant acceptance criteria and one or more of the following characteristics:

- Donor age > 40 years old
- Expected total cross clamp time ≥ 6 hours or
- Donor after Cardiac Death (DCD donor) with age ≤ 55 or
- Liver steatosis > 0% and ≤ 40% at time of retrieval

Early Randomization

Randomization took place when an available donor liver was matched to a consented WL patient, before in situ liver evaluation and organ retrieval.

"Early randomization" allowed the PI to know the donor, recipient, and method of preservation before deciding whether to accept the donor liver for transplantation.

Early randomization could have influenced the PI decision to accept or reject an organ for transplantation, resulting in screen failures or dry runs.

Screening Failures

Screen Failure (SF): Randomized WL patient matched to a donor liver that is withdrawn and not transplanted in the study.

Dry Run: Randomized WL patient is matched to a donor liver that is not accepted for transplantation and the patient returns to the waiting list for re-randomization.

Dry runs were not considered screening failures.

Screening Failure Adjustments

Initially, an imbalance arose among donor liver screening failures between the two trial arms: OCS 17, Control 6.

(66 out of 300 recipients were enrolled in the PROTECT group at this time)

- *The sponsor introduced the concept of "dry run" recipients; the Agency considers these livers to be screen failures.*

(66 out of 300 recipients were enrolled in the PROTECT group at this time)

- *Most donor liver screen failures were a result of accessory vessels*
  - *3 donor liver screen failures added to Control after review of post-op reports*

(142 out of 300 recipients in the PROTECT group)

Final Report, screen failures were balanced: OCS 88, Control 88

(300 of 300 recipients in the PROTECT group)

Discussion Question 5

Donor Demographic and Baseline Characteristics

AT Population (N=298)	**OCS** (N=152)	**Control** (N=146)
Donor Characteristics		
Donor Age (yrs.): mean ± SD (min-max)	45.84 ± 14.90 (10.9 – 83.7)	46.96 ± 15.22 (13.0 – 80.6)
≥ 40 years old	102 (67.1%)	93 (63.7%)
Mean Total cross clamp	7.6 hours	5.6 hours
Total cross clamp ≥ 6 hours	48 (31.6%)	56.(38.4%)
Mean Ischemic time (min)	2.9 hours	5.6 hours
DCD ≤ 55 years old	28 (18.4%)	13 (8.9%)
Liver Steatosis > 0% and ≤ 40%	95 (62.5%)	86 (58.9%)
Cause of Death		
Cerebrovascular Hemorrhage	44 (28.9%)	50 (34.2%)
Head trauma	35 (23.0%)	29 (19.9%)
Cardiac	13 (8.6%)	10 (6.8%)
Other (Anoxia, CSF infection, Suicide, Stroke)	60 (39.5%)	57 (39.0%)

Recipient Demographic and Baseline Characteristics

AT Population (N=299)	**OCS** (N=153)	**Control** (N=146)
Recipient Age (yrs), mean ± SD (min-max)	57.07 ± 10.33 (19.5 - 76.6)	58.59 ± 10.04 (20.8 – 77.8)
Male	102 (66.7%)	100 (68.5%)
BMI (kg/m^2), mean ± SD (min-max)	29.67 ± 5.38 (16.3 - 45.5)	29.51 ± 5.51 (17.1 - 44.7)
MELD Score, mean ± SD median (min - max)	**28.4 ± 6.90** 29.0 (6 - 49)	**28.0 ± 5.71** 29.0 (9 - 46)
Recipient Baseline Characteristics		
History of diabetes	44 (28.8%)	44 (30.1%)
History of liver cancer	60 (39.2%)	63 (43.2%)
Primary Diagnosis		
Cholestatic Diseases	9 (5.9%)	8 (5.5%)
Chronic Hepatitis	27 (17.6%)	36 (24.7%)
Alcoholic Cirrhosis	54 (35.3%)	48 (32.9%)
Metabolic Diseases	6 (3.9%)	6 (4.1%)
Primary Hepatic Tumors	14 (9.2%)	15 (10.3%)
NASH	24 (15.7%)	20 (13.7%)
Other	19 (12.4%)	13 (8.9%)

Primary Endpoint: EAD, 7 days

Population (Completers)	OCS % (n/N)	Control % (n/N)	%Difference (2-sided 90% UCB) (OCS-Control)	P-value*	P-value**
				Non-inferiority margin=7.5%	Superiority
mITT	17.9% (27/151)	32.4% (47/145)	-14.5% (-6.2%)	<0.0001	0.0047
PP	18.0% (27/150)	31.2% (44/141)	-13.2% (-4.9%)	<0.0001	0.0096

* 90% two-sided upper confidence bound based on the Farrington and Manning score statistic, p-value based on the 90% two-sided Farrington and Manning score statistic. The non-inferiority margin is set to 7.5%. P-value associated with non-inferiority testing.

