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### **Subject to technical changes**

Because of continuous product improvements, the illustrations and technical information found in the XPS User's Guide may differ (slightly) from the current version of the device.

### **User Guide References**

This document was created using information from:

- 1) CardioHelp User's Manual/English/0.9.0
- 2) CardioHelp XVIVO/Technical Data/Maintenance/ English/100813
- 3) Flow/bubble sensor/ Technical Data/English/100812
- 4) Hamilton C2 Operator's Manual 624131/02 Software version 1.1.x (April 2009)
- 5) Hico-Variotherm 550 Instructions for Use/ REF 542801 Rev.2-08/05

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# XVIVO Perfusion System (XPS™) with Steen Solution™

## Professional Labeling

### CAUTION

**Humanitarian Device.** Authorized by Federal law for use in flushing and temporary continuous normothermic machine perfusion of initially unacceptable excised donor lungs during which time the *ex-vivo* function of the lungs can be reassessed for transplantation. The effectiveness of this device for this use has not been demonstrated.

#### XVIVO Perfusion Clinical & Technical Support Phone Numbers

**US Clinical Support**

**U.S. Technical Support**

**U.S. Main Switchboard                      303-395-9171**

### READ ENTIRE CONTENTS PRIOR TO USING THIS PRODUCT

#### Product Indication for Use

The XVIVO Perfusion System (XPS™) with STEEN Solution™ Perfusate is indicated for the flushing and temporary continuous normothermic machine perfusion of initially unacceptable excised donor lungs during which time the *ex-vivo* function of the lungs can be reassessed for transplantation.

#### User Qualifications

This product is intended for use only by qualified medical professionals trained in the particular technique and/or surgical procedure to be performed.

#### Rx ONLY - PRESCRIPTION USE ONLY

Caution: Federal law restricts this device to sale by or on the order of a physician.

#### CONTRADICTIONS

There are no known contraindications.

#### WARNINGS

##### General Warnings

The safety and probable benefit of the XPS™ System with STEEN Solution™ Perfusate device were not evaluated with ideal criteria donor lungs.

##### ***Risk for contamination and mechanical trauma:***

The degree of organ manipulation required for airway and vascular cannulation carries the potential for contamination and mechanical trauma of the donor lungs. Even though not contraindicated, it is not recommended to use an organ with evident signs of mechanical trauma or major contamination.

##### ***Transplant Suitability Post-Ex Vivo Lung Perfusion (EVLP)***

The responsibility for correct clinical use and interpretation of the lung function evaluations during EVLP in determining transplant suitability resides exclusively with the transplant surgeon.

Like in any other clinical decision, all available data should be taken into consideration when determining the suitability of an organ for transplantation; that is, the transplant surgeon is clinically satisfied with the lung evaluation. This criterion should take priority, since the transplant surgeon is the ultimate responsible person for safely transplanting EVLP lungs. The use of the EVLP lung physiologic evaluations in determining transplantability (e.g., EVLP transplantability criteria) has been evaluated in the clinical studies, including the NOVEL trial (see

summary of NOVEL study below). Validation has not occurred as to whether the parameters are adequate as surrogates for *in vivo* performance.

### **XPS™ Machine operation-related WARNINGS**

See Warnings and Precautions in the XPS™ System Instructions for Use manual.

### **STEEN Solution™**

The responsibility for correct clinical use and technique rests with the user. The Instructions for Use are only provided as suggestions for procedure. The user must, on the basis of his or her medical training and experience, evaluate the suitability of this procedure.

Adverse Effects – When administered systemically, human serum albumin and Dextran have been associated with rare allergic reactions. However, no such reactions have been reported with either of these substances when used for *ex vivo* lung preservation.

### **PRECAUTIONS**

#### **XVIVO Cannula set**

Store at room temperature. Use only undamaged/ unopened containers. Single Use Only.

#### **XVIVO™ Organ Chamber**

Store at room temperature. Use only undamaged/ unopened containers. Single Use Only.

#### **XPS™ Lung Circuit**

Store at room temperature. Use only undamaged/ unopened containers. Single Use Only.

#### **XVIVO™ Lung Disposables Kit**

Store at room temperature. Use only undamaged/ unopened containers.

### **XPS™ Machine operation-related PRECAUTIONS**

See Warnings and Precautions in the XPS™ System Instructions for Use manual.

### **STEEN Solution™**

STEEN Solution™ is intended for single use only and MAY NOT BE REUSED. Any leftover solution must be disposed of after the procedure.

Do not use STEEN Solution™ if the solution is not clear, the bottle is damaged, the flip-tear seal has been tampered with, or if the “use by” date has expired.

### **DESCRIPTION**

The XPS™ with STEEN Solution™ Perfusate consists of the XPS Perfusion Cart Hardware, fluid path and non-fluid path disposables, XPS Cart Software, and STEEN Solution™.

The STEEN Solution™ is a clear, sterile, non-pyrogenic, non-toxic, physiological, extracellular (low potassium) electrolyte solution containing human serum albumin (HSA) and dextran 40. The solution has a colloid-osmotic pressure (COP) so that during perfusion a physiological pressure and flow can be maintained in the lung without the development of pulmonary edema (fluid accumulation in the air spaces and parenchyma of the lungs).

The XPS™ System is an integrated cardiac bypass system comprised of various components, such as a Maquet CardioHelp centrifugal pump (K102726), the HicoVariotherm Heater/Cooler, the Hamilton C2 ICU (intensive care unit) pressure-controlled ventilator (K092148), the perfusate gas monitors, and the display monitors.

The XPS™ System is responsible for housing the organ for preservation, providing the normothermic environment, and perfusing the organ with the STEEN Solution™. Please see the XPS™ Instructions for Use manual for a more detailed device description and system set-up and operation information, including flow and perfusion rates, ventilation rates, duration of flushing, and other operational parameters.

## **STEEN Solution™**

The STEEN Solution™ is supplied sterile in a bottle made of PETg and equipped with a PE screw cap lined with a silicone septum closure, which facilitates aseptic transfer of the solution. The screw cap is sealed by a temper evident plastic sleeve. The STEEN Solution™ product insert should be read prior to use of this product.

## **XPS™ Machine**

The XVIVO Perfusion Cart will be shipped in a large wooden crate container.

## **XVIVO Cannula set™**

The XVIVO Lung Cannula Set™ is a sterile, single-use Set intended to be used to connect isolated donor lungs to an extracorporeal perfusion system for ex-vivo assessment

## **XVIVO Organ Chamber™**

The XVIVO Organ Chamber™ is a sterile, single-use container intended to be used as a temporary receptacle for isolated donor lungs in preparation for eventual transplantation into a recipient.

## **XPS™ Lung Circuit**

The XPS™ Lung Circuit is a single-use, disposable extracorporeal perfusion circuit intended to be used with the XVIVO Perfusion System (XPS™) to facilitate perfusion of STEEN Solution™ through isolated donor lungs in preparation for eventual transplantation into a recipient.

## **XVIVO Lung Disposables Kit**

The XVIVO Lung Disposables Kit contains a number of single-use, disposable sterile and non-sterile items intended to be used with the XVIVO Perfusion System (XPS™) for *ex-vivo* evaluation of donor lungs.

