OrganOx Ltd.

A multicenter randomized controlled trial to compare the efficacy of ex-vivo normothermic machine perfusion with static cold storage in human liver transplantation

Statistical Analysis Plan
Version 4.0
09 September 2020

Authors:

Title	Name	Signature	Date
Biostatistician, Biostatistics NAMSA	[redacted]	[redacted]	

Approval:

Title	Name	Signature	Date
Clinical Study Manager, NAMSA	[redacted]	[redacted]	
Director of Quality & Regulatory Affairs, OrganOx	[redacted]		

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1. Purpose

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analysis of data collected under a trial conducted by OrganOx Ltd.: "A multicenter randomized controlled trial to compare the efficacy of *ex-vivo* normothermic machine perfusion with static cold storage in human liver transplantation protocol" (Clinical Trial Protocol ID #: WP01).

2. Scope

This SAP should be read in conjunction with the study protocol and electronic case report forms (eCRF). This version of the plan has been developed with respect to the clinical protocol version 10.0, dated 24 June 2016. Any further changes to the protocol or eCRF may necessitate updates to the SAP.

3. Applicable Documents

Document Number	Document Title
WP01	A multicenter randomized controlled trial to compare the efficacy of *ex-vivo* normothermic machine perfusion with static cold storage in human liver transplantation

4. Software

All tables, listings and figures will be produced using SAS Version 9.3 (SAS Institute, Cary, NC.) or a later version of SAS. All output will be in Microsoft Word or RTF format.

5. Definitions

ALP	-	Alkaline Phosphatase
ALT	-	Alanine Aminotransferase
AST	-	Aspartate Transaminase
CRF	-	Case Report Form
DBD	-	Donation after Brain Death
DCD	-	Donation after Circulatory Death
EAD	-	Early Allograft Dysfunction
GGT	-	Gamma-Glutamyl Transferase
ICU	-	Intensive Care Unit
INR	-	International Normalized Ratio
IQR	-	Interquartile Range
NMP	-	Normothermic Machine Perfusion
PNF	-	Primary Non-Function
SAP	-	Statistical Analysis Plan

SCS	-	Static Cold Storage
VAS	-	Visual Analog Scale

6. Trial Objectives

The trial objectives are:

1. To compare the effect of NMP to SCS in preventing preservation-related graft injury
2. To compare graft and subject survival between NMP and SCS livers.
3. To compare evidence of post-reperfusion syndrome between NMP and SCS livers on transplantation.
4. To compare biochemical liver function between NMP and SCS livers.
5. To compare evidence of ischemia-reperfusion injury between NMP and SCS livers.
6. To compare evidence of biliary complications between NMP and SCS livers.
7. To assess the feasibility and safety of NMP as a method of organ storage and transportation.
8. To compare organ utilization between NMP and SCS livers.
9. To assess the health economic implications of normothermic liver perfusion.

7. Trial Hypotheses

The primary analyses will be performed on all transplanted subjects. The primary endpoint in this study is severity of immediate graft injury as measured by early allograft dysfunction (EAD). The hypothesis can be written as follows:

H_0: $EAD_{NMP} \geq EAD_{SCS}$
H_A: $EAD_{NMP} < EAD_{SCS}$,

where EAD is a binary outcome defined by the presence of one of the following 3 outcomes [1]:

1. Serum bilirubin ≥ 10 mg/dL at day 7 post-transplant
2. International normalized ratio ≥ 1.6 at day 7 post-transplant
3. ALT or AST > 2000 IU/L within the first 7 days post-transplant

No formal hypothesis testing will be done for the secondary endpoints.

8. Trial Success Criteria

A one-sided significance level of $\alpha = 0.025$ will be used to test the primary endpoint. That is, if the hypothesis test results in a one-sided p-value that is less than 0.025, the study will be considered a success.

9. Trial Design

This is a multi-center, randomized, controlled, non-blinded clinical trial comparing NMP versus SCS for organ preservation prior to liver transplantation.

9.1 Randomization

Donor livers will be randomly assigned to NMP or SCS with 1:1 allocation as per a computer generated randomization schedule using variable block randomization using the following stratification factors: participating (recipient) center and donor type (DBD or DCD). The randomization schedule will be created by the study statistician, and will remain confidential.

Allocation concealment will be ensured by use of central computerized randomization. Allocation will not be revealed until the recipient has been recruited to the trial and donor and recipient inclusion/exclusion criteria have been recorded. Random permuted block length will be used; block sizes will not be disclosed.

Prior to randomization, the local Investigator will confirm the availability of the investigational *metra*® device. Once informed consent has been verified from the potential recipient of an organ and recipient and donor inclusion and exclusion criteria has been confirmed, the local recipient investigative site staff will proceed with randomization. Recipients will be considered enrolled in the study once a randomized liver has been assigned and there is an attempt to transplant the randomized liver. An attempt to transplant a liver is considered when there is knife-to-skin contact in the operating room during the recipient transplant procedure. A subject is considered to be transplanted when there is reperfusion of the donor liver in the recipient subject.

9.2 Re-Randomization

Because there is the potential for a donor liver to be randomized and the intended recipient to not receive the liver, the randomization schedule has been built such that the randomization assignment is unique to a donor liver, not a recipient. That is, if the intended recipient is unable to receive the liver and a new recipient is identified, the randomization assignment that was initially assigned remains, even if the new recipient is at a different site than the initial recipient.

It is also possible that a donor could be identified as one type (either DBD or DCD), and then switch to the other type after randomization has occurred. As in the previously mentioned scenario, the initial randomization assignment will be kept and it will be documented that the initial donor type has switched. See Section 11.5 for specific analysis plans in these instances.

9.3 Blinding

While it is not possible to blind the local Investigators to the method of organ preservation, Histopathologists at the central laboratory interpreting the biopsy specimens will remain blinded to the randomization group to the extent possible.

10. Sample Size Considerations

Power calculations of the superiority of NMP versus SCS were based on a test of inequality for two proportions using a pooled Z-test and one-sided α=0.025.

The following assumptions were considered:

EAD_{NMP}=10%

EAD_{SCS}=25%

Based on the above assumptions, it is estimated that 266 (approximately 356 total sample size considering approximately 25% attrition) transplanted livers will provide 90% overall power. Power calculations were conducted using PASS 14. Power for the primary analysis based on logistic regression is similar to this, and stratification based on sites will provide additional power if site is prognostic.

11. Data Structure and Handling

11.1 Data Handling and Transfer

Data management will be undertaken by NAMSA. NAMSA Biostatistics will be provided access to download SAS datasets or will be provided them upon request.

Programming of analysis datasets, tables, figures, and listings will be conducted during the data management phase of the study. Tables, figures, and listings may be reviewed prior to final data lock for data review. Any data values requiring investigation or correction will be identified, and protocol deviations will be reviewed. The final run of outputs will take place after the data are deemed final.

11.2 Missing Data

Endpoints may be missing because results of any of the 3 components of the EAD score are not analyzable, or because subjects have died, refused follow-up, or have withdrawn from the study. Section 12.5.1.3 outlines additional clinical decision techniques that will be used for those enrolled recipients where the endpoint is missing. If EAD is still unable to be determined after using these techniques, imputation methods will be used. Analyses that include imputation for missing data, are considered the standard analyses and will be used to analyze the primary endpoint.