** P-value from a two-sided Fisher's Exact Test, testing the null hypothesis that the true difference in proportions equals 0 versus the alternative hypothesis that it does not equal 0. This will be done only if the null hypothesis of inferiority is rejected.

Discussion Questions 1a and 3

Early Allograft Dysfunction (EAD)

EAD within the first 7 postoperative days is defined as the presence of one or more of the following criteria:

- 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 or
- Primary non-functioning graft within the first 7 days

Early Allograft Dysfunction

	OCS	Control
Incidence of EAD, mITT	**27/151 (18%)**	**47/145 (32%)**
Cases of EAD based only on one criteria		
• AST > 2000 IU/L Within 7d	17/27 (63%)	36/47 (77%)
• Total Bilirubin ≥ 10 mg/dL on POD7	4/27 (15%)	2/47 (4%)
• INR ≥ 1.6 on POD7	3/27 (11%)	2/47 (4%)

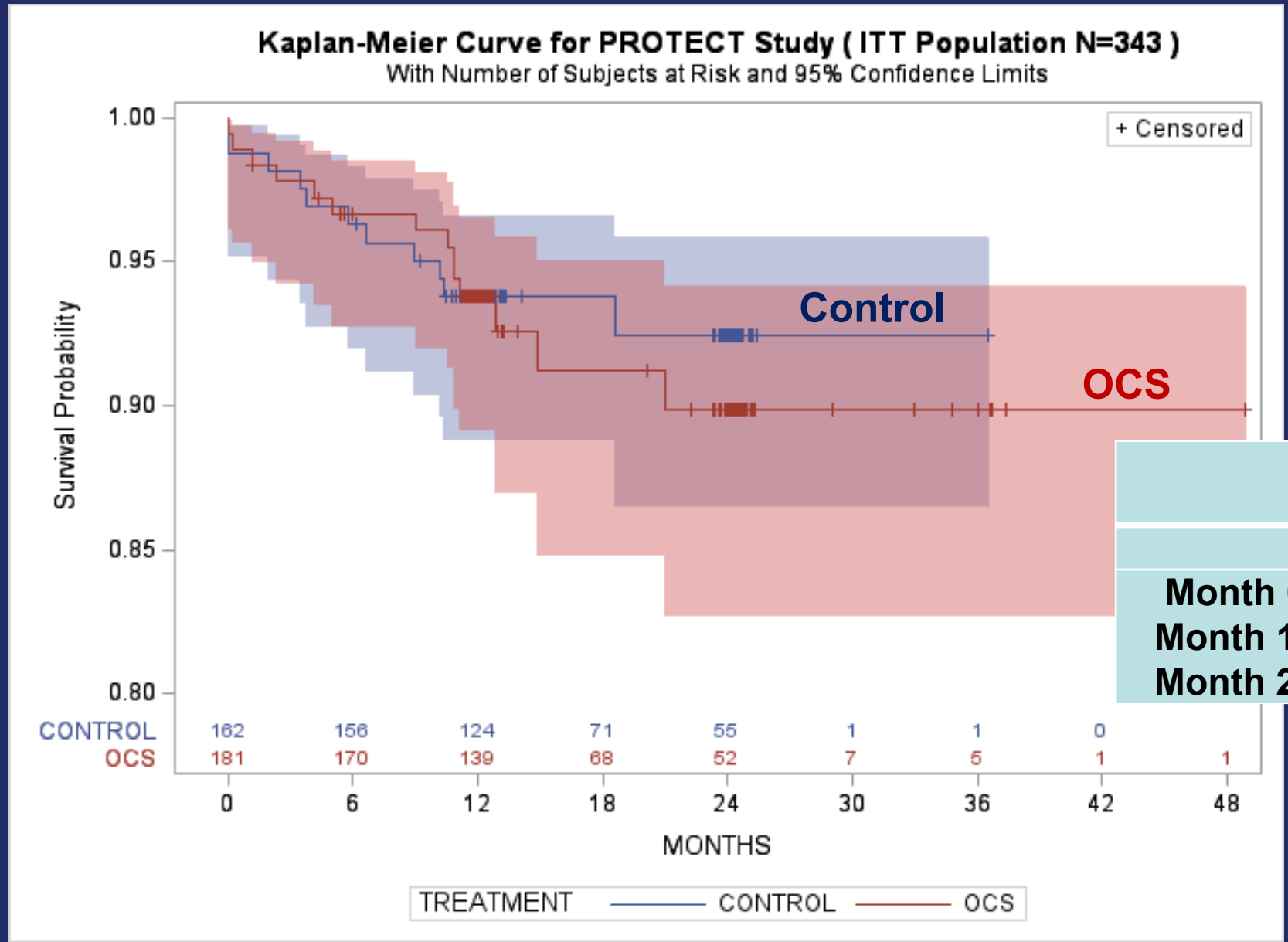
Discussion Question 1b

Secondary Endpoints: Survival

Population	OCS % (n/N)	Control % (n/N)
Survival at Day 30		
mITT (N=298)	99.3 (151/152)	99.3 (145/146)
PP	99.3 (150/151)	99.3 (141/142)
Survival at Time of Initial Hospital Discharge Post Liver Transplantation		
mITT	98.7 (150/152)	98.6 (144/146)
PP	98.7 (149/151)	98.6 (140/142)