The XVIVO Lung Disposable Kit contains the following items: Fluid Level Sensor, Pressure Sensor Line, sterile XVIVO Lung Cannula Set™, Limb-o Breathing Circuit, Ventilator Flow Sensor, sterile Bacterial/Viral Filter, and sterile Drape. The Fluid Level Sensor, Pressure Sensor Line, and Limb-o Breathing Circuit are not organ contacting.

## **OPERATIONS**

Refer to the XPS™ Instructions for Use manual and product inserts for the operation and performance of each component of the XVIVO Perfusion System.

## **NORMOTHERMIC EXVIVO LUNG PERFUSION (EVLP)**

Normothermic EVLP may permit utilization of initially unacceptable excised donor lungs which are currently often discarded despite the relatively reversible nature of their imperfections. The ultimate objective of the EVLP procedure is to expand the donor organ pool and thus possibly reduce mortality and morbidity on the transplant waiting list.

EVLP with STEEN Solution™ will help increase the pool of available organs by allowing assessment of marginal lungs in optimized conditions. Several mechanisms have been proposed to contribute to this:

- The warming and reperfusion period allows time for lung preservation in an optimized environment. The *ex vivo* perfusion is carefully controlled using a lung-protective strategy (see the XPS™ Instructions for Use manual).
- The physiologic problems caused by neurogenic pulmonary edema in the organ donor with respect to electrolytic balance, colloid-osmotic pressure, and temperature may be restored during this protective reperfusion period.
- Any remaining donor blood still in the lungs (containing coagulation factors, complement, activated white cells, inflammatory cytokines, and non-physiological substances, including drugs used during donor management) is diluted and filtered away during EVLP. This washing out benefit is not achieved with hypothermic perfusion as the cold temperature induces vascular constriction within the lung, preventing complete flushing.
- It may facilitate removal of clots in the pulmonary circulation through the use of transient retrograde perfusion at the beginning of the procedure.
- The *ex vivo* system provides an environment for recruitment and re-expansion of atelectatic lung areas because it allows for all ventilatory volumes and pressures to be transferred directly to the lungs without interference of the chest wall and diaphragm.
- It allows time to assess and clean/suction bronchial secretions.

- The dextran in the perfusate solution facilitates perfusion of the pulmonary micro-vasculature.

### EVLP STEP-BY-STEP OVERVIEW

Step One: Identify if lung meets non-acceptance criteria, pre-EVLP assessments

Step Two: If, yes retrieve lung per standard lung protocol.

Step Three: Perform the EVLP procedure in accordance with the XPS™ Instructions for Use manual

Step Four: Evaluate lung for transplant suitability

Step Five: Transplant or discard lung in accordance with the center policy.

See the XPS™ System Instructions for Use manual for more detailed device description and system set-up and operation information, including flow and perfusion rates, ventilation rates, duration of flushing, and other operational parameters.

### PATIENT EDUCATION

It is important to adequately inform patients who might be receiving initially unacceptable, reassessed lungs treated with EVLP about the risks to health and probable benefits. Patient education is critical so that they may be able to make informed decisions, and should be performed when a patient is added to the organ transplant waiting list. EVLP treatment and reassessment of initially unacceptable lungs should be discussed with patients when they are awaiting an organ as an option for their eventual transplantation.

### CLINICAL SUMMARY

Data from two clinical trials were considered to support the safety and probable benefit of EVLP when used to reassess initially unacceptable donor lungs perfused at near normal body temperature (normothermia) in an ex vivo setting (see Table 1, below).

Table 1 - Supporting Clinical Studies

	EVLP-Transplanted	Cold Storage (Control)
HELP Trial (Canadian Trial) <sup>1</sup> : Normothermic EVLP for an Improved Assessment of Donor Lungs for Transplantation (2008-2010)	n= 50	n= 253
NOVEL Trial (U.S. Trial) <sup>2</sup> : Normothermic EVLP as an Assessment of Extended/Marginal Donor Lungs (2011-2013)	n= 31	n=31

The HELP study was a prospective, non-randomized, single-center study that reviewed clinical outcomes between initially rejected donor lungs treated with 4 hours of EVLP using STEEN Solution™ (Study group) and all other lung transplants performed during the same study period and preserved using standard static cold storage (CS) method with Perfadex™ (Control group). While the HELP study used STEEN Solution™ as the perfusate, they used available off-the-shelf equipment. This hardware and single-use disposable equipment set was functionally equivalent to the subsequent components of the XPS™ System and, in fact, provided a basis for the development of the XPS™ System.

Initially rejected lungs were defined as those not meeting the clinical donor lung criteria based on the 2003 International Society of Heart and Lung Transplantation (ISHLT) consensus document on lung transplant acceptability criteria.<sup>3</sup>

<sup>1</sup> Cypel M., et al., Experience with the first 50 ex vivo lung perfusions in clinical transplantation. J Thorac Cardiovasc Surg, 2012 Nov. 144(5): p. 1200-6

<sup>2</sup> Cohort submitted in HDE application

<sup>3</sup> Orens JB, Boehler A, de Perrot M, et al; Pulmonary Council, International Society for Heart and Lung Transplantation. A review of lung transplant donor acceptability criteria. J Heart Lung Transplant 2003; 22(11): 1183–1200.

The study's primary endpoint was the incidence of primary graft dysfunction (PGD) grades 2 and 3 at 72 hours after transplantation.

The NOVEL study was a prospective, controlled, multicenter, open label, non-inferiority study that compared the clinical outcomes between initially unacceptable donor lungs treated with up to 4 hours of EVLP using the XPS™ System with STEEN Solution™ Perfusate (Study group) to the outcomes of other lung transplants performed during the same study period that were preserved using standard CS methods (Control group). The NOVEL study included patients transplanted with "extended criteria donor lungs," that were initially considered unacceptable for transplantation. Unacceptable donor lungs were defined as those not meeting the clinical donor lung criteria, based on the 2003 ISHLT consensus document on lung transplant acceptability criteria.<sup>4</sup>

The NOVEL study included 31 EVLP and 31 Control (CS) patients. The primary outcome for this study was 30-day mortality.

Both the HELP and the NOVEL studies were not powered to demonstrate statistical differences across study groups for the studied endpoints.

**Studies Results:**

Both the HELP (Canadian) and the NOVEL (U.S.) Clinical studies showed that the EVLP treatment group had no significant difference in comparison to the cold static storage control group for the studied endpoints (e.g., PGD and 30 day mortality).

- Survival: The 30-day and 12-month survival was similar between the two treatment arms in both studies (i.e., 30-day survival was 96% in the EVLP arm and 97.5% in the control arm in the HELP study, and 97% in the EVLP arm and 100% in the control arm in the NOVEL study) (please see Tables 2 and 3).
- Primary graft dysfunction (PGD), a predictor of post-transplant mortality, showed no significant differences between study arms (i.e., in the HELP study the incidence of PGD Grade 3 at 72 hours was 2% versus 8.5% in the EVLP arm *versus* CS group, respectively<sup>5</sup>. In the NOVEL trial, the incidence of PGD Grade 3 at 72 hours was 10% *versus* 3% for the EVLP *versus* CS groups, respectively).
- The rate of rejection episodes was the same between the two treatment arms in both studies.