Every effort will be made to obtain information regarding EAD for all recipients. If unavailable, the sponsor will report the reason for recipients with missing endpoint data. If the recipient is missing data and EAD cannot be determined using the additional clinically justified decision rules, the EAD endpoint will be imputed using baseline characteristics (i.e. treatment group, center, and donor type (DCD/DBD) as well as all available components of EAD collected during study follow-up (bilirubin, INR, and ALT/AST). This will be based on multiple imputation via full conditional specification imputation with the variables listed as above with logistic regression (and the endpoint listed last). Individual covariates may be omitted to still allow for

imputation of the endpoint for the full randomized cohort if there are fitting issues with the covariate imputation process. An augmented likelihood approach will be used if there are fitting issues due to the separation or quasi-separation of data points. Imputation will be performed for 100 data sets. In line with multiple imputation, imputed data sets will be appropriately combined to produce a single estimate of treatment effect, along with the associated p-value for the hypothesis test.

Additional sensitivity analyses could include "completers only", last observation carried forward, and/or mixed models.

11.3 Visit Windows

The following outlines the scheduled visits post-transplant and the eligibility window:

Visit	Timing (from end of transplant procedure)
Day 1	12-24 hours
Day 2	24-48 hours
Day 3	48-72 hours
Day 4	72-96 hours
Day 5	96-120 hours
Day 6	120-144 hours
Day 7	144-168 hours
Day 10	216-288 hours
Day 30	30 days ± 7 days
Month 3	3 months ± 14 days
Month 6	6 months ± 14 days
Month 12	12 months ± 30 days

11.4 Pooling of Data

11.4.1 Across Trial Sites

Up to 15 sites will enroll recipients in the study. Statistical investigation of the homogeneity of results across investigational sites will be performed in order to ensure the poolability of results to address the primary endpoint. Statistical analyses used to assess the site by treatment interaction will be tested at a significance level of p=0.10.

11.4.2 Across Donor Types

Livers received from both DBD and DCD donors will be included in this study. Statistical investigation of the homogeneity of results across donor type will be performed in order to

ensure the poolability of results to address the primary endpoint. Statistical analyses used to assess the donor type by treatment interaction will be tested at a significance level of p=0.10.

11.5 Sensitivity Analysis

As mentioned in section 9.2, there may be instances where a donor type was reported as either DBD or DCD prior to randomization and then after the randomization is assigned, the donor type converts. Also, there may be a scenario where a liver is randomized within a stratification factor that is not actually appropriate for the liver (i.e., randomized in the DBD arm but actually a DCD liver). In both of these instances, subjects will be analyzed for the primary analysis in the original donor type group that the randomization assignment was based on. As a sensitivity analysis, those that switched donor types will be analyzed in the donor type group that they switched to, or those that were inappropriately randomized in the wrong stratification group will be analyzed in the correct donor type group, and the analysis will be re-run. If there is no significant impact on the results, subjects will be analyzed according to their original donor type group for all relevant analyses. A similar approach will be taken to investigate the impact of those donor livers that were randomized to the NMP arm, and needed to be converted to SCS at some point during the transport process. Additionally, sensitivity analyses will be conducted to demonstrate the impact on primary endpoint results using multiple imputation for EAD status that is unable to be confirmed by complete labs or at least 1 lab value meeting criteria for EAD.

12. Statistical Analyses

12.1 General Considerations

Continuous measures will be summarized with sample size, mean, median, standard deviation, minimum, and maximum; categorical measures will be presented with the counts and percentages of subjects in each category. Exact 95% binomial confidence intervals will also be computed and presented for binomial variables; such as EAD.

The date of attempted transplant will be considered study day 1.

Both DRI and MELD scores will be calculated outside of the database using the following calculations:

Donor risk index (DRI) = exp[(0.154 if 40≤ age <50) + (0.274 if 50≤ age <60) + (0.424 if 60≤ age <70) + (0.501 if 70 ≤ age) + (0.079 if COD = anoxia) + (0.145 if COD = CVA) + (0.184 if COD = other) + (0.176 if race = African American) + (0.126 if race = other) + (0.411 if DCD) + (0.422 if partial/split) + (0.066 ((170–height)/10)) + (0.105 if regional share) + (0.244 if national share) + (0.010 × cold time)]. (Feng, 2006)

Given the data collected in the OrganOx study, the following gives specific detail on fields collected and how they are used to calculate DRI:

Field in database	Parameter in Feng,2006 calculation
Cause of death:	
CVA	CVA
Anoxia	Anoxia

Hypoxia	Anoxia
Trauma	reference
Other	Other
Race:	
American Indian or Alaska Native	Other
Asian	Other
Black or African American	African American
Native Hawaiian or other Pacific Islander	Other
White	reference
Other	Other
Partial/Split	excluded from study
Location	
Local	reference
Regional	Regional
National	National
Cold time	all livers will be assumed to have a stored cold time Of 8 hours (which is the reference), thus no coefficient will be included for cold time.

$$\text{MELD Score} = 0.957 \times \text{Log}_e(\text{creatinine mg/dL}) + 0.378 \times \text{Log}_e(\text{bilirubin mg/dL}) + 1.120 \times \text{Log}_e(\text{INR}) + 0.643$$

The MELD score is then multiplied by 10 and rounded to the nearest whole number. Any lab values that are less than 1 are set to 1 one for the purpose of the calculation, and the maximum serum creatinine considered is 4.0 (values over 4.0 are set to 4.0). If a recipient had dialysis twice in the week prior to the serum creatinine test or received 24 hours of continuous veno-venous hemodialysis (CVVHD) within the prior 7 days, the serum creatinine value is also set to 4.0 for the purposes of the calculation (https://www.unos.org/wp-content/uploads/unos/MELD_PELD_Calculator_Documentation.pdf).

The maximum MELD score is 40. For recipients with an initial MELD score greater than 11, then MELD score is then re-calculated as follows:

$$\text{MELD Score} = \text{MELD(i)} + 1.32*(137-\text{Na}) - (0.033*\text{MELD(i)}*(137-\text{Na}))$$

Sodium values less than 125 mmol/L will be set to 125, and values greater than 137 mmol/L will be set to 137. (see Appendix)

12.2 Analysis Populations

The primary endpoint will be analyzed among all transplanted subjects.

12.3 Subject Disposition

Subject disposition will be presented by:

- Summary of subjects (completed and expected) per office visit and completed outcome data from obtained medical records.
- Summary of discontinuation in the study and reason for discontinuation.

12.4 Demographics and Baseline Characteristics

Demographics and baseline characteristics of enrolled subjects will be summarized. These factors will include (but not be limited to):

- Age
- Gender
- Ethnicity
- Race

12.5 Primary Analysis

12.5.1 Primary Objective

The primary objective of this study is to compare the effect of NMP to SCS in the prevention of preservation injury and graft dysfunction, as measured by early allograft dysfunction (EAD).

12.5.1.1 *Endpoint Definition*

The primary endpoint in this study is the severity of immediate graft injury as measured by EAD in the NMP group as compared to SCS.