Discussion Question 2

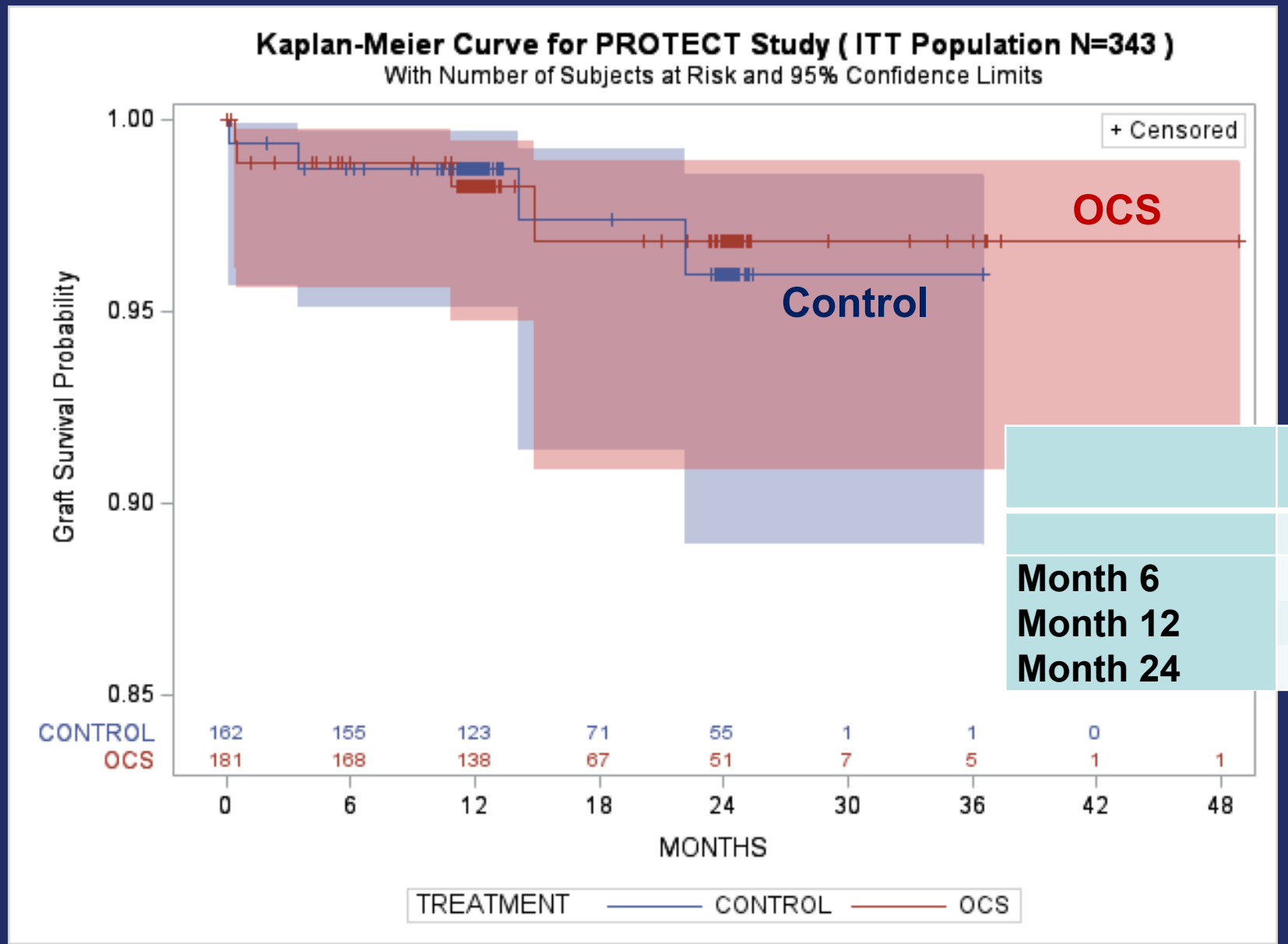
Kaplan-Meier Curve, Recipient Survival, ITT



	OCS N=181	Control N=162
	# death	# death
Month 6	6	6
Month 12	11	10
Month 24	14	11

Discussion Questions 2 and 3

Kaplan-Meier Curve, Graft Survival, ITT



	OCS N=181	Control N=162
	# graft loss	# graft loss
Month 6	4	2
Month 12	5	2
Month 24	6	4

Discussion Questions 2 and 3

Other Endpoints: Hospital and ICU Stay

PP Population	**OCS** N=151	**Control** N=142
Initial Post-Transplant Hospital Stay (days) Mean [Median]	11.7 [8.2]	11.3 [8.4]
Initial Post-Transplant ICU Stay (days) Mean [Median]	4.5 [2.5]	4.6 [2.3]

Differences in EAD rates in the OCS and Control arm are not associated with differences in hospital or ICU stay.