Table 2 - HELP Study Survival Outcomes

	<b>EVLP</b>	<b># at risk</b>	<b>Control</b>	<b># at risk</b>
Survival 1 year	83.7%	49	85.1%	262
Survival 2 years	75.0%	44	78.4%	236
Survival 3 years	67.9%	28	71.2%	163
Number of acute rejections/year	0.54+0.72	39	0.47+0.65	204

<sup>4</sup> Orens JB, Boehler A, de Perrot M, et al; Pulmonary Council, International Society for Heart and Lung Transplantation. A review of lung transplant donor acceptability criteria. J Heart Lung Transplant 2003; 22(11): 1183–1200.

<sup>5</sup> Cypel M., et al., Experience with the first 50 ex vivo lung perfusions in clinical transplantation. J Thorac Cardiovasc Surg, 2012 Nov. 144(5): p. 1200-6

Table 3 - NOVEL Study Outcomes

	<b>EVLP N=31</b>	<b>Control N=31</b>
Survival 30 days	97%	100%
Survival 1 year	84%	94%
Survival 1 year (IPFs Only)	76% (13/17)	75% (6/8)
Survival 1 year (IPF excluded)	93% (13/14)	100% (23/23)
Number of patients with A2B2 or greater rejection in one year	4	3

### **TYPE OF LUNGS - PRE-EVLP ASSESSMENTS**

An EVLP lung undergoes two eligibility assessments: the first is to determine if initially unacceptable lungs meet the criteria to go through the EVLP procedure. The second eligibility assessment is post-EVLP to determine if the lungs meet transplant suitability. The transplant surgeon performs their standard lung evaluation of acceptability for transplantation. Lungs considered initially unacceptable are recommended for the EVLP procedure using this product.

In the two studies the following were the inclusion criteria for the donor lung to be placed on EVLP and entered into the study:

Group A:  $PaO_2/FiO_2 \leq 300$ mmHg

**OR**

Group B:  $PaO_2/FiO_2 > 300$ mmHg

One or more factors makes them unacceptable for transplant:

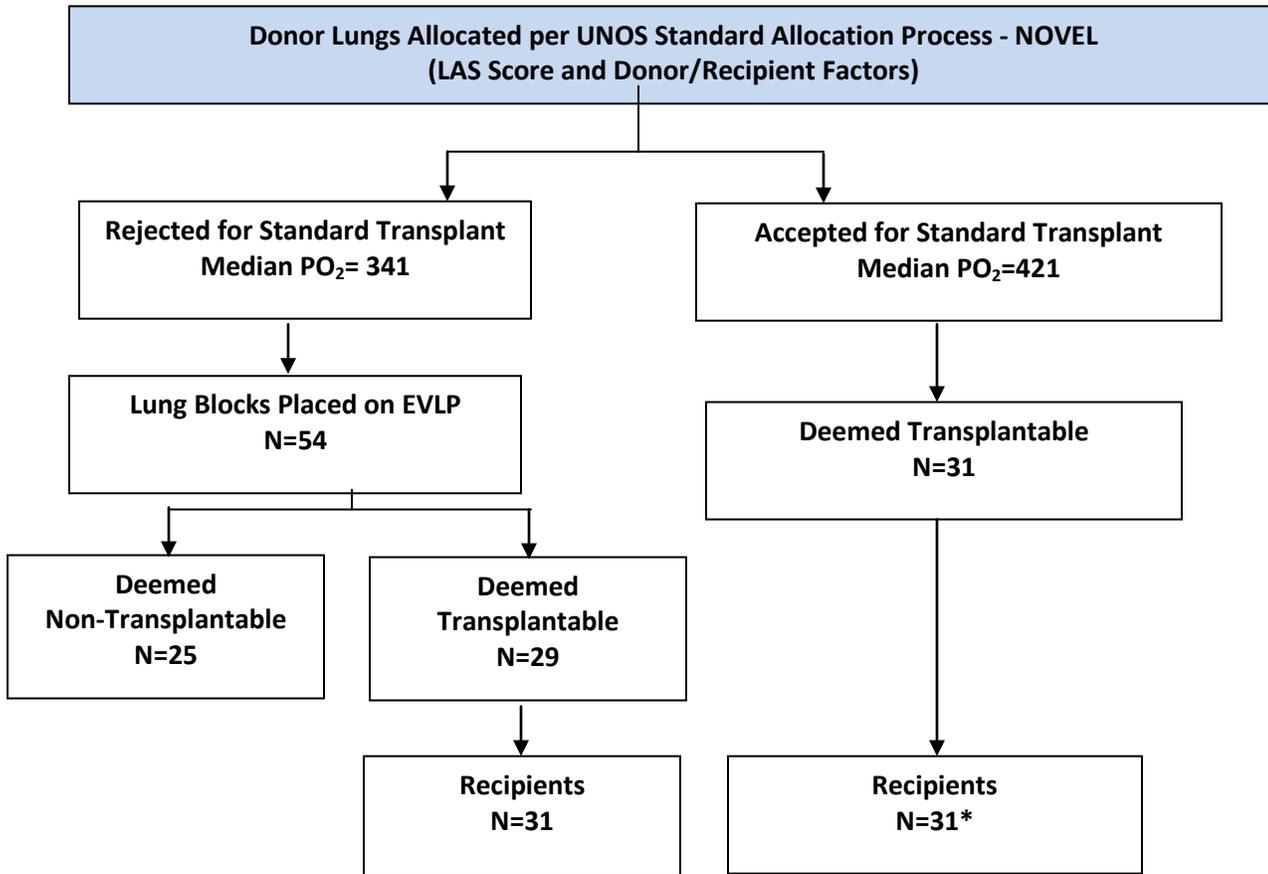
- Multiple blood transfusions.
- Pulmonary edema detected via CXR, bronchoscopy or palpation of lungs.
- Donation after Circulatory Death (DCD).
- Investigator evaluation of donor lung as “unsuitable” for standard criteria for lung transplant.

### **The donor exclusion criteria for the lung to be placed into the study were the following:**

- Donor has significant pneumonia and/or persistent purulent secretions on bronchoscopy, as determined by investigator.
- Donor has aspirated gastric contents in to the lung. Donor lung has significant mechanical lung injury or trauma.
- Donor lung has active infectious disease such as HIV, Hepatitis B or C, HTLV or Syphilis.

The standard donor lungs used as the control group did not have inclusion/exclusion criteria but were deemed standard by the study lung transplant surgeon.

Figure 1 – Donor Lung Allocation – NOVEL Study



\* Next available conventional transplants enrolled after EVLP transplants

The results of the NOVEL trial of initially unacceptable lungs included a total of 54 lungs evaluated by the research centers as being initially unacceptable. Twenty out of the 54 were single lungs and 33 were bilateral. All lungs were allocated in accordance with the UNOS standard allocation process. The median PO<sub>2</sub> of the lungs initially rejected for transplant (pre-EVLP) was 341 mmHg, in comparison to standard lungs, which had a median PO<sub>2</sub> of 421 mmHg.

All lungs were offered to study and non-study centers per UNOS regulation. Lungs placed onto EVLP in the NOVEL trial had been declined due to quality by other non-study centers. A total of 54 lungs met the Pre-EVLP eligibility assessment criteria and proceeded through the EVLP procedure. After EVLP, n=29 EVLP donor lungs were transplanted and n=25 EVLP donor lungs were not transplanted.

The table below shows the number of match runs prior to a lung being accepted by an EVLP transplant center and the furthest zones that were attempted for this match.