12.5.1.2 *Hypothesis and/or parameters to be estimated*

The primary endpoint analysis will be performed on all transplanted subjects. The objective of the primary analysis is to show EAD in the NMP cohort less than the observed EAD rate from the SCS cohort. The hypothesis can be written as follows:

H_0: $EAD_{NMP} \geq EAD_{SCS}$
H_A: $EAD_{NMP} < EAD_{SCS}$,
where EAD is a binary outcome defined by the presence of one of the following 3 outcomes [1]:

1. Serum bilirubin ≥ 10 mg/dL at day 7 post-transplant
2. International normalized ratio ≥ 1.6 at day 7 post-transplant
3. ALT or AST > 2000 IU/L within the first 7 days post-transplant

12.5.1.3 *Data Collection and Analysis Methods*

Serum bilirubin at day 7 post-transplant, International normalized ratio at day 7 post-transplant, and ALT or AST within the first 7 days post-transplant (collectively "Lab Values") are all reported on the Inpatient Stay (Day 1 through Day 10 Follow-up) CRF. In the event that a recipient is missing information for the endpoint, the following techniques will be employed to impute the primary endpoint outcome for the recipient:

a. If day 7 INR is missing and day 6 is available, the day 6 value will be used.
b. If a recipient has been discharged from hospital prior to day 7 post-transplant and the recipient had complete Lab Values before discharge that did not meet the definition of EAD, the recipient will be considered to not have an EAD event.
c. If the last INR value recorded for a recipient is less than the threshold for EAD and the recipient has complete Lab Values for all other components of EAD that do not meet the definition of EAD, the recipient will be considered to not have an EAD event. Available follow-up Lab Values must also be below the threshold and no re-admissions reported to be considered to not have an EAD event.

The primary analysis will be a logistic model, adjusted for participating (recipient) center using SAS `proc logistic` or a similar procedure. Significance for the treatment effect will be assessed by the p-value associated with the treatment group assignment.

12.6 Secondary Endpoints

All secondary endpoints will be assessed for all transplanted subjects with analyzable results. No formal statistical hypothesis testing will be performed.

During preparation of the 30-day clinical study report, it was discovered that the outcome measures for secondary endpoints #6 and #7 were inadvertently switched during preparation of the study protocol; therefore, the correct outcome measures for these endpoints have been updated and are reported below.

12.6.1 Secondary Objective #1

To compare graft and subject survival between NMP and SCS livers.

12.6.1.1 *Endpoint Definition*

The following compose the secondary objective #1: 1) Primary non-function rates: irreversible graft dysfunction requiring emergency liver replacement during the first 10 days after liver transplantation; 2) Graft survival rates at 30 days, 3 months, and 6 months following transplantation; and 3) Subject survival rates at 30 days, 3 months, and 6 months following transplantation.

12.6.1.2 *Hypothesis and/or parameters to be estimated*

No formal statistical hypothesis testing will be performed for the secondary endpoint. Primary non-function, graft survival, and subject survival will be reported.

12.6.1.3 *Data Collection and Analysis Methods*

The time of knife-to-skin contact (used as study day 0) is collected on either the Transplant Operation NMP or Transplant Operation SCS CRF. Primary Graft Non-Function (Yes/No) is reported on the Inpatient Stay (Day 1 through Day 10 Follow-up) CRF as well as the date of primary graft non-function. The day 30, 3 month, and 6 month follow-up assessment forms have information regarding graft survival (yes/no) and graft failure dates, and the Adverse Event. The end of study CRFs report whether or not a subject is deceased.

The incidence of primary non-function rates will be measured, as well as the Kaplan-Meier rate and corresponding 95% confidence interval based on Greenwood's formula for both graft survival and subject survival.

12.6.2 Secondary Objective #2

To compare evidence of post-reperfusion syndrome between NMP and SCS livers on transplantation.

12.6.2.1 *Endpoint Definition*

Secondary endpoint #2 is the assessment of mean arterial pressure (MAP) pre- and post-reperfusion and requirement for vasopressor use.

12.6.2.2 *Hypothesis and/or parameters to be estimated*

No formal statistical hypothesis testing will be performed for the secondary endpoint. Occurrence of post-reperfusion syndrome and use of vasopressors will be reported within each treatment arm.

12.6.2.3 *Data Collection and Analysis Methods*

Both occurrence of post-reperfusion syndrome and use of vasopressors will be collected and reported on the Transplant Operation NMP and Transplant Operation SCS CRF.

The incidence of post-reperfusion syndrome and use of vasopressors will be measured. Post-reperfusion syndrome is defined as a decrease in mean arterial pressure (MAP) of more than 30% from the baseline value for more than one minute during the first five minutes after reperfusion.

12.6.3 Secondary Objective #3

To compare biochemical liver function between NMP and SCS livers.

12.6.3.1 *Endpoint Definition*

The components of secondary endpoint #3 are: 1) Bilirubin, GGT, ALT, AST, ALP, and INR at days 1-7, day 30, month 3, and month 6 post-transplant.; and 2) Lactate at days 1-7 while the subject is in ICU.

12.6.3.2 *Hypothesis and/or parameters to be estimated*

No formal statistical hypothesis testing will be performed for the secondary endpoint. Statistics for Bilirubin, GGT, ALT, AST, ALP, and INR at the different time points will be summarized, as well as lactate.

12.6.3.3 *Data Collection and Analysis Methods*

All variables of interest will be collected and reported on in the Inpatient Stay (Day 1 through Day 10 – Follow-up) CRF. In addition, Bilirubin, GGT, ALT, AST, ALP, and INR are also reported on the 30 Day Follow-up, 3 Month Follow-Up, and 6 Month Follow-Up CRFs.

The mean, median, min, max, and interquartile range (IQR) will be summarized for all variables at all appropriate time points.

Data that are not required will be reported for those subjects with data available.

12.6.4 Secondary Objective #4

To compare evidence of ischemia-reperfusion injury between NMP and SCS livers.

12.6.4.1 *Endpoint Definition*

Post-reperfusion biopsies will be compared to baseline pre-reperfusion biopsies and graded according to standard histological criteria.

12.6.4.2 *Hypothesis and/or parameters to be estimated*

No formal statistical hypothesis testing will be performed for the secondary endpoint, however evidence of ischemia reperfusion injury between NMP and SCS livers will be reported.

12.6.4.3 *Data Collection and Analysis Methods*

Post-reperfusion biopsies will be compared to baseline pre-reperfusion biopsies and graded according to standard histological criteria and collected on the Core Lab CRF.

12.6.5 Secondary Objective #5

To compare evidence of biliary complications between NMP and SCS livers.

12.6.5.1 *Endpoint Definition*

Incidence of biliary investigations and/or interventions between 7 days and 6 months post-transplant.

12.6.5.2 *Hypothesis and/or parameters to be estimated*

No formal statistical hypothesis testing will be performed for the secondary endpoint; however, incidence of biliary investigations and/or interventions will be reported.

12.6.5.3 *Data Collection and Analysis Methods*

Date of knife-to-skin contact is available on either the Transplant Operation NMP or Transplant Operation SCS CRF. The 'Action Taken' and 'If biliary investigation checked: Was there a biliary intervention' on the Adverse Event CRF as well as the Date of onset of the event are used to calculate time to event

The Kaplan-Meier rate and corresponding 95% confidence interval based on Greenwood's formula will be reported at 7-days, 30-days, 3-months, and 6-months post-transplant.

