

## ***At-a-Glance***

### **Proposal to Collect Ex Vivo Lung Perfusion (EVLN) Data for Transplant Recipients**

- **Affected/Proposed Policy:** No policies or bylaws are affected by this proposal.

- **Thoracic Organ Transplantation Committee**

Ex vivo lung perfusion (EVLN) is an emerging technology that can be used during transport, and to preserve and condition lungs prior to transplantation. The utilization of EVLN is not currently reported to the OPTN, so the OPTN cannot determine how many lungs have been perfused and then transplanted. In the spring of 2015, the OPTN will implement changes to the OPTN Tiedi forms, including the Deceased Donor Registration form (DDR). Through the modified DDR, Organ Procurement Organizations (OPOs) will report whether an accepting transplant program intends to perfuse the lungs prior to transplant. However, there is no corresponding field on the Transplant Recipient Registration form (TRR) for transplant programs to report whether lungs were perfused prior to transplant. The Thoracic Committee believes it is important to capture this information to monitor lung allocation, recipient safety, and organ and patient outcomes. This information will also be important for future policy development and risk adjustment for member-specific performance measures.

- **Affected Groups**

Transplant Administrators  
Transplant Data Coordinators  
Transplant Physicians/Surgeons  
Organ Recipients

- **Number of Potential Candidates Affected**

This proposal requires data to be reported for all lung and heart-lung transplant recipients. In 2013, there were 1,923 lung transplant recipients, and 23 heart-lung transplant recipients.

- **Compliance with OPTN Strategic Goals and Final Rule**

This proposal meets the OPTN strategic goal of “promoting patient safety” by increasing the Thoracic Committee’s ability to identify potential patient safety risks posed by EVLN technology.

This proposal also meets the strategic goal of “increasing the number of transplants” by increasing the number of organs transplanted from each donor and reducing the number of organs donated but unused, because the Thoracic Committee will monitor the effectiveness of this technology and potentially use the data to develop guidance or policies that account for the effect of EVLN in lung transplantation. For example, if EVLN increases the number of organs transplanted from each donor, the Thoracic Committee may develop guidance or policy that incentivizes the use of EVLN.

## **Proposal to Collect Ex Vivo Lung Perfusion (EVLP) Data for Lung Transplant Recipients**

### **Affected/Proposed Policy:**

No policies or bylaws are affected by this proposal.

### **Thoracic Organ Transplantation Committee**

**Public comment response period: January 27, 2015 – March 27, 2015**

### **Summary and Goals of the Proposal:**

Ex vivo lung perfusion (EVLP) is an emerging technology that can be used during transport, and to preserve and condition lungs prior to transplantation. The utilization of EVLP is not currently reported to the OPTN, so the OPTN cannot determine how many lungs have been perfused and then transplanted. In the spring of 2015, the OPTN will implement changes to the OPTN Tiedi forms, including the Deceased Donor Registration form (DDR). Through the modified DDR, Organ Procurement Organizations (OPOs) will report whether an accepting transplant program intends to perfuse the lungs prior to transplant. However, there is no corresponding field on the Transplant Recipient Registration form (TRR) for transplant programs to report whether lungs were perfused prior to transplant. The Thoracic Committee believes it is important to capture this information to monitor lung allocation, recipient safety, and organ and patient outcomes. This information will also be important for future policy development and risk adjustment for member-specific performance measures.