Table 4 - Donor Match Run Data – NOVEL Study

Match Run Data	EVLP Transplanted	EVLP Not Transplanted
Rejection due to "Poor Quality"	100%	100%
Number of Match Attempts	Attempts in each category	Attempts in each category
3-10	5	1
11-20	4	6
21-30	1	4
31-40	4	4
41-50	3	3
51-100	4	1
101-150	4	1
151-200	2	0
>200	1	2
Furthest Zone Attempted	# in each category	# in each category
Local	4	2
A	18	17
B	5	2
C	0	2
D	1	0

Lungs are declined for transplant due to a variety of reasons. In general, it is the totality of the donor lung being assessed for transplant and not one specific parameter. Of the 29 EVLP lungs transplanted across 31 recipients (3 splits), 5 met the criteria of PaO<sub>2</sub> less than 300 mm Hg, with the other 24 having a PaO<sub>2</sub> of greater than 300 mm Hg with other reasons for inclusion being: 2 donation after circulatory death (DCD) lungs, 20 pulmonary edema/infiltrates/contusions/drowning/multiple blood transfusions, and one asphyxiation (secondary to hanging).

Surgeons use the International Society for Heart and Lung Transplantation (ISHLT) as a guideline to assess the lung and decide on whether to use it for transplant. Donor acceptability criteria have a wide variation range across centers<sup>6</sup> and what is not acceptable for one center could be acceptable for another. Recent publications have noted that some of the historical risk factors used to define an extended, non-ideal, or marginal donor lung do not always produce significantly inferior outcomes<sup>7, 8</sup>.

However, the ISHLT recommendations are guidelines and a clinical decision is made based on the transplant surgeon's experience, expertise and ultimately what is best for their patient. The two main groups of donor lungs surgeons identify as least likely to be accepted for transplantation are lungs with a PaO<sub>2</sub> of less than 300 mm Hg and DCD donors. In the NOVEL trial, seven lungs had a PaO<sub>2</sub> of less than 300 mm Hg, or were from a DCD donor. These lungs were transplanted across seven recipients who all lived past 30 days. One (1) subject died eight (8) months post-transplant, due to an aortic injury that occurred prior to transplant. The other EVLP lungs transplanted had various extended criteria reasons, such as edema, infiltrates, contusions, and/or multiple blood transfusions.

Pulmonary edema (59%), and PaO<sub>2</sub> less than 300 mm Hg (28%) were the main reasons for non-acceptance, i.e., "rejection," of the donor lungs for transplantation. Pulmonary edema plus lungs boggy, was the only reason for considering the donor lungs unacceptable in 16/32 (50%) donors. The other 50% presented pulmonary edema and another abnormality.

Seven DCD donor lungs were considered unacceptable for transplantation. After EVLP, two of them were accepted for transplant and five remained unacceptable. All seven DCD lungs placed onto EVLP had other reasons for EVLP. Two for PaO<sub>2</sub> less than 300 mm Hg, four for pulmonary edema, and one death due to hanging.

<sup>6</sup>Van Raemdonck D., et al. Lung Donor Selection and Management. Proc Am Thorac Soc, 2009 Jan 15. 6(1):28–38

<sup>7</sup>Snell GI et. al. Donor selection and Management. Semin Respi Crit Care Med, 2013 Jun. 34 (3): 361-370

<sup>8</sup>Snell GI, Griffiths A, Levvey BJ, Oto T. Availability of lungs for transplantation: exploring the real potential of the donor pool. J Heart Lung Transplant 2008. 27(6):662–667

Table 5 lists the reasons why donor lungs were considered unacceptable for transplantation and rejected by a non-EVLP transplant center (donor may present more than one cause for non-acceptance; 73 causes for non-acceptance were listed for 54 donors).

Table 5 - Donor Evaluation – NOVEL Study: Donor lungs considered unacceptable for transplantation and accepted for EVLP preservation and evaluation

Donor Evaluation	Donor lungs considered unacceptable for transplantation and accepted for EVLP preservation and evaluation n=54		
	Reasons why donor lungs were considered unacceptable for transplantation*	Total n=54	Transplanted after EVLP
Pulmonary edema + lungs boggy	32/54 (59%)	20/32 (62.5%)	12/32 (37.5%)
PaO <sub>2</sub> Less than 300	15/54 (28%)**	5/15 (33%)	10/15 (67%)
Donation after cardiac death (DCD)	7	2	5
Infiltrates	6	4	2
Contusions	5	5	0
Infarction only	1	-	-
Multiple blood transfusions	4	2	2
Asphyxiation / Donor hanged	2	1	1
Drowning donor	2	1	1

\* Donor may present more than one cause for non-acceptance. 73 causes for non-acceptance were listed for 54 donors.

\*\* There were two (2) DCD lungs that also presented PaO<sub>2</sub> < 300. These two (2) donors were included in the DCD category, and excluded from the PaO<sub>2</sub> < 300 mm Hg category.

In the NOVEL trial, lungs from 29 (54%) out of 54 EVLP donors were transplanted across 31 recipients (EVLP utilization rate of 54%) and lungs from 25 (46%) out of 54 EVLP donor were not transplanted (see Table 6 below).

Donor lungs with edema alone or in combination with infiltrates, contusions, or multiple blood transfusions before EVLP were transplanted after EVLP in 62% (20/32) of cases.

Lungs from 15 / 54 (28%) donors underwent EVLP because of donor PaO<sub>2</sub>/FiO<sub>2</sub> was less than 300 mm Hg as the only reason for EVLP. Lungs from five of these donors (33%) were subsequently transplanted.

Lungs from donors with PaO<sub>2</sub> / FiO<sub>2</sub> greater than 300 and other alternative reasons for EVLP (11 pulmonary edema/infiltrates/multiple blood transfusions, two infarcts/unable to perform bronchoscopy, and two DCDs) were observed in 39 / 54 EVLP donors (72%). Twenty-four (24) of the 39 (62%) were subsequently transplanted.

Seven DCD lungs were considered unacceptable for transplantation. After EVLP, two of them were accepted for transplant and five remained unacceptable (see Table 5 above).

Table 6 - Donors Baseline Characteristics – NOVEL study

Donors data	Cold Storage controls n=31	EVLP- Tx n=29	EVLP-Not-Tx n=25
<b>Donor Type</b>			
BDD	30 (97%)	27 (93%)	20 (80%)
DCD	1 (3%)	2 (7%)	5 (20%)
<b>Donor Gender M/F</b>	21/10	17/12	13/12
<b>Age</b>			
≤ 54	27 (87%)	27 (93%)	23 (92%)
55 – 59	1 (3%)	0	0
60+	3 (10%)	2 (7%)	0
Median years ( range)	37 (19-70)	31(16-65)	28 (13-48)
<b>Best PaO<sub>2</sub> Median (Range)</b>	421 (285-589)	348 (165-500)	333 (119-501)
<b>CMV+</b>	16 (52%)	10 (34%)	13 (48%)
<b>Bal + Cultures</b>	13 (42%)	12 (41%)	9 (36%)
<b>Smoking History</b>			
Positive	13 (42%)	13 (45%)	9 (36%)
Negative or NA	18 (58%)	16 (55%)	15 (60%)
<b>Cause of death</b>			
Anoxia / Hypoxia	10 (32%)	12 (41%)	6 (24%)
Trauma	11 (35%)	14 (48%)	11 (44%)
CVA/Stroke	10 (32%)	3 (10%)	8 (32%)
<b>Partial pressure of arterial oxygen / Fraction of inspired oxygen (PaO<sub>2</sub> / FiO<sub>2</sub>)</b>			
>350	26 (84%)	12 (41%)*	11 (44%)
301-350 & NA	3 (10%)	12 (41%)**	4 (16%)
≤ 300	2 (6%)	5(17%)***	10 (40%)

^ Donor last PO<sub>2</sub> / FiO<sub>2</sub> before organ retrieval

\* Transplanted as 5 SLTx and 7 DLTx

\*\* Transplanted as 6 SLTx and 7 DLTx

\*\*\* Transplanted as 5 SLTx and 1 DLTx

The results of the HELP Study showed that donor lungs had significantly lower *in vivo* PaO<sub>2</sub>/FiO<sub>2</sub> levels, abnormal bronchoscopies, positive cultures and tended to have more abnormal chest X-rays.