12.6.6 Secondary Objective #6

To assess the feasibility and safety of NMP as a method of organ storage and transportation.

12.6.6.1 *Endpoint Definition*

Incidence of one or more of the following per randomized liver: (i) EAD; (ii) discard (non-transplant) of a retrieved liver; (iii) primary non-function.

12.6.6.2 *Hypothesis and/or parameters to be estimated*

No formal statistical hypothesis testing will be performed for this secondary endpoint; however, the following composite measure will be reported: incidence of one or more of the following per randomized liver: (i) EAD; (ii) discard (non-transplant) of a retrieved liver; (iii) primary non-function.

12.6.6.3 *Data Collection and Analysis Methods*

The Inpatient Stay (Day 1 through Day 10 Follow-up) CRF contains all variables to report on EAD as well as primary non-function. The Study Withdrawal Form CRF contains all variables pertaining to the discard (non-transplant) of a retrieved liver.

The incidence of either EAD, discard of a retrieved liver, or primary non-function will be measured.

12.6.7 Secondary Objective #7

To compare organ utilization between NMP and SCS.

12.6.7.1 *Endpoint Definition*

Incidence of livers randomized but not transplanted and reasons for not-transplanting.

12.6.7.2 *Hypothesis and/or parameters to be estimated*

No formal statistical hypothesis testing will be performed for the secondary endpoint, however, incidence of livers randomized but not transplanted will be reported for both NMP and SCS.

12.6.7.3 *Data Collection and Analysis Methods*

All relevant information to this endpoint can be found on the Study Withdrawal Form CRF (Questions: 'Reason for Study Withdrawal', 'If liver not suitable for retrieval', 'If liver discarded before transportation', 'If liver discarded following transportation', and 'If subject was not eligible to proceed with transplant').

The incidence of livers randomized but not transplanted will be reported.

12.6.8 Secondary Objective #8

To assess the health economic implications of normothermic liver perfusion.

12.6.8.1 *Endpoint Definition*

Logistical and healthcare costs (length of stay in ICU and hospital) and quality of life measures.

12.6.8.2 *Hypothesis and/or parameters to be estimated*

No formal statistical hypothesis testing will be performed for the secondary endpoint, however, the following will be reported: length of stay in high level care (ICU) post-transplant, total length of hospital stay post-transplant, and mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and VAS score (all part of the EQ-5D).

12.6.8.3 *Data Collection and Analysis Methods*

Length of stay in high level care (ICU) post-transplant as well as total length of hospital stay post-transplant are reported on the Discharge Form CRF. The Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression, and VAS Score are all reported on the EQ-5D CRF.

Length of hospital stay (total and in ICU) will be summarized continuously. The EQ-5D measures will be summarized at each available time point. Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are all categorical variables and will be reported as such. VAS Score is continuous and will be summarized appropriately.

12.7 Exploratory Analyses

A logistic regression model will be used to examine the possible explanatory effects of baseline subject characteristics (in the presence of the treatment indicator variable), namely: race, age, gender, and number of liver transplants received (primary or secondary).

Secondary analysis may be stratified by recipient center and donor type (DBD or DCD) for exploratory purposes.

Additional exploratory analyses will include those that assess a learning curve or enhanced training effect.

12.8 Subgroup Analyses

Subgroup analyses will be performed for donor type (DBD vs. DCD), by Donor Risk Index (DRI), and by duration of machine preservation in the NMP arm of the trial.

Additional subgroup Analyses may be performed.

12.9 Safety Analysis

12.9.1 Enrollment Expansion Request

After 30-day safety data is available for the first 10 subjects, an IDE supplement including a clinical report summarizing the demographics, screening/testing results, and safety data for all enrolled subjects, including but not limited to the first 10 subjects, will be submitted. Safety data will include detailed descriptions, as well as supporting information regarding all adverse events as well as descriptions of all protocol deviations.

12.9.2 Conditional Phase

During the conditional phase, the study will be limited to 20 enrolled subjects. Data will be reported on these first 20 subjects through 30-day follow-up. If there are 3 more subjects experiencing an event (EAD, 30-day PNF, or 30-day Recipient death) in the NMP than in the SCS arm, the study will be suspended.

12.9.3 Attempted Transplants

Safety data, through 30-days post-transplant attempt, will be summarized for those recipients that are matched to a liver and have an attempt to transplant the liver but ultimately do not receive a donor liver.

12.10 Other Data

Protocol deviations, device deficiencies, liver incidents, and re-allocation variances will be listed and summarized. Also, those livers that were randomized and re-allocated under emergency use will be summarized and reported on.

12.10.1 COVID-19 Reporting

Although enrollment was complete prior to the COVID-19 pandemic, the opportunity to perform follow-up visits may be impacted. Protocol deviations as well as visits that were performed remotely due to COVID-19 will be reported.

13. Version History

Version	Date	Changes
1.0	10MAR2017	Initial version.
2.0	14JAN2019	Additional detail added to DRI calculation; section 11.5 now includes detail on the handling of livers that were randomized within the wrong strata; additional detail added to section 11.2 Missing Data
3.0	14FEB2020	Additional detail added to EAD derivation for recipients without complete lab data. Detail added in sections 11.2 Missing Data and 12.5.1.3 Data Collection and Analysis Methods. These updates were communicated with the FDA at a pre-submission meeting on 22JAN2020. Section 11.5 Sensitivity Analysis now includes a planned sensitivity analysis based on multiple imputation for EAD status unable to be confirmed by complete labs or at least 1 lab value meeting criteria for EAD. Learning curve and retraining analyses also identified in section 12.7 Exploratory Analyses
4.0	09SEP2020	Description of secondary endpoints #6 and #7 corrected to correspond to the appropriate objective in sections 12.6.6 and 12.6.7. Description of reporting due to COVID-19 added (section 12.10.1).

14. References

1. Olthoff, K.M., et al., *Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors.* Liver Transpl, 2010. **16**(8): p. 943-9.
2. Feng, S., et al., *Characteristics associated with liver graft failure: the concept of a donor risk index*. American Journal of Transplantation, 2006. **6**(4): p.783-790.

15. Appendix

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Brian M. Shepard
Executive Director & CEO

IMPORTANT POLICY NOTICE

To: Transplant Professionals

From: James B. Alcorn
UNOS Policy Director

RE: Changes to OPTN Bylaws and Policies from actions at OPTN/UNOS Exectuive Committee Meetings July 2015-November 2015

Date: November 23, 2015

This report summarizes changes to the OPTN Policies and Bylaws approved by the OPTN/UNOS Executive Committee at meetings from July 2015 through November 2015. This policy notice provides the specific Policy and Bylaws language changes and the corresponding implementation dates.

When reviewing the language changes, please note that underlined language is new and what will be in effect upon implementation and language that is ~~struck~~ will be deleted upon implementation. The policy language used to denote the approved changes reflects the most recent version of policy that has been approved, but not necessarily what is currently implemented.

This policy notice, as well as changes from previous Board of Directors meetings, can be found at http://optn.transplant.hrsa.gov/governance/policy-notices/.