### **Background and Significance of the Proposal:**

The Food and Drug Administration (FDA) recently designated one type of EVLP as a Humanitarian Use Device through the Humanitarian Device Exemption pathway.<sup>1</sup> With this approval, and several more trials of alternative non-FDA approved EVLP systems underway, EVLP technology is quickly being introduced to the lung transplant community. Studies reveal the benefits of using EVLP for assessment, preservation, improvement, and reparation of donated lungs, particularly those that are “marginal,” “less than ideal,” “injured,” or lungs procured from donors after cardiac death (DCD). In doing so, EVLP introduces the hope that lungs that may have otherwise been discarded can be safely transplanted, thereby increasing the number of potential donors and donated lungs.<sup>2</sup>

There are various approaches and techniques for using EVLP. Some studies are exploring the use of EVLP for lungs brought to the transplant center that “do not meet the standard clinical criteria for donor lung utilization.”<sup>3,4</sup> Others are examining whether EVLP can be used “to preserve and transport donor lungs” “in a normothermic state through continuous normothermic perfusion and ventilation,”<sup>5</sup> including “donor lungs that may not meet current standard donor lung acceptance criteria for transplantation.”<sup>6</sup> One institution is examining the “safety of transplanting lungs obtained from non-heart beating donors (NHBDs) that have been ventilated and perfused

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<sup>1</sup> FDA News Release: “FDA approves donor lung preservation device that may result in more lung transplants,” August 12, 2014. <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm409488.htm> (Accessed on December 12, 2014)

<sup>2</sup> Cypel M, Van Raemdonck D, “Ex vivo Lung Perfusion: Where are We...and What's Next?” ISHLT Links, August 2014: Vol 6:4. [http://www.ishlt.org/ContentDocuments/2014AugLinks\\_EVLP.html](http://www.ishlt.org/ContentDocuments/2014AugLinks_EVLP.html) (Accessed on December 12, 2014).

<sup>3</sup> Cypel M, Yeung J, “Normothermic Ex Vivo Lung Perfusion in Clinical Lung Transplantation,” *N Engl J Med*. 2011 Apr 14;364(15):1431-40. DOI: 10.1056/NEJMoa1014597.

<sup>4</sup> Novel Lung Trial: Normothermic Ex Vivo Lung Perfusion (EVLP) As An Assessment of Extended/Marginal Donor Lungs. <http://clinicaltrials.gov/ct2/show/NCT01365429?term=xvivo&rank=1> (Accessed on December 12, 2014).

<sup>5</sup> International Randomized Study of the TransMedics Organ Care System (OCS Lung) for Lung Preservation and Transplantation (INSPIRE). <http://clinicaltrials.gov/ct2/show/NCT01630434?term=transmedics&rank=1> (Accessed on December 12, 2014)

<sup>6</sup> International EXPAND Lung Pivotal Trial (EXPANDLung) <https://clinicaltrials.gov/ct2/show/NCT01963780?term=transmedics&rank=3> (Accessed on December 12, 2014).

with a lung perfusion solution...”<sup>7</sup> Another trial will examine the safety of transplanting a lung that is first “packaged and transported on ice” to the trial sponsor’s “dedicated facility,” where the “EVLP procedure will be performed by Certified Ex Vivo Lung Specialists using the Toronto EVLP System™...” prior to being subsequently cooled and transported to the transplant hospital.<sup>8</sup>

Due to the proliferation of studies examining the effectiveness of EVLP, in 2012 the Thoracic Committee formed an EVLP workgroup, comprised of representatives from the Thoracic Committee, OPO Committee, and other EVLP experts in the transplant community to discuss allocation, data collection and lung utilization with regard to EVLP. The Work Group ultimately determined that the introduction of EVLP into the market does not warrant changes to current lung allocation policy at this time. However, the Work Group recommended that the OPTN begin collecting data on EVLP to monitor adherence to current allocation policy, EVLP use, and transplant recipient outcomes.

### Proposed Data Fields

Based on the EVLP workgroup’s recommendation to collect these data, the Lung Subcommittee of the Thoracic Committee identified data fields that they believe will be most critical to detecting potential patient safety risks, and developing potential changes to allocation policy and risk adjustment in the future. For a visual depiction of the proposed data fields, please see the Exhibits at the end of this document.

The Subcommittee first reviewed the current TRR for kidney transplant recipients to determine whether changes to the lung TRR could be modeled after it.<sup>9</sup> The kidney TRR includes fields for total cold ischemia time (per side), total warm ischemia time (per side) and asks how kidneys were received in the OR (on ice, on pump, n/a).