Table 7 - Donor Characteristics - HELP Trial

Donor Variable	EVLP (n=50)	Conventional/ Control* (n=253)
Age (Y)	45	45
DCD (%)	44	5.1
Best P/F ration (mmHg)	334	452
Chest X-ray abnormalities (%)	67	45
Positive BAL cultures (%)	70	55
<b>Recipient variable</b>		
Age	56	56
Diagnosis of pulmonary fibrosis or PAH (%)	32	38.7
<b>Transplantation variable</b>		
Bilateral (%)	76	88
Retransplantation (%)	2	3.5
Cardiopulmonary Bypass	30	39

\*Conventional refers to Standard Cold Storage Lungs that did not receive EVLP<sup>9</sup>.

<sup>9</sup>Cypel M, Yeung JC, Machuca T, Chen M, Singer LG, Yasufuku K, de Perrot M, Pierre A, Waddell TK, Keshavjee S. Experience with the first 50 ex vivo lung perfusions in clinical transplantation. J Thorac Cardiovasc Surg. 2012 Nov. 144(5):1200-6

In the NOVEL trial, there were seven DCD donors whose lungs were placed onto EVLP. All DCD lungs had one other reason for being considered for EVLP prior to transplantation. The table below includes these reasons, plus the outcome of the lungs post-EVLP and of the recipients who received these lungs.

Table 8 – Donation after Cardiac Death – Reasons for Decline after EVLP – NOVEL Study

<b>DCD Donor</b>	<b>Other reason for EVLP besides DCD</b>	<b>Recipient Diagnosis</b>	<b>Reason for Decline after EVLP</b>	<b>Outcome of Recipient</b>
1 EVLP not Transplanted	Smoker Pulmonary Edema Lower lobe infiltrate	N/A	Decreased compliance  Surgeon not clinically satisfied	N/A
2 EVLP Not Transplanted	Smoker Pulmonary Edema	N/A	Low Delta pO <sub>2</sub>	N/A
3 EVLP Not Transplanted	Smoker Pulmonary Edema	N/A	Pulmonary Edema, Increased PVR, Decreased compliance	N/A
4 EVLP Not Transplanted	Smoker Asphyxiation/Hanging	N/A	Frothy Secretions, obvious edema, Increased PVR, Low Delta pO <sub>2</sub> , Clinical decision	N/A
5 EVLP Transplanted same donor as #6	Smoker/<300 PaO <sub>2</sub>	Pulmonary Fibrosis	N/A	Aortic injury occurring during transplant surgery prior to implantation
6 EVLP Transplanted same donor as #5	Smoker/pO <sub>2</sub> <300	Pulmonary Fibrosis	N/A	Alive
7 EVLP Transplanted	Smoker/Pulmonary Edema	Pulmonary Fibrosis	N/A	Alive
8 EVLP Not Transplanted	Smoker/<300 PaO <sub>2</sub>	N/A	Delta pO <sub>2</sub> <350, decreased compliance and functional deterioration	N/A