The Evaluation Plan, which reviews specific details regarding how members will be assessed for compliance with OPTN policies and bylaws, has also been updated to reflect the changes resulting from the meeting. It can also be found at http://optn.transplant.hrsa.gov/governance/compliance/optn-evaluation-plan/.

Thank you for your careful review of this policy notice. If you have any questions about a particular Board of Directors' action, please contact your regional administrator at (804) 782-4800.

Policy Clarification to KPD Histocompatibility Requirements – Test Date

Policy/Bylaws Affected:	**Policy 13.5.B (Antibody Screening Requirements for OPTN KPD Candidates)**
Distributed for Public Comment:	**No**
Effective Date:	**Pending programming and notice to OPTN members**

Problem Statement

In November 2014, the OPTN/UNOS Board of Directors approved a proposal to move kidney paired donation (KPD) histocompatibility testing requirements from OPTN/UNOS KPD Pilot Program Operational Guidelines into OPTN policy. Included in these policies was a requirement for candidate transplant hospitals to test KPD candidates for antibodies "at least once every 90 days (+/- 20 days) from the date of the first antibody test." During IT programming meetings, staff found that although the policy specifically mentions that candidates must be tested every 90 days from the date of the first antibody test, the intent of the policy was to prohibit a candidate from going longer than 90 days without being retested. However, if the candidate was more recently tested due to a potentially sensitizing event or unacceptable positive crossmatch, the candidate would need to be retested again within that 90 day timeframe. By tying the testing requirement to the date of the first antibody test, members might have to test more frequently which could be unnecessary and overly burdensome for both the member and the candidates.

Summary of Changes

This change ties the 90 day requirement to the most recent antibody test date. The change also removes the window created by the +/- 20 days language and simplifies the timeframe by changing it to "within 110 days from the date of the most recent antibody test." This change only clarifies the timeframe for the policy, but does not make the requirement more stringent as members have up to 110 days for compliance whether it is written as 90 (+ 20) days or simply "within 110 days."

These changes will allow transplant hospitals to test KPD candidates within 110 days from the most recent test date, in order to reduce the number of potentially unnecessary tests.

What Members Need to Do

This change lessens the amount of member burden by reducing the number of potentially unnecessary tests for KPD candidates. Members will still need to comply with all other testing and reporting requirements. This policy change will not require additional data collection. This policy modification does not change how members will be evaluated for compliance.

Affected Policy/Bylaw Language:

New language is <u>underlined</u> and language that will be deleted is ~~struck through~~.

13.5.B Antibody Screening Requirements for OPTN KPD Candidates

The paired candidate's transplant hospital must complete antibody screening tests and report to the OPTN Contractor as follows:

1. Use an antibody testing method that is at least as sensitive as the crossmatch method. If antibodies are detected, then identify unacceptable antigens using a solid-phase single phenotype or solid-phase single-antigen test.
2. If no HLA antibodies or unacceptable antigens are detected, then report the paired candidate as unsensitized.
3. Report donor antigens that are considered absolute contraindications to transplant with the paired candidate as unacceptable antigens.
4. Before candidates can appear on their first OPTN KPD match run, each paired candidate's physician or surgeon or their designee and the histocompatibility laboratory director or the director's designee must review and sign a written approval of the unacceptable antigens listed for the paired candidate. The paired candidate's transplant hospital must document this review in the paired candidate's medical record.
5. Retest active candidates for antibodies according to #1 above at all of the following times:

    - ~~At least once every 90 days (+/- 20 days)~~ Within 110 days from the date of the ~~first~~ most recent antibody test
    - When any potentially sensitizing event occurs
    - When a paired candidate who has been inactive for more than 90 days has been reactivated
    - When an unacceptable and positive physical crossmatch occurs that precludes transplantation of the matched candidate

If any new unacceptable antigens are identified, then the paired candidate's transplant hospital must report these antigens using the process outlined in #3 and #4 above. If no new unacceptable antigens are identified, the paired candidate's transplant hospital must document the antibody screening results in the paired candidate's medical record.

Clerical Changes for Implementation of Adding Serum Sodium to the MELD Score

Sponsoring Committee:	**Liver and Intestinal Organ Transplantation Committee**
Policy/Bylaws Affected:	**9.1.D (MELD Score)**
Distributed for Public Comment:	**No**
Effective Date:	**January 2016 (Estimated)**

Problem Statement

The goal of this proposal is to make clerical changes to policy 9.1.D MELD Score (Adding Serum Sodium to the MELD Score) for the purposes of implementation. In July 2014, the OPTN/UNOS Board of Directors approved a policy to incorporate serum sodium into the MELD score for those with a MELD score greater than 11. Some candidates whose MELD scores increase as a result will be subject to recertification of their lab values on a more frequent basis, as outlined in OPTN Policy 9.2. In July 2015, the Executive Committee approved clerical changes to provide a grace period for members who need to recertify labs as a result of this policy change.

Summary of Changes

Once programmed, the system will automatically calculate candidates' new MELD score. There will be a 7-day grace period during implementation for those candidates whose scores would be moved from one recertification category to another, and may as a result require immediate recertification.

What Members Need to Do

To prepare for the implementation of this policy in January, we recommend that you begin to identify candidates who may be affected by this change and make advance preparations to schedule lab testing and reporting. To help you identify candidates whose scores are most likely to increase, UNOS has added currently reported serum sodium values to the Liver Candidate MELD/PELD Report available in UNet^{SM} under Waitlist: Reports. In addition, UNOS has added all data fields used to calculate MELD and PELD scores, including serum sodium, to the "Create Custom Report" function, also available under Waitlist: Reports. You may use either report to sort candidates by their currently reported serum sodium values, then use the attached resource chart to determine those whose MELD score is likely to change significantly upon policy implementation.

If a center has not recertified these candidates on the 8th day after implementation, the candidates will be downgraded to their previous lower MELD score as is done currently when certification expires.

Affected Policy/Bylaw Language:

New language is <u>underlined</u> and language that will be deleted is ~~struck through~~.

9.1.D MELD Score

Candidates who are at least 12 years old receive a<u>n initial</u> MELD$_{(i)}$ score equal to: *0.957 x Loge(creatinine mg/dL) + 0. 378 x Log$_e$(bilirubin mg/dL) + 1.120 x Loge (INR) + 0.643*

Laboratory values less than 1.0 will be set to 1.0 when calculating a candidate's MELD score.

The following candidates will receive a creatinine value of 4.0 mg/dL:

- Candidates with a creatinine value greater than 4.0 mg/dL
- Candidates who received two or more dialysis treatments within the prior 7 days
- Candidates who received 24 hours of continuous veno-venous hemodialysis (CVVHD) within the prior 7 days

The maximum MELD score is 40. The MELD score derived from this calculation will be rounded to the tenth decimal place and then multiplied by 10.

For candidates with an initial MELD score greater than 11, the MELD score is then re-calculated as follows:

$$MELD = MELD_{(i)} + 1.32*(137-Na) - [0.033*MELD_{(i)}*(137-Na)]$$

Sodium values less than 125 mmol/L will be set to 125, and values greater than 137 mmol/L will be set to 137.