Safety Endpoint: LGRSAEs

AT Population (N=299)	Number of Recipients (%)	
	OCS N=153	**Control** N=146
Recipients with at least one LGRSAE within 30 days post-transplant	7(4.6%)	11(7.5%)
Recipients with at least one LGRSAE within 6 months post-transplant	9 (5.9%)	23 (15.8%)
➢ Non-functioning graft	0	0
➢ Ischemic biliary complications	2 (1.3%)	12 (8.2%)
➢ Vascular complications	7 (4.6%)	12 (8.2%)
➢ Liver allograft infections	0	1 (0.7%)

Discussion Question 4

CEC-Adjudicated Treatment-Emergent SAEs

System Organ Class, Preferred Term AT Population	OCS N=153 n (%)	Control N=146 n (%)
Hepato-biliary Disorders	12 (7.8%)	22 (15.1%)
Bile Duct Obstruction	1 (0.7%)	0
Bile Duct Stenosis	1 (0.7%)	0
Cholangitis	1 (0.7%)	1 (0.7%)
Biliary Ischemia	4 (2.6%)	14 (9.6%)
Post Procedural Biliary Leak	4(2.6%)	11 (7.5%)
Biliary Anastomotic Complications	13 (8.5%)	6 (4.1%)

**

Ischemic and Non-ischemic Biliary Complications

AT Population	OCS N=153	Control N=146
Overall biliary complications		
30 Days Post-Transplant	12 (7.8%)	8 (5.4%)
Non-ischemic biliary complications		
30 Days Post-Transplant	13 (8.5%)	6 (4.1%)
Overall Ischemic biliary complications		
6-Months	2 (1.3%)	12 (8.2%)
12-Months	4/103 (3.9%)	13/110 (11.8%)

Discussion Questions 4, 8d

Post Reperfusion Syndrome (PRS) Exploratory Analysis

AT Population	**OCS** N=153	**Control** N=146
Lactate profile after reperfusion, Slope > 0 (*lactate rising*)	67/146 (46%)	**75/136** (55%)

PROTECT CAP Results

- Single Arm
- 74 Enrolled recipients, April 2021
  - 100% 30-days post transplant
  - 68% (50/74) 6 months post-transplant
- More DCD donors (23%) than PROTECT (18%)
- EAD rate 26% (PROTECT: 18% OCS, 32% Control)
- Recipient and Graft Survival
  - 30-day 98.7% and 98.7%
  - 1 graft failure on POD 0 and was re-transplanted 9 days later with Cold Storage and subsequently died from sepsis
  - 4 other recipient deaths within the 4-month post-operative period; all deaths CEC adjudicated as not liver graft-related
    - Sepsis/Infection (3)
    - Respiratory failure (1)

Device Operation

- Organ assessment
- Device malfunctions
- Turndown livers

OCS Liver System Assessment

- OCS Donor Liver Assessment was defined as the proportion of livers on which measurements of lactate levels, bile production, hepatic artery pressure, and portal vein pressure were obtained during perfusion on OCS device.
- These parameters were successfully measured during preservation.
- There were no predefined transplantability or viability criteria implemented in the study for **v**erification and validation.
- Three DCD livers were turned down for transplantation following preservation and assessment on the OCS, one due to biopsy results, the other two due to rising lactate during perfusion on the OCS Liver System.

Discussion Question 8a

Device Malfunctions

There were three OCS device malfunctions. One case required use of cold storage.

None of the three device malfunctions led to organ loss. However, there is always potential for organ damage or recipient harm when a device failure presents.

Discussion Question 6

Turn Down Livers

Donor meets inclusion criteria

Liver is retrieved and assessed for transplant/inclusion in PROTECT

Organ is cannulated to OCS

- Organ is stabilized on OCS (preservation parameters in range)
- Lactate, pH & bile production are monitored
- Machine parameters are adjusted if needed
- Prior to disconnection from OCS at Recipient site, enzymes, pH, and lactate are measured

Three turndowns were on OCS ~ 2 hours

- Turndown 1 & 2 turned down because of high lactate on OCS
- Turndown occurred because of bridging fibrosis from the donor pathology slides

Organ is placed in cold, static storage

No organs were turned down

Discussion Question 7

Turn Down Livers
OCS Machine Parameters*

	OCS Perfusion Time (Minutes)	HAP mmHg	HAF L/min	PVP mmHg	PVF L/min	Initial Lactate [Final Lactate] mmol/L
Case 1 • female • 46 years • DCD	158	88.27	0.75	7.44	1.42	9.9 [10.25]
Case 2 • male • 19 years • DCD	166	75.68	0.85	8.08	1.33	10.08 [10.98]
Case 3 • female • 29 years • DCD	102	75.92	0.36	4.29	1.15	11.11 [7.73]