Total ischemia time is already collected for lung and heart-lung transplant recipients, and the Subcommittee proposes only minor changes to the question, changing “Total Organ Ischemia Time (include cold, warm and anastomotic time)” to “Total organ ischemia time from cross clamp to in situ reperfusion (include warm and cold time).” The Subcommittee believes the modified question more clearly communicates the information the transplant center should report.

Some types of EVLP may necessitate more cold and warm ischemia time than others. Ischemia time will help determine whether lungs were simply transported from the donor directly to the transplant center using a warm EVLP device, or whether they were perfused or re-conditioned prior to transplant. The Subcommittee members hypothesize the difference in ischemia times may ultimately affect a candidate’s waiting list mortality or post-transplant survival. The Subcommittee therefore determined that total ischemia time is critical for future analysis.

Following the kidney TRR model, the Subcommittee determined it is not as important to collect data regarding the EVLP technique or provider as it is to simply know whether ex vivo perfusion was utilized. Therefore, the Subcommittee proposed adding a new question to the lung and heart-lung TRR: “Lung(s) perfused prior to transplant?” If the transplant program answers “no” it will not be required to provide any more information. If the transplant program answers “yes,” it will be prompted to report where the perfusion occurred. The Subcommittee outlined a number of locations in which perfusion may occur, including: at the OPO; at the recovery site (donor hospital); at the transplant hospital that performed the transplant; at a different transplant hospital;

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<sup>7</sup> Ex-vivo Perfusion and Ventilation of Lungs Recovered From non-Heart-Beating Donors to Assess Transplant Suitability. <http://clinicaltrials.gov/ct2/show/NCT01615484?term=xvivo&rank=4> (Accessed on December 12, 2014).

<sup>8</sup> Extending the Preservation and Assessment Time of Donor Lungs Using the Toronto EVLP System<sup>SM</sup> at a dedicated Ex Vivo Lung Perfusion (EVLP) Facility. <http://clinicaltrials.gov/ct2/show/NCT02234128?term=perfusix&rank=1> (Accessed on December 12, 2014)

<sup>9</sup> [http://www.unos.org/docs/Kidney-Adult\\_Transplant\\_Recipient\\_Registration.pdf](http://www.unos.org/docs/Kidney-Adult_Transplant_Recipient_Registration.pdf) (Accessed on December 12, 2014)

or “other.” If the transplant program selects “other,” there will be a field in which they can describe where the perfusion occurred.

After indicating where EVLP occurred, the transplant program will be required to report who performed EVLP. The choices are “the transplant program,” “the OPO,” or “other.” If the transplant program selects “other,” there will be a field in which they can describe who performed the perfusion. The transplant program will also report the total time the lungs were perfused.

Along with total ischemia time and determining whether the lungs were perfused, the Subcommittee proposes adopting the kidney TRR’s question regarding whether the lungs were received at the transplant center on ice or on a pump. If the lungs arrived on a pump, the transplant program will be required to answer, for the right lung and the left lung individually, whether the lung stayed on the pump or was put on ice.

Lastly, the Subcommittee reviewed the existing options on the Deceased Donor Registration form (DDR) that allow OPOs to accurately report why lungs were recovered but not transplanted. The Subcommittee determined that the current list of reasons on the DDR is sufficient to communicate to the OPTN that an organ was recovered and allocated by the OPO, accepted and perfused by a transplant program but ultimately not transplanted.<sup>10</sup>

The Subcommittee believes that collecting this additional information, combined with other information that is already collected for lung transplant candidates, will enable future analyses of the effect of EVLP on lung transplant recipient outcomes. The Subcommittee also believes that the questions are ample to be able to distinguish between various types of EVLP procedures and techniques.