If a candidate's recalculated MELD score requires recertification within 7 days of implementation based on *Table 9-1: Liver Status Update Schedule*, the transplant hospital will have 7 days to update laboratory values. If after 7 days the laboratory values are not updated, the candidate will be re-assigned to the previous lower MELD score.

Modifications to the Open Variance for the Recovery and Transplantation of Organs from HIV Positive Donors

Policy/Bylaws Affected: **OPTN Policy 15.6**

Distributed for Public Comment: **January 2016**

Effective Date: **November 21, 2015**

Problem Statement

During the June 2015 Board of Directors meeting the Board of Directors approved policy changes to create a variance for the allocation and transplantation of HIV positive organs into HIV positive recipients. However, a Board member expressed concern that the language in *Policy 15.6: Open Variance for the Recovery and Transplantation of Organs from HIV Positive Donors* addressing the allocation of HIV positive organs to HIV positive recipients not appearing on the match run did not clearly limit the practice to directed donations. During the development of the policy language, it was the OPO Committee's intent to only allow for an exception in cases where an HIV positive donor or legal next of kin wishes to directly donate organs to an HIV positive candidate, even if the candidate does not appear on the match run due to ABO incompatibility.

The HOPE Act states that "not later than 4 years after the date of enactment and annually thereafter, the Secretary shall review the results of scientific research in conjunction with the Organ Procurement and Transplant Network to determine whether the results warrant revision of the standards of quality." UNOS leadership discussed the OPTN's role in this review and how to best meet the statutory requirements. These discussions resulted in a recommended modification to the variance to require members participating in a HOPE Act research study to provide periodic reports from their data safety monitoring boards to the OPTN.

In addition, while preparing for the implementation of the HOPE Act on November 21, 2015, UNOS staff identified a proposed policy change that was not submitted to the Board of Directors in June 2015 as part of the HOPE Act proposal. This policy change was distributed for public comment during the September-December 2014 period; the policy had strong support during public comment and was approved by the OPO Committee. This policy change is necessary to remove the existing prohibition on the recovery and transplantation of organs from deceased donors known to be infected with HIV, and to allow for the conduct of research as outlined in OPTN Policy 15.6, the HOPE Act, and the OPTN Final Rule, and necessary for the successful implementation of the HOPE Act.

Summary of Changes

- Policy 2.7 was modified to remove the prohibition on the recovery and transplantation of organs from HIV positive donors to allow for the conduct of research.

- Policy 15.6.A was modified to clarify that allocation of HIV positive organs to HIV positive recipients not on the match run can only occur in the event of a directed donation. Additionally, UNOS staff revised the introductory paragraph of Policy 15.6 to remove the parentheses.

- Policy 15.6 was modified to include a requirement for members participating in a HOPE Act research study to provide periodic reports from their data safety monitoring boards to the OPTN.

What Members Need to Do

Members will be permitted to recover and transplant livers and kidneys from HIV positive donors as part of an IRB approved HOPE Act research study as outlined in OPTN Policy 15.6 (Open Variance for the Recovery and Transplantation of Organs from HIV Positive Donors) and the OPTN Final Rule.

The OPO must only allocate HIV positive organs to HIV positive candidates appearing on the match run, except in cases of directed donation. The OPO must verify that the potential recipient is registered as an HIV positive candidate at a transplant hospital that meets the requirements in *Policy 15.6.C Transplant Hospital Requirements for Transplantation of HIV Positive Organs*.

Transplant hospitals participating in this variance must submit a detailed schedule of required deadlines for IRB data safety monitoring reports that addresses the requirements in the HHS research criteria. Transplant hospitals will be required to submit the IRB data safety monitoring reports at each deadline in the schedule.

Affected Policy Language:

New language is underlined and language that will be deleted is ~~struck through~~.

2.7 HIV Screening of Potential Deceased Donors

~~Members may not participate in the recovery or transplantation of organs from deceased donors known to be infected with HIV. Members may only recover organs if the laboratory data, medical history, and behavioral history indicate that the donor is not HIV infected.~~

The host OPO must accurately document HIV test results for every deceased donor. All deceased donors must be tested for HIV according to *Policy 2.9: Required Deceased Donor Infectious Disease Testing*.

The host OPO must report the results of all HIV tests it performs directly to all receiving OPOs and transplant programs.

15.6 Open Variance for the Recovery and Transplantation of Organs from HIV Positive Donors

This variance applies to members participating in an institutional review board (IRB) approved research protocol that meets the requirements in the OPTN Final Rule regarding the recovery of organs from donors that test positive for human immunodeficiency virus (HIV) and the transplantation of these organs into HIV positive recipients,(including Health and Human Services (HHS) research criteria pertaining to the transplantation of organs from HIV positive donors, as applicable.) ~~regarding the recovery of organs from donors that test positive for human immunodeficiency virus (HIV) and the transplantation of these organs into HIV positive recipients.~~

Transplant hospitals participating in this variance must submit *all* of the following to the OPTN Contractor:

1. A detailed schedule of required deadlines for IRB data safety monitoring reports that addresses the requirements in the HHS research criteria.
2. IRB data safety monitoring reports at each deadline in the schedule.

15.6.A Requirements for Allocating HIV Positive Deceased Donor Organs

In addition to the requirements of the OPTN Final Rule, the OPO may allocate HIV positive organs only after determining the potential deceased donor is HIV positive and the HIV positive candidate is willing to accept an HIV positive organ as part of a research protocol. The OPO must only allocate HIV positive organs to HIV positive candidates appearing on the match run, except in cases of directed donation. ~~In the case of a directed donation and prior to transplant, the~~ The OPO must verify that the potential recipient is registered as an HIV positive candidate at a transplant hospital that meets the requirements in *Policy 15.6.C Transplant Hospital Requirements for Transplantation of HIV Positive Organs*.

15.6.B Requirements for Allocating HIV Positive Living Donor Organs

In addition to the requirements of the OPTN Final Rule, the recovery hospital must confirm that the potential living donor is HIV positive and the potential recipient is willing to accept an HIV positive organ as part of a research protocol.

15.6.C Transplant Hospital Requirements for Transplantation of HIV Positive Organs

In addition to the requirements of the OPTN Final Rule, transplant hospitals may transplant HIV positive organs only if *all* of the following conditions are true:

1. The transplant hospital notifies and provides documentation to the OPTN Contractor that it is participating in an institutional review board approved research protocol that meets the requirements in the OPTN Final Rule regarding the recovery and transplantation of organs from HIV positive individuals.
2. The transplant hospital obtains informed consent from the potential transplant recipient to participate in the institutional review board protocol that meets requirements in the OPTN Final Rule.
3. The transplant hospital meets the informed consent requirements according to *Policy 15.3 Informed Consent of Transmissible Disease Risk.*

In order for an HIV positive candidate to appear on a match run for HIV positive donor kidneys or livers, the transplant hospital must complete a two-person reporting and verification process. This process must include two different individuals who each make an independent report to the OPTN Contractor that the candidate is willing to accept an HIV positive organ as part of a research protocol.

Transplant hospitals must notify the OPTN Contractor if they will no longer participating in an IRB approved research protocol that meets the requirements in the OPTN Final Rule regarding the recovery and transplantation of organs from HIV positive individuals.