** Recommended ranges for parameters are in FDA executive summary, Table 6, pages 18-19*

Turn Down Liver Pathology

Donor Pre-Retrieval Biopsy [Whole Liver Evaluation – Post-Turn Down]					
	Lobular Steatosis	**Periportal Fibrosis**	**Portal Inflammation**	**Lobular Inflammation**	**Lobular Necrosis**
Case 1	0% [5%]	None [none]	None [none]	None [none]	None [Severe]
Case 2	0% [0%]	None [none]	None [none]	Minimal [none]	Minimal [Severe]
Case 3	0% [0%]	None [none]	Minimal [Minimal]	Mild [Mild]	Mild [Moderate]

Discussion Question 7

Lobular Necrosis Severity Scores

Biopsies AT Population	**Pre-Retrieval**		**Post-Preservation**		**Post-Reperfusion**	
	OCS N=153	Control N=139	OCS N=152	Control N=139	OCS N=153	Control N=140
None/Minimal	95%	96%	78%	94%	56%	52%
Mild	2%	4%	**16%**	5%	26%	28%
Moderate/Severe	3%	1%	5%	1%	17%	20%

DCD Livers

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 liver allografts from donors after circulatory death (DCD) ≤55 years old in a near-physiologic, normothermic and functioning state intended for a potential transplant recipient."

Discussion Question 8b

Criteria for DCD Donor Quality

Criteria DCD donor quality, British Transplant Society Guidelines, 2010		PROTECT Study Subgroup Analysis, DCD		
Optimal DCD ***All Transplantable***	**Suboptimal** ***Transplantable, use selectively***	**PROTECT**	**OCS-DCD 28/152 (18%)**	**Control-DCD 13/146 (9%)**
Donor age <50	Donor age >50	Donor age <50	23/28 **(82%)**	12/13 **(92%)**
fWIT <20	fWIT 20-30 min	Warm Ischemic Time (WIT) 20-30 min	18/25 **(72%)**	7/12 **(58%)**
CIT <8 hrs	CIT 8-12 hr	Cold Ischemic Time (CIT) 8-12 hrs	8/28 **(28.5%)**	0
Macrosteatosis <10%	Macrosteatosis >15%	Macrosteatosis <15%	28/28 (**100%**)	10/11 **(91%)**
Wt <100 kg	Wt >100 kg	Wt <100 kg	21/28 (**75%**)	9/13 (**69.2%**)

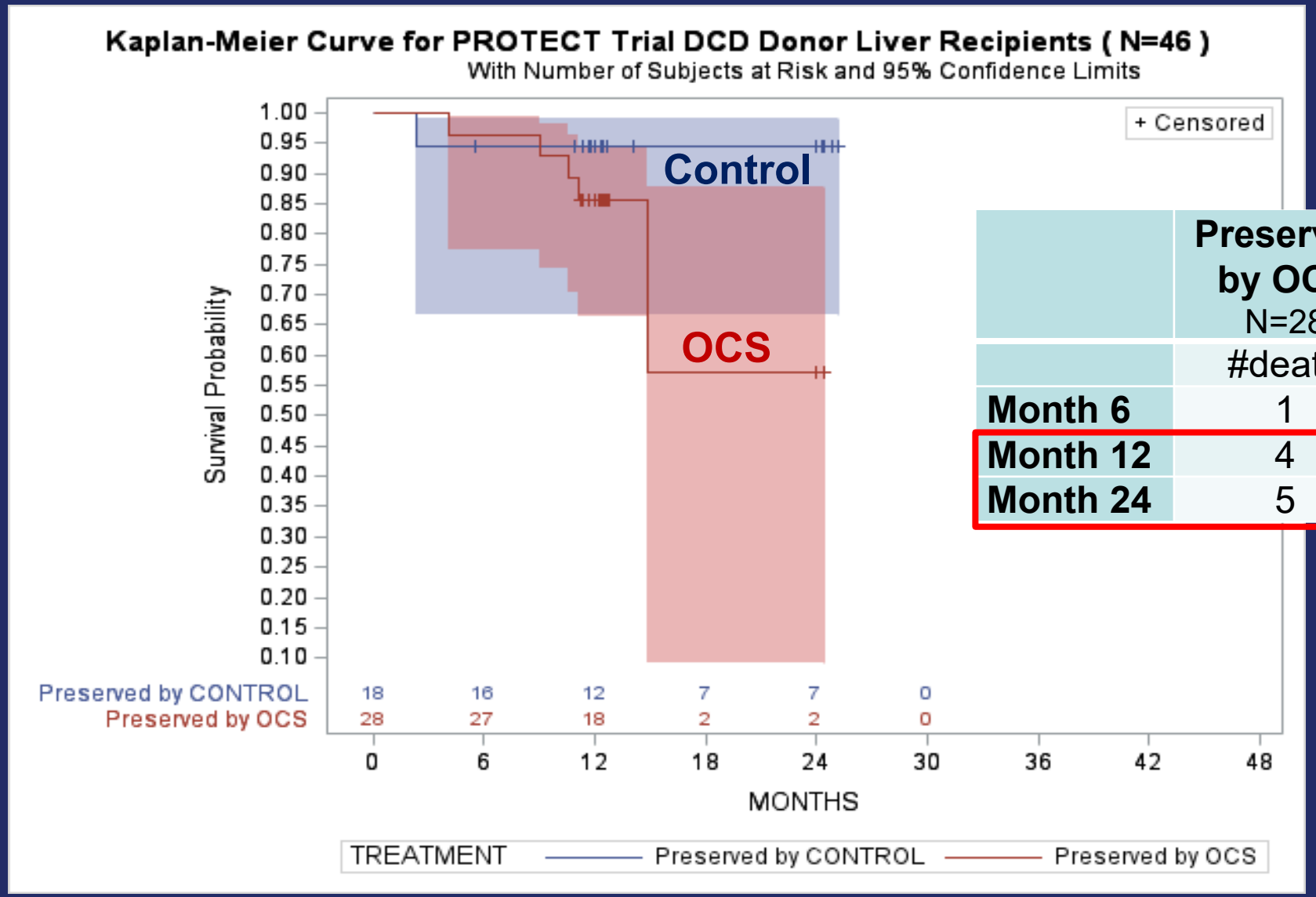
DCD livers appeared suitable for transplantation