The Subcommittee considered whether to require transplant centers to report even more detailed information, such as measurements that can be obtained while the lungs are being perfused. Though the Subcommittee believes such information would be interesting to analyze from a research perspective, it does not believe such information is critical to achieve their stated goals of identifying potential patient safety risks associated with lungs transplanted post-EVLP, determining which patients are being transplanted with perfused lungs, and potentially using these data for future policy development or risk adjustment. Additionally, the Subcommittee weighed the benefits of collecting more detailed information against the risk that more detailed or complicated data entry may lead to less reliable information. It determined that proposing a minimal number of additional fields, modeled after a currently existing form, will make the data gathering and reporting less burdensome for transplant centers while still providing the OPTN with ample information.

The Subcommittee also discussed whether the OPTN is the appropriate entity to collect these information. There are several published studies and several transplant hospitals already using EVLP; can the OPTN collect these data through a sharing arrangement rather than requiring new data collection? Ultimately, the Subcommittee determined it is critical that the OPTN collect these data independently. Many of the studies and centers participating in the studies cannot share information until the results are published. Additionally, there is no guarantee that every transplant center that transplants a perfused lung will share this information unless it is required by the OPTN. Because the Subcommittee is concerned about patient safety as well as improving its policies and risk adjustment, it is critical that the OPTN obtain the most accurate and complete information regarding EVLP as possible.

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<sup>10</sup> See Appendix for current list of reasons for non-transplant available on the DDR

The Subcommittee presented its recommendations to the full Thoracic Committee on December 18, 2014. After discussion, the Thoracic Committee voted to distribute this proposal for public comment in January 2015 (11 support; 0 oppose; and 0 abstain).

### **Supporting Evidence and/or Modeling:**

With the FDA's recent decision to approve use of one type of EVLP under a humanitarian device exemption, the Thoracic Committee believes the time is ripe to begin collecting EVLP data. Multiple studies report the observed benefits of EVLP thus far. EVLP provides transplant teams with additional time to "further test and improve the function of questionable lungs and to follow the trajectory of the performance of these lungs before making the decision to transplant."<sup>11</sup> Additional cold ischemic times necessitated by the use of some EVLP techniques may not negatively impact transplant recipients.<sup>12</sup> Recipients transplanted with lungs that were initially "marginal" prior to perfusion appear to achieve similar post-transplant results as candidates transplanted with conventional lungs.<sup>13</sup> Outcomes in recipients whose transplanted lungs were perfused and preserved during transportation from the donor hospital to the transplant hospital also appear to be promising and comparable to standard cold transportation techniques.<sup>14</sup>

In the future, EVLP may even change the landscape of the traditional lung procurement and allocation process by enabling transplant hospitals to use EVLP services provided by a centralized regional perfusion center.<sup>15</sup> A study to examine the effectiveness of this practice in the United States is soon to begin.<sup>16</sup>

As studies of the use of EVLP indicate its short-term effectiveness in increasing the number of usable donor lungs by preserving and improving donated lungs, the technology appears likely to be adopted by transplant hospitals and OPOs across the country. Its use may even expand to other organs, and to other non-OPO and non-transplant hospital providers. The long-term effect on post-transplant functionality and outcomes is still largely unknown due to the newness of the technology, however, studies are beginning to show that functional outcomes are similar when comparing recipients transplanted with lungs that were perfused with recipients transplanted with conventional lungs.<sup>17</sup> Therefore, the Thoracic Committee believes it is imperative to begin to collect the proposed data to monitor the use of EVLP. Monitoring the use of EVLP will help the Thoracic Committee identify potential patient safety risks and will also inform the Thoracic Committee's analysis for future policy development and risk adjustment.