The OPTN Contractor may release to the public the names of members participating in this variance.

Clarification of Policy 18.1 Changes from June 2015 Board Meeting

Policy/Bylaws Affected: **OPTN Policies 18.1**

Distributed for Public Comment: **Yes; January 2015**

Effective Date: **Pending programming and notice to OPTN members**

Problem Statement

In June 2015, the Board approved numerous proposals that affected OPTN Policy 18.1: Data Submission Requirements. All five resolutions made changes to the language in this policy:

- Resolution 18 (VCA)
- Resolution 23 (Living Donation)
- Resolution 27 (VCA)
- Resolution 33 (OPO), as amended
- Resolution 35 (POC)

Upon updating the policy language for the September 1 implementation date, staff discovered that there was one line in Policy 18.1, Table 18.1 where the Board-approved language was in conflict. This conflict resulted in slight differences in phrasing in Resolution #27 and Resolution #33 as presented and approved at the June 2015 Board meeting. The Executive Committee reviewed and approved the resolved language, which corrects differences in language approved by the Board but does not make substantive changes to either proposal's language, nor does it change member data submission requirements from what was approved by the Board in June.

Summary of Changes

This change represents policy language that was approved by the Board but required resolution with another proposal that affected the same policy; both proposals were approved by the Board in June 2015. This conflict was created by slight differences in phrasing of the same language as shown in Resolution #27 and Resolution #33 below, as presented at the June 2015 Board meeting:

RESOLUTION 27

Table 18-1: Data Submission Requirements

~~This e following member:~~	~~Must submit the following materials to the OPTN Contractor:~~	~~Within:~~	~~For the following groups:~~
Host OPO	Deceased donor feedback	5 business days after the procurement date	All deceased donors

RESOLUTION 33
Amendment 1

Table 18-1: Data Submission Requirements

Host OPO	~~Deceased donor feedback~~ Donor organ disposition (feedback)	5 business days after the procurement date	Individuals, except living donors, from whom at least one organ is recovered

What Members Need to Do

Members who print out copies of their Policies or Bylaws as reference should print the updated versions when policy proposals are implemented.

Affected Policy/Bylaw Language:

New language is underlined and language that will be deleted is ~~struck through~~.

18.1 Data Submission Requirements

Members must report accurate data to the OPTN Contractor using standardized forms according to *Table 18-1* below.

Table 18-1: Data Submission Requirements

The following member:	***Must submit the following materials to the OPTN Contractor:***	***Within:***	***For:***
Histocompatibility Laboratory	*Donor histocompatibility* (DHS)	30 days after the OPO submits the deceased donor registration	Each heart, intestine, kidney, liver, lung, or pancreas donor typed by the laboratory
Histocompatibility Laboratory	*Recipient histocompatibility* (RHS)	*Either* of the following: • 30 days after the transplant hospital removes the candidate from the waiting list because of transplant • 30 days after the transplant hospital submits the *recipient feedback*	Each heart, intestine, kidney, liver, lung, or pancreas transplant recipient typed by the laboratory

The following member:	Must submit the following materials to the OPTN Contractor:	Within:	For:
OPOs, all	*Death notification records* (DNR)	30 days after the end of the month in which a donor hospital reports a death to the OPO or the OPO identifies the death through a death record review	All imminent neurological deaths and eligible deaths in its DSA
OPOs, all	*Monthly Donation Data Report: Reported Deaths*	30 days after the end of the month in which a donor hospital reports a death to the OPO	All deaths reported by a hospital to the OPO
Allocating OPO	*Potential transplant recipient* (PTR)	30 days after the match run date by the OPO or the OPTN Contractor	Each deceased donor heart, intestine, kidney, liver, lung, or pancreas that is offered to a potential recipient
Allocating OPO	VCA Candidate List	30 days after the procurement date	Each deceased donor VCA organ that is offered to a potential VCA recipient
Host OPO	*Donor organ disposition (feedback)*	5 business days after the procurement date	Individuals, except living donors, from whom at least one organ is recovered
Host OPO	*Deceased donor registration* (DDR)	30 days after the *donor organ disposition (feedback)* form is submitted and disposition is reported for all organs	All deceased donors
Recovery Hospitals	*Living donor feedback*	The time prior to donation surgery	Each potential living donor organ recovered at the hospital This does not apply to VCA donor organs

The following member:	Must submit the following materials to the OPTN Contractor:	Within:	For:
Recovery Hospitals	*Living Donor Feedback* Members must amend the form or contact the OPTN Contractor to amend this form according to *Policy 18.6: Reporting of Liver Donor Adverse Events*	72 hours after the donor organ recovery procedure	Any potential living donor who received anesthesia but did not donate an organ or whose organ is recovered but not transplanted into any recipient
Recovery Hospitals	*Living donor registration* (LDR)	60 days after the Recovery Hospital submits the *living donor feedback* form	Each living donor organ recovered at the hospital This does not apply to VCA donor organs
Recovery Hospitals	*Living donor follow-up* (LDF)	60 days after the six-month, 1-year, and 2-year anniversary of the donation date	Each living donor organ recovered at the hospital This does not apply to VCA donor organs
Transplant hospitals	*Organ specific transplant recipient follow-up* (TRF)	*Either* of the following: • 30 days after the six-month and annual anniversary of the transplant date until the recipient's death or graft failure • 14 days from notification of the recipient's death or graft failure	Each recipient followed by the hospital
Transplant hospitals	*Organ specific transplant recipient registration* (TRR)	60 days after transplant hospital removes the recipient from the waiting list	Each recipient transplanted by the hospital

The following member:	Must submit the following materials to the OPTN Contractor:	Within:	For:
Transplant hospitals	*Liver Post-Transplant Explant Pathology*	60 days after transplant hospital submits the *recipient feedback* form	Each liver recipient transplanted by the hospital
Transplant hospitals	*Recipient feedback*	24 hours after the transplant	Each heart, intestine, kidney, liver, lung, or pancreas recipient transplanted by the hospital
Transplant hospitals	Candidate Removal Worksheet	24 hours after the transplant	Each VCA recipient transplanted by the hospital
Transplant hospitals	*Recipient malignancy* (PTM)	30 days after the transplant hospital reports the malignancy on the *transplant recipient follow-up* form	Each heart, intestine, kidney, liver, lung, or pancreas recipient with a reported malignancy that is followed by the hospital
Transplant hospitals	*Transplant candidate registration* (TCR)	30 days after the transplant hospital registers the candidate on the waiting list	Each heart, intestine, kidney, liver, lung, or pancreas candidate on the waiting list or recipient transplanted by the hospital

Clarification of Policy 18.1 Changes from June 2015 Board Meeting

Policy/Bylaws Affected: **OPTN Policies 18.1**

Distributed for Public Comment: **Yes; January 2015**

Effective Date: **Pending programming and notice to OPTN members**

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RESOLUTION 33
Amendment 1

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What Members Need to Do

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Affected Policy/Bylaw Language:

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Recovery Hospitals	*Living donor feedback*	The time prior to donation surgery	Each potential living donor organ recovered at the hospital This does not apply to VCA donor organs

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Clerical Changes to OPTN Bylaws and Policies

Policy/Bylaws Affected: **OPTN Bylaws D.5 and Appendix K**
OPTN Policies 14.4.B and 14.4.C

Distributed for Public Comment: **No**

Effective Date: **August 11, 2015**

Problem Statement

In November 2014, the Board approved changes to the OPTN Bylaws that enable staff to make clerical, or non-substantive, changes to the Bylaws and Policies as they're identified, without prospective approval from the Executive Committee or Board of Directors as was previously required. This enables staff to make simple, clerical corrections that are then reviewed and approved by the Executive Committee at a subsequent meeting.