Primary Endpoint: DCD, DBD subgroup analysis

EAD mITT Population	**OCS** n/N (%)	**Control** n/N (%)
All subjects	27/151 (18%)	47/145 (32%)
DBD	20/123 (16.3%)	36/132 (27.3%)
DCD	7/28 (25.0%)	11/13 (84.6%)

Discussion Question 8b

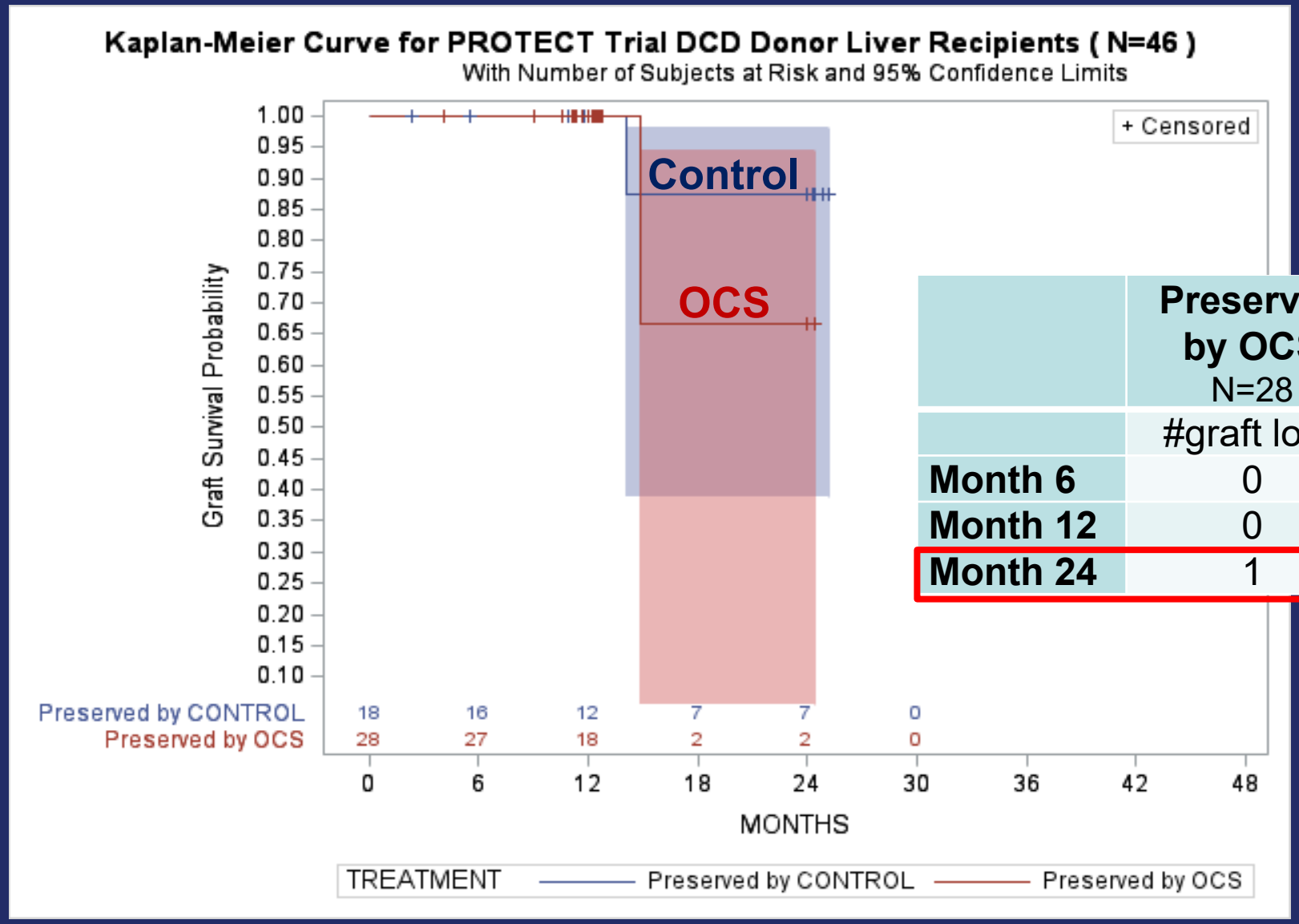
Kaplan-Meier Curve, Recipient Survival, DCD, ITT