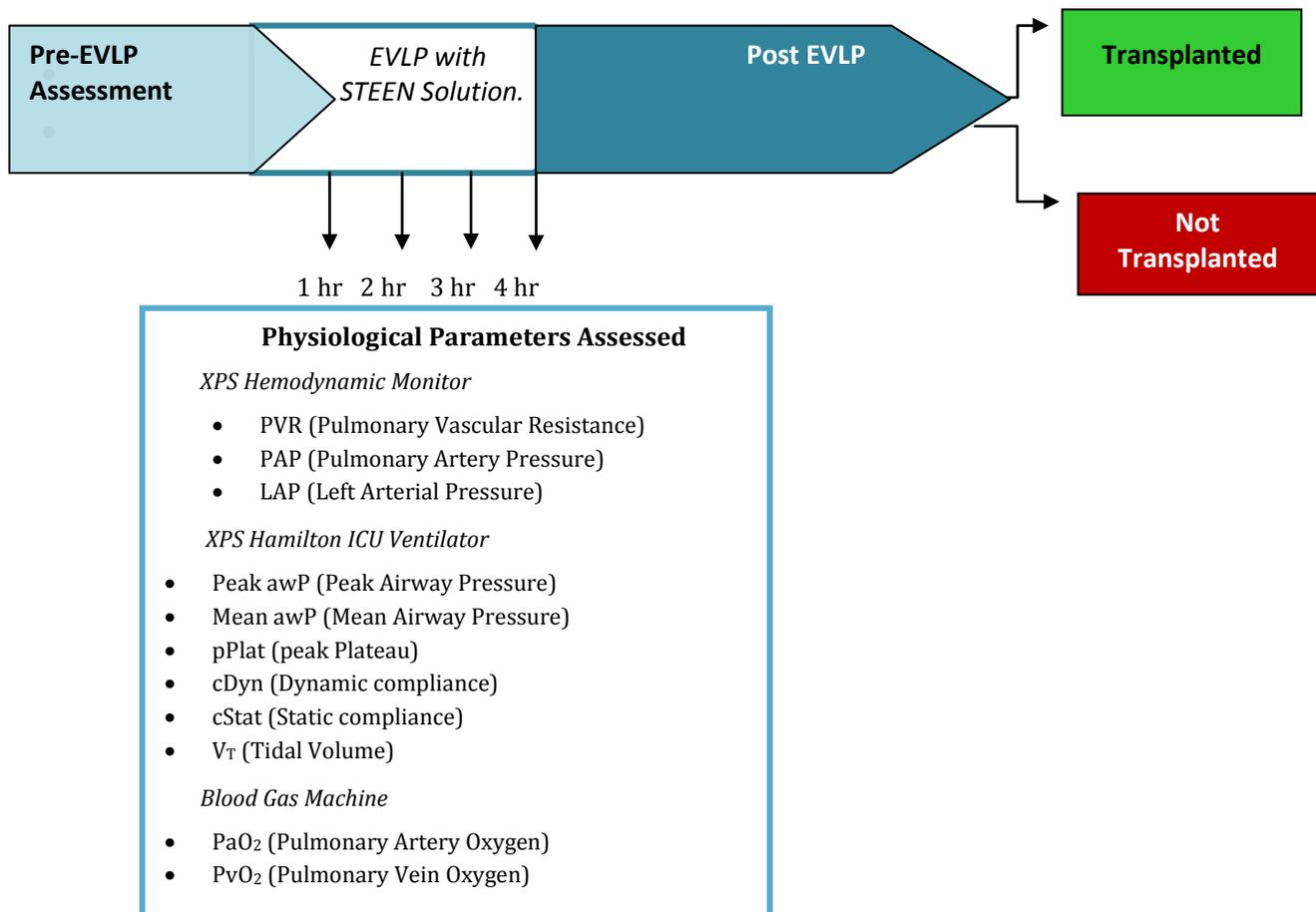
## EVLP PROCEDURE

Lungs are retrieved and flushed with Perfadex® and stored at 4-8 degrees Centigrade per standard lung procurement protocol. The lung is then transported to the study transplant center for EVLP with STEEN Solution™ and the XPS™ machine. Methylprednisolone, heparin, and antibiotics are added to the STEEN Solution™. The lungs are perfused using lung-protective flow rates. For a double lung, the maximum flow rate is 40% of calculated cardiac output for the donor. For a single right lung, the maximum flow rate is 24% and for a single left lung, the maximum flow rate is 16%. Mechanical ventilation settings are based on ideal body weight ( $V_T$  7ml/kg, rate of 7 Beats per Minute (BPM), Positive End-Expiratory Pressure (PEEP) of 5 cm H<sub>2</sub>O, Fraction of Inspired Oxygen (FiO<sub>2</sub>) 21%). Please see the XPS™ Instructions for Use manual for more information.

The EVLP procedure, per NOVEL trial protocol, occurs for up to four hours but can end at three hours, if deemed transplant-suitable. EVLP can end at any time if the donor lung is considered **NOT** transplant suitable. Every hour, physiological parameters are measured and assessed. An x-ray is performed at one and three hours. The determination of transplant suitability is based on the totality of the assessments and the overall trend of improvement. This assessment is not principally different to the initial assessment made in the deceased donor. The physiological parameters measured are as follows:

- Pulmonary Vascular Resistance (PVR)
- Airway pressures (mAwP, PAwP, platAwP, mean, peak and plateau airway pressures).
- PvO<sub>2</sub>
- PaO<sub>2</sub>
- Static Compliance
- Dynamic Compliance (a variable calculated based on the static compliance)

Figure 2 - EVLP Timeline



## RECOMMENDED TRANSPLANT SUITABILITY GUIDELINE POST-EVLP

The responsibility for correct clinical use and interpretation of the lung function evaluation during EVLP in determining transplantability resided exclusively on the transplant surgeon. Similar to other clinical decisions, all available data should be taken into consideration to determine the suitability of an organ for transplantation; that is, the transplant surgeon is clinically satisfied with the lung evaluation. This criterion should take priority, since the transplant surgeon is the ultimate responsible person for safely transplanting EVLP lungs.

The XPS™ system is a tool assisting the transplanting surgeon in assessing if the lung meets transplant criteria. This assessment involves multiple variables, which include  $PO_2$  values, PVR, static and dynamic compliance, airway pressures, and visual inspection of the lung.

The HELP trial used two different  $PaO_2/FiO_2$  ratio cut-offs, a  $\Delta PaO_2/FiO_2 \geq 350$  mm Hg for the initial phase of the trial, and a  $\Delta PaO_2/FiO_2 \geq 400$  mm Hg during the extension or compassionate use phase. The NOVEL trial use a  $\Delta PaO_2/FiO_2 \geq 350$  mm Hg at two consecutive time evaluations.

Stability of pulmonary vascular resistance, compliance and peak inspiratory pressure parameters was required in both studies. Stability was defined as  $< 15\%$  or  $\leq 10\%$  deterioration from baseline in the HELP and NOVEL studies, respectively.

There were criteria differences across studies and study time periods, with the NOVEL study having the more rigorous criteria. For this reason, the results obtained using different transplantability criteria should be evaluated separately.

It is not clear whether the lung function assessments during EVLP provide comparable or better prognostic value to those obtained directly from the donor prior to lung retrieval, although the device does allow for more time to make the determination and allows more studies to be performed, compared to *in-vivo* testing, especially for DCD donors. The use of the *ex vivo* lung function parameters to determine transplantability has been evaluated in the NOVEL trial in this controlled sample of patients, but validation has not occurred as to whether these parameters are adequate as surrogates for *in vivo* performance. The most relevant and predictive parameters (e.g., trends over time, cut-off values, time measurements) remain to be determined and are partly based on clinical judgment. It is the totality of the lung function evaluation and not one parameter that at this time determines lung transplant suitability. It is recommended that donor lungs be considered for transplant based upon trends towards improvement of the parameters tested.

Based upon the data from the clinical trial, the improvement in static compliance along with good oxygenation were the two factors that the surgeons used to determine transplant suitability. The  $\Delta PO_2$  (e.g., oxygenation left atrium – oxygenation pulmonary artery) greater than 350mmHg (i.e., absolute  $PO_2$  of ~400 mmHg) at two consecutive time points, stability (e.g., deterioration of hemodynamics and airway pressures was not more than 10%) or improvement of PVR, static /dynamic compliance, air way pressures, and x-ray images during the EVLP procedure, and surgeon clinically satisfied with lung were the listed transplantability criteria. Lungs that do not meet the  $\Delta PO_2 \geq 350$  mmHg, but have an absolute  $PO_2 \geq 400$  mm Hg, overall lung function improvement, such as decreasing PVR, improvement in static and dynamic compliance, or improved x-ray findings may be considered for transplant, if the surgeon is clinically satisfied with the totality of the lung assessment.

It is also important to adjust the  $PO_2$  value for elevations of greater than 3000 ft. Adjustments in  $PO_2$  values for high altitude during EVLP functional assessments was not part of the original NOVEL trial protocol, although used in standard practice. Clinical experience from one of the NOVEL trial's sites, University of Colorado, recommends that  $PO_2$  needs to be adjusted for the barometric pressure differences at altitude, when determining the  $\Delta PaO_2$  during the EVLP donor lung function evaluations. For example, Denver is at an altitude one mile above sea level and typically has a barometric pressure of 620mmHg, compared to a sea level pressure of 760mmHg. To compare a  $PO_2$  at Denver's altitude to that of one at sea level, one must convert by dividing the two ( $620/760=82\%$ ). Then taking the measured  $PO_2$  in Denver and dividing by the conversion factor, gives the converted  $PO_2$  (e.g.  $287 \text{ mm Hg}/0.82=350\text{mmHg}$ ).

During the NOVEL trial, five patients at Colorado did not meet the  $\Delta PaO_2$  criterion during EVLP donor lung function evaluation and were transplanted, per the transplant surgeons' recommendations. After correction of  $\Delta PaO_2$  for high altitude, three of the patients met the criterion and were transplanted. Two out of the three recipients died at 141 and 203 days after transplantation and the cause of death was determined to be unrelated to the EVLP procedure (please see Table 16 for a detailed clinical rationale for transplanting these donor lungs).

The effects of altitude on barometric pressure and  $PO_2$  are seen in Table 9 below.