Summary of Changes

These clerical changes will increase the accuracy and clarity of our Policies and Bylaws. The table below summarizes the changes and the reason for each change.

Clerical Change	Reason
Bylaws D.5 Transplant Program Key Personnel	Deleted obsolete reference to *Appendix J: Membership and Personnel Requirements for Joint Heart and Lung Programs*, which no longer exists as of June 2014.
Bylaws Appendix K: Transplant Program Inactivity, Withdrawal, and Termination	Corrected typo that said "The following provisions of Appendix D do not apply to VCA transplant programs," with the correct reference to **Appendix K**.
Policy 14.4.B: Living Donor Medical Evaluation Requirements, Table 14-6: Requirements for Licind Donor Medical Evaluations	Removed unnecessary period.
Policy 14.4.B: Living Donor Medical Evaluation Requirements, Table 14-6: Requirements for Licind Donor Medical Evaluations	Corrected typo from *preventative* to *preventive* in "U.S. Preventive Services Task Force"
Policy 14.4.C, Table 14-7: Additional Requirements for Medical Evaluation of Living Kidney Donors	Deleted repeated language that introduces list of items required for the kidney-specific person history. Removed the first colon to combine the two lead clauses to only one, using a comma between. This also required making the letter "A" before *kidney-specific* a small "a."

What Members Need to Do

Members who print out copies of their Policies or Bylaws as reference should print the updated versions.

Affected Policy/Bylaw Language:

New language is underlined and language that will be deleted is ~~struck-through~~.

D.5 Transplant Program Key Personnel

Designated transplant programs must have certain key personnel on site. These key personnel include a qualified primary surgeon and primary physician that meet the requirements set forth in these Bylaws. For the detailed primary surgeon and primary physician requirements for specific organs, see the following appendices of these Bylaws:

- *Appendix E:Membership and Personnel Requirements for Kidney Transplant Programs*
- *Appendix F: Membership and Personnel Requirements for Liver Transplant Programs*
- *Appendix G: Membership and Personnel Requirements for Pancreas and Pancreatic Islet Transplant Programs*
- *Appendix H: Membership and Personnel Requirements for Heart Transplant Programs*
- *Appendix I: Membership and Personnel Requirements for Lung Transplant Programs*
- ~~*Appendix J: Membership and Personnel Requirements for Joint Heart and Lund Transplant Programs*~~

Appendix K: Transplant Program Inactivity, Withdrawal, and Termination

This appendix defines transplant program inactivity, withdrawal, and termination, and outlines what members must do to be in compliance with OPTN obligations during these periods.

The following provisions of Appendix ~~D~~K do *not* apply to VCA transplant programs:

- *K.1: Transplant Program Inactivity*
- *K.2: Short-term Inactive Transplant Program Status*
- *K.3: Long-term Inactive Transplant Program Status*

OPTN Policies

14.4.B Living Kidney Donor Medical Evaluation Requirements

Table 14-6: Requirements for Living Kidney Donor Medical Evaluations

Transmissible disease screening	Infectious disease testing must be performed in a CLIA-certified laboratory or in a laboratory meeting equivalent requirements as determined by Centers for Medicare and Medicaid Services (CMS) using FDA-licensed, approved, or cleared tests. Testing must include *all* the following: 1. CMV (Cytomegalovirus) antibody 2. EBV (Epstein Barr Virus) antibody 3. HIV antibody (anti-HIV) testing or HIV antigen/antibody (Ag/Ab) combination test as close as possible, but within 28 days prior to organ recovery 4. Hepatitis B surface antigen (HBsAg) testing as close as possible, but within 28 days prior to organ recovery 5. Hepatitis B core antibody (anti-HBc) testing as close as possible, but within 28 days prior to organ recovery 6. Hepatitis C antibody (anti-HCV) testing as close as possible, but within 28 days prior to organ recovery 7. HCV ribonucleic acid (RNA) by nucleic acid test (NAT) as close as possible, but within 28 days prior to organ recovery 8. Syphilis testing If a living donor is identified as being at increased risk for HIV, HBV, and HCV transmission according to *the U.S. Public Health Services (PHS) Guideline*, testing must also include HIV ribonucleic acid (RNA) by NAT or HIV antigen/antibody (Ag/Ab) combination test. This does not apply to donors whose only increased risk factor is receiving hemodialysis within the preceding 12 months, as they are at risk only for HCV according to the *U.S. Public Health Services (PHS) Guideline.* For tuberculosis (TB), living donor recovery hospitals must determine if the donor is at increased risk for this infection. If TB risk is suspected, testing must include screening for latent infection using *either*: • Intradermal PPD • Interferon Gamma Release Assay (IGRA).

Cancer screening	Recovery hospitals must develop and comply with protocols consistent with the American Cancer Society (ACS) or the U.S. Preventative Services Task Force to screen for: • Cervical cancer • Breast cancer • Prostate cancer • Colon cancer • Lung cancer

14.4.C Additional Requirements for the Medical Evaluation of Living Kidney Donors

Table 14-7: Additional Requirements for the Medical Evaluation of Living Kidney Donors

This evaluation must be completed:	Including evaluation for and assessment of this information:
Kidney - specific donor history	A personal history of significant medical conditions which include, but are not limited to: aA kidney-specific personal history including: a. Genetic renal diseases b. Kidney disease, proteinuria, hematuria c. Kidney injury d. Diabetes including gestational diabetes e. Nephrolithiasis f. Recurrent urinary tract infections
Kidney-specific family history	• Kidney disease • Diabetes • Hypertension • Kidney Cancer
Physical Exam	• Blood pressure taken on at least two different occasions or 24-hour or overnight blood pressure monitoring
Other metabolic testing	• Fasting blood glucose • Fasting lipid profile (cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol) • Glucose tolerance test or glycosylated hemoglobin in first degree relatives of diabetics and in high risk individuals
Kidney-specific tests	• Urinalysis or urine microscopy • Urine culture if clinically indicated • Measurement of urinary protein and albumin excretion • Measurement of glomerular filtration rate by isotopic methods or a creatinine clearance calculated from a 24-hour urine collection • Hospitals must develop and comply with a written protocol for polycystic kidney disease or other inherited renal disease as indicated by family history • Patients with a history of nephrolithiasis or nephrolithiasis (>3 mm) identified on radiographic imaging must have a 24-hour urine stone panel measuring: o Calcium o Oxalate o Uric acid o Citric acid o Creatinine o Sodium

This evaluation must be completed:	Including evaluation for and assessment of this information:
Anatomic assessment	Determine: • Whether the kidneys are of equal size • If the kidneys have masses, cysts, or stones • If the kidneys have other anatomical defects • Which kidney is more anatomically suited for transplant