	Preserved by OCS N=28	Preserved by Control N=18
	#death	#death
Month 6	1	1
Month 12	4	1
Month 24	5	1

Discussion Question 8b

Kaplan-Meier Curve, Graft Survival, DCD, ITT



	Preserved by OCS N=28	Preserved by Control N=18
	#graft loss	#graft loss
Month 6	0	0
Month 12	0	0
Month 24	1	1

Discussion Question 8b

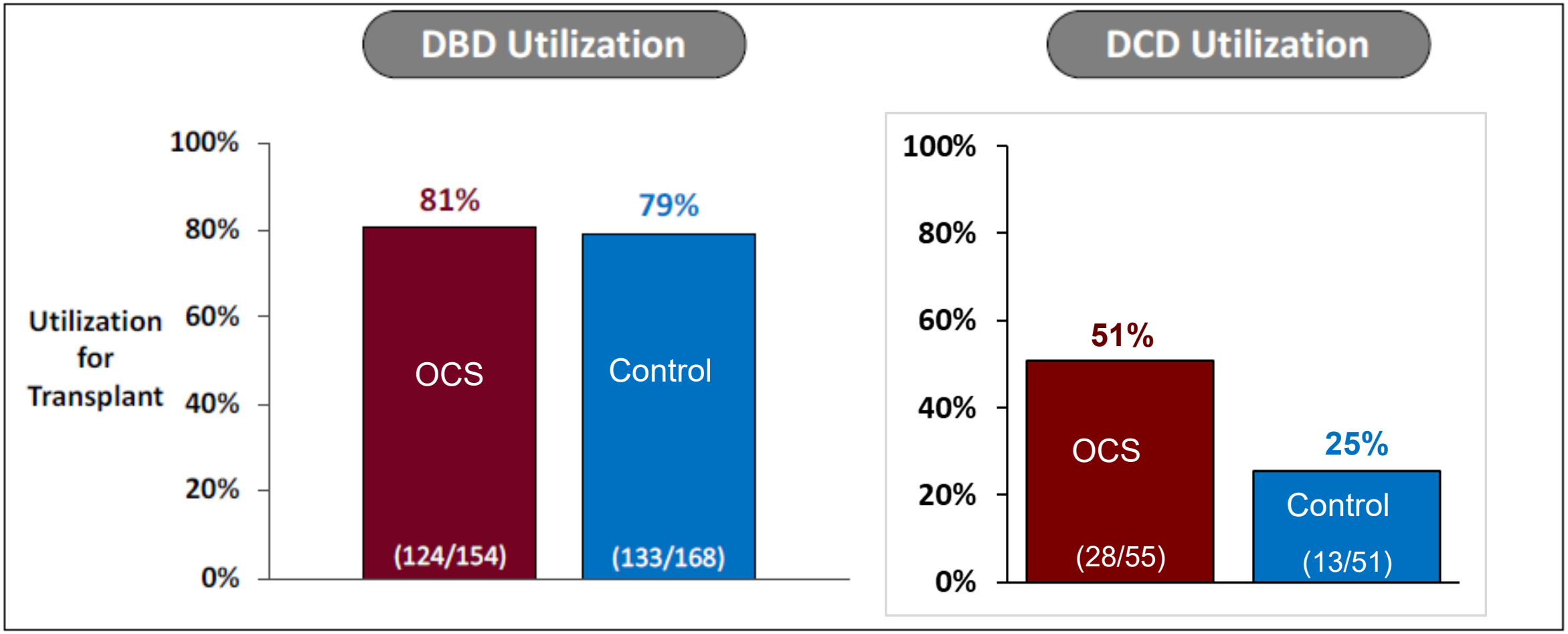
DCD Livers, Summary

	OCS	Control
Number of recipients of DCD livers	28	13
EAD at 7 days	7 (25.0%)	11 (84.6%)
Recipient deaths at 12 months	4	1
Graft loss at 12 months	0	0
Livers turned down	3	0

Livers appeared suitable for transplantation

Discussion Question 8b

Utilization of DCD Livers



Discussion Question 8c

Utilization of Livers

Utilization defined as transplant of livers for which OCS or Control preservation was initiated and the liver was subsequently transplanted:

- **Control:** 100% utilization
- **OCS, DCD:** 3 livers turned down
- **OCS, DBD:** 1 liver switched to Control following device malfunction prior to OCS instrumentation and then transplanted

Discussion Question 8c

Benefits

- Reduced rate of Early Allograft Dysfunction (EAD)
- Similar observed survival to cold storage control
- Lower observed rate of biliary ischemic complications
- Lower observed rate of Post-Reperfusion Syndrome
- Monitoring of physiological parameters of donor livers

Uncertainty Surrounding the Benefits

- Reduction in EAD did not translate into clinically significant improvement in survival, ICU stay, or hospital stay, as seen in other studies.