Table 9 - Altitude, barometric pressure, ambient PO<sub>2</sub>, and PIO<sub>2</sub>

Altitude, barometric pressure, ambient PO<sub>2</sub>, and PIO<sub>2</sub>

Altitude		Barometric pressure (mm Hg)	Ambient PO <sub>2</sub> (mm Hg)	PIO <sub>2</sub> (mm Hg)
(m)	(ft)			
0	0	759.6	159.1	149.1
1000	3281	678.7	141.2	132.2
2000	6562	604.5	124.9	116.7
3000	9843	536.9	110.1	102.5
4000	13,123	475.4	96.9	89.7
5000	16,404	419.7	84.8	78.0
6000	19,685	369.4	79.1	67.5
7000	22,966	324.2	67.8	58.0
8000	26,247	283.7	59.3	49.5
8850	29,035	252.7	52.9	43.1

The partial pressure of oxygen (PO<sub>2</sub>) in ambient air and inspired air (PIO<sub>2</sub>) fall nearly exponentially as a function of increasing altitude and falling barometric pressure.

*Adapted from Hackett PH, Roach RC. High-altitude medicine. In: Auerbach PS, editor. Wilderness medicine. Philadelphia: Mosby; 2001. p. 2–43; with permission.*

These adjustments should be made prior to making your decision to qualify a lung for transplantation and also when making your decision to transplant after EVLP.

In the NOVEL study, 13 out of 31 EVLP donor lungs (42%) did not meet the two consecutive delta PO<sub>2</sub> ≥ 350 mm Hg criterion and still were transplanted. After correction of delta PaO<sub>2</sub> delta for high altitude, three of them met the delta PaO<sub>2</sub> criterion and were transplanted. These lungs did have a static compliance between 35-60 C<sub>dyn</sub> and one had delta PO<sub>2</sub> ≥ 350 mm Hg or absolute PO<sub>2</sub> ≥ 400 mm Hg, improved x-rays, acceptable visual lung inspection, and surgeon clinically satisfied with the lung (please see Table 13 for a detailed clinical rationale for transplanting these donor lungs).

A lung could also have physiological parameters appearing to improve, but based on the clinical judgment of the lung transplant surgeon be deemed unsuitable for transplant. This occurred in the NOVEL trial due to contusions seen on visual inspection. Lungs with a greater than 10-15% lung function deterioration may not be acceptable for transplant.

The reasons were the low delta PO<sub>2</sub>, pulmonary edema, decreased compliance, increase airway pressures, and/or increased pulmonary vascular resistance (see Table 10 below). The EVLP lungs not transplanted had a best PO<sub>2</sub> of 386 mm Hg, delta PO<sub>2</sub> of 268 mm Hg, in comparison to the EVLP group transplanted, which had a best PO<sub>2</sub> of 514 mm Hg and delta PO<sub>2</sub> of 401 mmHg.

Table 10 - Major reasons for not transplanting lungs after EVLP – NOVEL Trial

Major Reasons For Rejection After EVLP	N
Pulmonary Edema	16
Increased Pulmonary Vascular Resistance (PVR)	10
Decreased Compliance	11
Airway Pressures	5
Low Delta P <sub>O2</sub> /F <sub>iO2</sub>	18
Fluid level in Reservoir Decreasing (edematous lungs)	3
Logistics	1

Note: The term “Rejection” used in Table 10 indicates non-acceptance for transplantation. It does not refer to immunological allograft rejection.

A comparison of key parameters between EVLP not transplanted *versus* transplanted showed the median pulmonary artery (PA) and left atrial pressures (LAP) were similar, while the EVLP transplanted group had a lower median PVR and improved static and dynamic compliance. The results indicate that PO<sub>2</sub> in combination with the compliance of the lung are the major parameters used during EVLP to determine acceptability for transplantation. However, the prognostic value of these two parameters was not evaluated in this study. In reviewing all the major variables, the improvement in lung compliance appeared to be the higher priority parameter in assessing if a lung should be transplanted.

Table 11 - EVLP Transplantability Criteria and Protocol Deviations – NOVEL Trial

EVLP Donors (n=54)	EVLP-Tx (n=29)		EVLP Not-Tx (n=25) Did not meet criteria
	Met Criteria n=12	Did not met criteria, Protocol Deviations* n=17 (59%)	
1. Surgeon satisfied with lung evaluation	100%	-	0%
2. Delta PaO <sub>2</sub> > 350 mmHg at two consecutive time points during EVLP	16 (55%)	13 (45%)	28%
3. Stability (≤10% deterioration)			
• Pulmonary vascular resistance	26 (90%)	3 (10%)	60%
• Compliance	27 (93%)	2 (7%)	80%
• Peak airway pressure	24 (83%)	5 (17%)	80%

\* Includes three cases from the University of Colorado of delta PaO<sub>2</sub> being outside the specified criteria before correction for high altitude

In the HELP study, subject lungs received four hours of EVLP perfusion, with the lungs being evaluated for a delta PO<sub>2</sub>>350mmHg (at one time point), stable PVR, pAWp, and lung compliance. The EVLP and control, standard donor lungs have demonstrated satisfactory function after transplantation for as many as three years post-transplant. It was reported in the Journal of Thoracic and Cardiovascular Surgery (2012;144:1200-7) that the use of ex vivo lung perfusion at Toronto General Hospital improved that center's use of donor lungs, accounting for 20% of their current lung transplant activity.

### TARGET POPULATION

STEEN Solution™ with the XVIVO Perfusion System (XPS™) is designed to benefit those patients with *end stage lung disease* who are awaiting lung transplant.

A total of 54 donors provided lungs that received EVLP. Twenty-nine (29) of the donors provided lungs that were transplanted after EVLP and 25 donors did not provide any lungs after EVLP that were considered suitable for transplantation. Some bilateral lungs were tested then split and placed into single-lung recipients. Therefore, 29 donors became 31 recipients. There was no significant difference in demographics between lungs undergoing EVLP versus lungs transplanted in the control group. In the NOVEL trial, investigators evaluated more organs than they would have if EVLP were not available, including DCD lungs.

Recipient demographics (EVLP n=31 and control n=31) include the primary diagnosis, the presence of cytomegalovirus, and the Lung Allocation Score (LAS) at the time of transplant. All subjects met eligibility to enroll. The NOVEL trial was not randomized and not stratified, leading to a higher LAS score in the EVLP arm and a higher rate of Idiopathic Pulmonary Fibrosis (IPF) Lung diagnosis. The higher rate of IPF in the EVLP treatment arm (e.g., 17 IPF subjects in the EVLP arm, compared to eight IPF subjects in the control arm), was due to the study design and the adherence to the standard organ allocation process and matching of the recipients.

### REJECTION DATA

Patients post-lung transplant have a significant number of bronchoscopies performed in order to monitor their lung status. Some centers perform these routinely and others perform them when the patient's symptoms require more assessments. The NOVEL protocol required that clinically significant dehiscence, clinically significant stenosis, A2B2 rejection, and infections treated with a systemic antibiotic to be reported as an adverse event (AE).

Almost all lung transplant recipients experience rejection at some time post-transplant. The ISHLT registry indicates that acute rejection affects up to 55% of lung transplant recipients within the first year after transplantation.

There was no difference in the number of bronchoscopies performed nor in the number of rejection episodes that were seen in the two groups of recipients, and all of the 31 patients are at one year post-transplant.

During the course of follow-up, there have been no differences in the rate of rejection between EVLP and controls. Respiratory infection (pneumonia) was identified in four EVLP recipients and three controls. In these cases, the infections were treated and resulted in similar mortality between groups.