### **Expected Impact on Living Donors or Living Donation:**

This proposal will have minimal impact on living donors or living donation since living lung donation comprises a very small percent of lung transplant donors. However, if EVLP successfully increases the donor pool by converting marginal donor lungs to usable donor lungs, the number of living lobe donation of lungs may decrease even more. Alternatively, a lung from a living lung donor may be transplanted after undergoing EVLP; this will not require data collection on the

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<sup>11</sup> Tikkanen JM, Cypel M. "Functional Outcomes and quality of life after normothermic ex vivo lung perfusion lung transplantation." *J. Heart and Lung Transplantation*, October 2014, DOI:10.1016/j.healun.2014.09.044

<sup>12</sup> Krueger T., Machuca T. J. *Heart and Lung Transplantation. Impact of Extended Cold Ischemic Times on Outcome of Clinical Lung Transplantation Using Ex Vivo Lung Perfusion (EVLP)*. Vol.32, No 4S April 2014 (S94)

<sup>13</sup> Cypel M, Yeung J. "Normothermic Ex Vivo Lung Perfusion in Clinical Lung Transplantation," *N Engl J Med*. 2011 Apr 14;364(15):1431-40. DOI: 10.1056/NEJMoa1014597.

<sup>14</sup> Warnecke G, Moradiellos J, "Normothermic perfusion of donor lungs for preservation and assessment with the Organ Care System Lung before bilateral transplantation: a pilot study of 12 patients," *Lancet* 2012, 380:1851-58.

<sup>15</sup> Whitson BA, Black SM. Organ Assessment and repair centers: The future of transplantation is near. *World J Transplant* 2014; 4(2): 40-42. DOI: 10.5500/wjt.v4.i2.40.

<sup>16</sup> Extending the Preservation and Assessment Time of Donor Lungs Using the Toronto EVLP System<sup>SM</sup> at a dedicated Ex Vivo Lung Perfusion (EVLP) Facility. <http://clinicaltrials.gov/ct2/show/NCT02234128?term=perfusix&rank=1> (Accessed on December 12, 2014)

<sup>17</sup> Tikkanen JM, Cypel M. "Functional Outcomes and quality of life after normothermic ex vivo lung perfusion lung transplantation." *J. Heart and Lung Transplantation*, October 2014, DOI: 10.1016/j.healun.2014.09.044.

perfusion of living donor lungs.

**Expected Impact on Specific Patient Populations:**

There is no known impact on specific patient populations.

**Expected Impact on Program Goals, Strategic Plan, and Adherence to OPTN Final Rule:**

This proposal meets the OPTN strategic goal of “promoting patient safety” by increasing the Thoracic Committee’s ability to identify potential patient safety risks posed by EVLP technology.

This proposal also meets the strategic goal of “increasing the number of transplants” by increasing the number of organs transplanted from each donor and reducing the number of organs donated but unused, because the Thoracic Committee will monitor the effectiveness of this technology and potentially use the data to develop guidance or policies that account for the effect of EVLP in lung transplantation. For example, if EVLP increases the number of organs transplanted from each donor, the Thoracic Committee may develop guidance or policy that incentivizes the use of EVLP.

**Plan for Evaluating the Proposal:**

This proposal is designed to capture information about EVLP to monitor transplant recipient safety and outcomes. Tabulations will be provided at approximately 6 months after implementation, and then annually thereafter.

A tabulation of lung transplants involving ex vivo perfusion will be provided for lung transplants performed following implementation of the Tiedi form changes. At a minimum, this tabulation will include:

- The number of transplants involving perfusion
- Primary graft dysfunction at 72 hours
- Graft survival at 30 days and 1 year (after accrual of sufficient follow-up)

These results will be provided overall and, where possible, stratified by

- Donation after circulatory death vs. donation after brain death
- Procedure type (single vs. double)

For comparison, results will also be shown for lung transplants that did not involve ex vivo perfusion.

**Additional Data Collection:**

As described in depth above, additional data collection will be required as a result of this proposal. This data collection effort is justified by the OPTN Principle of Data Collection: “Institutional members must provide sufficient data to OPTN to allow it to: a) Develop transplant, donation and allocation policies; ... c) determine member-specific performance; and d) ensure patient safety when no alternative sources of data exist.”