- Ischemic biliary complications were captured as LGRSAE without a predefined protocol to assess these complications.

- While lactate levels decreased post-reperfusion in the OCS arm, the prevalence of mild lobular necrosis increased.

Uncertainty Surrounding the Benefits

- Early randomization and screening failures raised issues for selection bias; “Dry Runs” and re-randomization also created uncertainty for data interpretation.

- Ability to assess livers does not currently enable a determination of suitability for transplantation.

- Exploratory endpoints do not have prespecified hypothesis testing.

Risks

- Risk due to instrumentation on OCS device
  - Device malfunctions
  - Turn downs
  - Increased lobular necrosis following OCS preservation
- Risk to recipient of unnecessary procedures if liver is turned down or damaged after OCS treatment
- Higher observed rate of non-ischemic biliary complications at 30 days

Uncertainty Surrounding the Risks

- Device malfunctions only occurred in the OCS arm. The study was too small to assess the potential implications of device malfunctions.
- Unknown if livers turned down following OCS treatment were transplantable or would have been transplantable following cold storage.
- Non-ischemic biliary complication data were limited to 30 days and did not capture events at 6- and 12-months.

Benefit-Risk Determination

- Observed recipient survival and other clinically relevant outcomes were similar for recipients of OCS livers compared to cold storage Control livers.

- There is uncertainty surrounding the benefits of reduced EAD, liver assessment, reduced biliary complications, and reduced post-reperfusion injury.

- There is uncertainty surrounding the risks of device malfunctions, liver turndowns post-assessment, and non-ischemic biliary complications.

TransMedics®
Organ Care System™ (OCS) Liver System

Post-Approval Study (PAS) Considerations

Lauren J. Min, PhD
Epidemiologist

Center for Devices and Radiological Health (CDRH)

PAS Considerations

- Inclusion of a PAS section should not be interpreted to mean that FDA has made a decision on approvability of this device.
- Presence of a PAS plan does not alter the requirements for pre-market approval and a recommendation from the Panel on whether the benefits outweigh the risks.
- Issues presented here are FDA's comments regarding potential post-approval studies for the Panel to include in the deliberations, should FDA find the device approvable.

Sponsor's Proposed Extended Follow-up of PROTECT and CAP Cohorts

- TransMedics' PAS proposal: extended follow-up of premarket study cohorts

	PROTECT Trial	CAP Study
Study Objective	To evaluate long-term outcomes of OCS Liver patients	
Study Design	Observational study of patients who were enrolled and transplanted in premarket studies	
Sample Size	300 patients (OCS and Control)	Currently approved for 74 OCS patients
Primary Effectiveness Endpoint	Liver graft survival at 2 years post-transplant	
Other Clinical Endpoints	Recipient survival at 2 years post-transplant	
Follow-Up Duration	2 years post-transplant	

- **FDA agrees with TransMedics' proposal for extended follow-up PAS studies**
- **However, limitations in premarket studies would persist in the PAS**

Reasons for a New PAS

FDA also recommends a new PAS to address questions raised in the PROTECT trial including:

- Safety and effectiveness of OCS on DCD organs
- Donor organ transplantability criteria
- Device malfunctions
- Longer-term evaluation of clinically meaningful outcomes, such as recipient and/or graft survival, with hypothesis testing
- Timing of randomization may have biased the study results

Use of the TOP Registry for PAS

- Leverage the existing Thoracic Organ Perfusion (TOP) Registry
  - Currently used to fulfill PAS requirements for OCS Lung System
  - All-comers registry that collects real-world data on every patient who receives OCS-perfused lungs and every organ that comes into contact with OCS
  - Participants followed for 5 years
  - Most data extracted from UNOS but also collects information not available in UNOS, including device-specific parameters and device malfunctions
  - Also collects data on organ turndowns and conversion to cold storage
- Given its strengths and accessibility, TOP Registry may be used for donor livers and serve as an infrastructure for collecting postmarket data on different donor organ types in a centralized location.

Panel Input on PAS

The panel will be asked to discuss whether a new enrollment PAS is needed and, if so, to please comment on the key design elements of the study including the study objective, primary endpoint(s) and other endpoints, recipient follow-up duration, etc. Is it appropriate to leverage the existing TOP Registry to conduct a new post-approval study for the OCS Liver System?

Discussion Question 9