**Expected Implementation Plan:**

If approved, this proposal will require an additional public comment posted in the Federal Register sponsored by the Health Resources and Services Administration (HRSA) to adhere to the Office of Management and Budget’s guidelines for collecting additional information. If approved, this proposal will require programming to edit the Transplant Recipient Registration form in Tiedi<sup>SM</sup>.

Upon implementation, transplant programs will be required to provide the OPTN with EVLP data for all lung and heart-lung transplant recipients.

**Communication and Education Plan:**

This proposal will be monitored for specific instructional needs, but an instructional program is likely not needed. Specific communication efforts associated with the proposal will include:

- Policy notice
- System notice
- Updates to Help Documentation in UNet<sup>SM</sup>
- Presentation at Regional Meetings

**Compliance Monitoring:**

The proposed language will not change the current routine monitoring of OPTN members. Any data entered in UNet<sup>SM</sup> may be subject to OPTN review, and members are required to provide documentation as requested.

**Policy or Bylaw Proposal:**

This section is not applicable because policy language is not affected by this proposal. However, the OPTN Principles of Data Collection require that “new data collection will require approval by the Policy Oversight Committee and the Board of Directors of the OPTN, and be subject to public comment.” Because this proposal requires additional data collection from OPTN members, it must be circulated for public comment.

## Exhibits

These screen shots show the fields the Thoracic Committee proposes adding to the TRR. The first image reveals how the TRR would appear if the transplant program answered “yes” to the question: “Lung(s) perfused prior to transplant?”

Clinical Information : TRANSPLANT PROCEDURE

Multiple Organ Recipient

Were extra vessels used in the transplant procedure:

Procedure Type:

- SINGLE LEFT LUNG
- SINGLE RIGHT LUNG
- BILATERAL SEQUENTIAL LUNG
- EN-BLOC DOUBLE LUNG
- LOBE, RIGHT
- LOBE, LEFT

Total organ ischemia time from cross clamp to in situ reperfusion (include warm and cold time):

Left Lung:  min ST=  VIEW OPTIONS

Right Lung (OR EN-BLOC):  min ST=  VIEW OPTIONS

Lung(s) perfused prior to transplant:  YES  NO

Perfusion occurred at:

- Recovery site (donor hospital)
- OPO
- Transplant hospital - transplant site
- Transplant hospital - not transplant site
- Other Specify:

Perfusion performed by:

- OPO
- Transplant program
- Other Specify:

Total time on perfusion:  min ST=  VIEW OPTIONS

Lung(s) were received at transplant center:

On ice:  YES  NO

On pump:  YES  NO

Right lung:  Stayed on pump  Put on ice  N/A

Left lung:  Stayed on pump  Put on ice  N/A



The following image shows how the TRR would appear if the transplant program answered “no” to the question: “Lung(s) perfused prior to transplant?”

Clinical Information : TRANSPLANT PROCEDURE

Multiple Organ Recipient

Were extra vessels used in the transplant procedure:

Procedure Type:

- SINGLE LEFT LUNG
- SINGLE RIGHT LUNG
- BILATERAL SEQUENTIAL LUNG
- EN-BLOC DOUBLE LUNG
- LOBE, RIGHT
- LOBE, LEFT

Total organ ischemia time from cross clamp to in situ reperfusion (include warm and cold time):

Left Lung:  min ST=  VIEW OPTIONS

Right Lung (OR EN-BLOC):  min ST=  VIEW OPTIONS

Lung(s) perfused prior to transplant?  YES  NO

## Appendix

### List of Reasons for Non-Transplant Available on Current Deceased Donor Registration Form

- Too old on pump
- Too old on ice
- Vascular damage
- Ureteral damage
- Inadequate urine output
- Donor medical history
- Donor social history
- Positive CMV
- Positive HIV
- Positive Hepatitis
- Warm ischemic time too long
- Organ trauma
- Organ not as described
- Biopsy findings
- Recipient determined to be unsuitable for TX in OR
- Poor organ function
- Infection
- Diseased organ
- Anatomical abnormalities
- No recipient located - list exhausted
- Other, specify