### PRIMARY GRAFT DYSFUNCTION

PGD is characterized by radiographic pulmonary infiltrates and hypoxemia. The more severe forms of PGD have been associated with worse morbidity, and PGD is the leading cause of death in the early post-transplant period. The grading scheme for PGD considers 2 factors: the appearance of post-transplant chest X-ray images and the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ ) at multiple time points within the first 72 hours after transplantation.

PGD is defined as the following:

- Presence or absence of diffuse pulmonary radiographic infiltrates involving the lung allograft and, in the case of single lung transplant, sparing the native lung;
- $\text{PaO}_2/\text{FiO}_2$  ratio in mmHg; and
- No other secondary cause of graft dysfunction readily identified, including:
  - Cardiogenic pulmonary edema, defined as a pulmonary artery occlusion pressure exceeding 18 mm Hg or resolution of infiltrates with effective diuresis;
  - Pathologic evidence of rejection;
  - Pneumonia, as evidenced by the presence of fever, leukocytosis, and purulent secretions with positive cultures on bronchoscopy; or pulmonary venous outflow obstruction, as demonstrated by transesophageal echocardiogram, surgical reexploration, or post-mortem examination.

Table 12 - PGD Grades.

Grade	$\text{PaO}_2/\text{FiO}_2$	Radiographic Infiltrates consistent with pulmonary edema
0	>300	Absent
1	>300	Present
2	200-300	Present
3	<200	Present

Graft function after transplant was evaluated using PGD grading at 0, 24, and 72 hours. If a patient was unable to be evaluated accurately for PGD because of their poor condition (i.e., one patient who died prior to the 30 days), they were given a score of 3. Patients who were extubated and/or without a pulmonary artery line and needed to determine a PGD score were automatically scored as a 1.

In the NOVEL Trial, the incidence of PGD Grade 3 at 72 hours was 10% *versus* 3 % in the EVLP *versus* Cold Storage groups, respectively. This difference was not significant and well below the ISHLT reference for both groups. For detailed information on PGD Grades 2 and 3, please see Table 13. Table 13 also includes the NOVEL trial results on other secondary endpoints.

It is important to mention that patients that required ECMO support were automatically scored as PGD Grade 3, independent of their graft status. In two cases in the EVLP group, ECMO support was necessary in the operating room. One patient was put on V-A ECMO due to an aortic injury and a second patient was put on V-V ECMO because he could not tolerate single lung ventilation during the explant of his diseased lung. In both cases ECMO support was necessary before transplantation and peri-operatively, and though these patients were scored as having PGD 3, this score does not represent their graft status post-transplant.

A parameter used to evaluate graft function and or preservation is the number of airway complications that require intervention. In this study the number of airway-related incidents that required interventions was not different between the patients that received EVLP or control lungs.

Table 13 - Secondary Endpoints – NOVEL Trial.

Lung Tx Outcomes	ISHLT Reference Data	EVLV Tx (n=31)	Control (n=31)
PGD			
24 hrs			
2	18%	8 (26%)	5 (16%)
3	28%	5 (16%)	2 (6%)
72 hrs			
2	11%	3 (10%)	4 (13%)
3	18%	3 (10%)	1 (3%)
Patients ECLS post Tx # Days	n/a	2* (6%) 5	1 (3%) 4
Mech Ventilation Days Median (Range)	n/a	1 (1-196)	1 (1-29)
ICU Stay Days Median (Range)	n/a	4 (1-197)	3 (1-144)
Hospital Stay Days Median (Range)	n/a	13 (4-198)	11 (6-236)
1 Year Survival %	83%	88%	94%

Table 14 - NOVEL Trial Outcomes

	EVLP-Tx (n=31)	Cold Storage (n=31)
PGD Grade 3 at 72 hours	10%*	3%
Thirty-day survival	97%	100%
One-year survival	84%	93%
FEV1% and FVC% >6 to 12 months after transplantation	Lower mean values than CS	Higher mean values than EVLP
Infections and thoracic complications	19%	6%
Pneumonias	13%	10%

\* Two patients placed on ECMO prior to transplant in the OR, one due to inability to oxygenate on one lung ventilation and the other for an aortic dissection.

The NOVEL study was not powered to show statistical differences in outcomes. Differences across study groups in the previous table were not statistically significant.

Thirty-day survival was comparable across arms. One-year survival was 84% and 93% in the CS and EVLP arms, respectively.

### PULMONARY FUNCTION TEST OUTCOMES

Pulmonary function test (PFT) data were collected retrospectively in the NOVEL study. The outcomes of these tests are shown in the figures below.

Figure 3 - Pulmonary Function Test (PFT) Evaluations

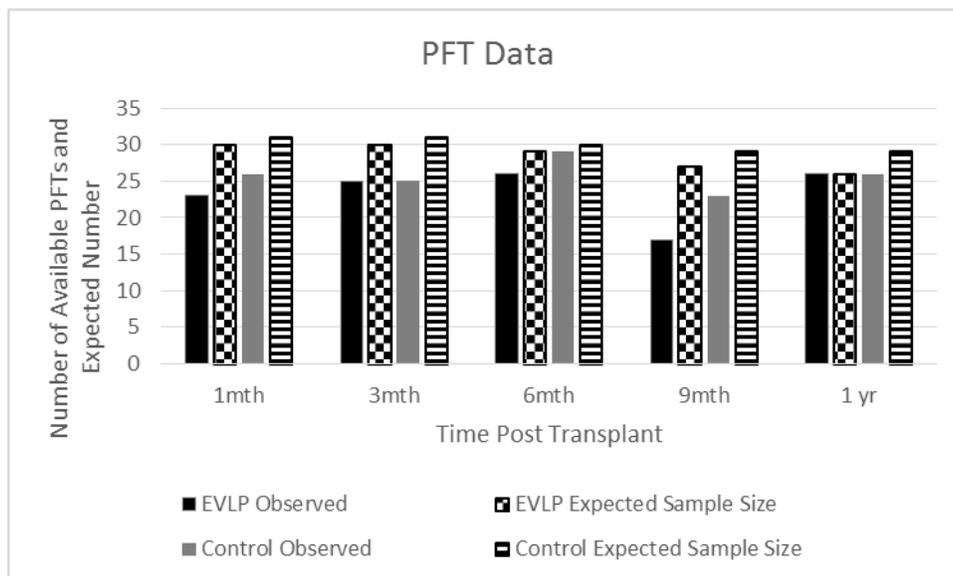
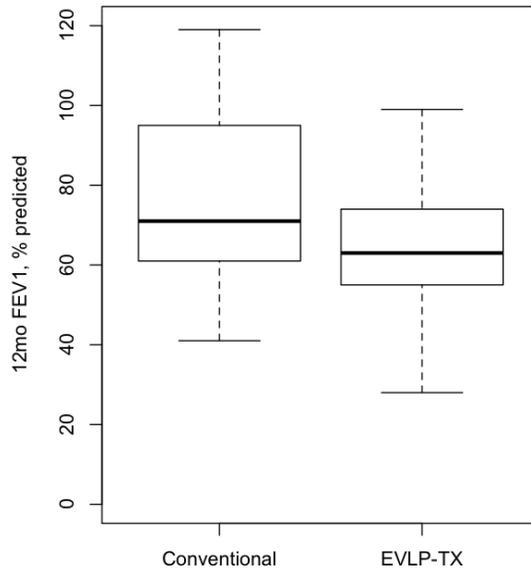
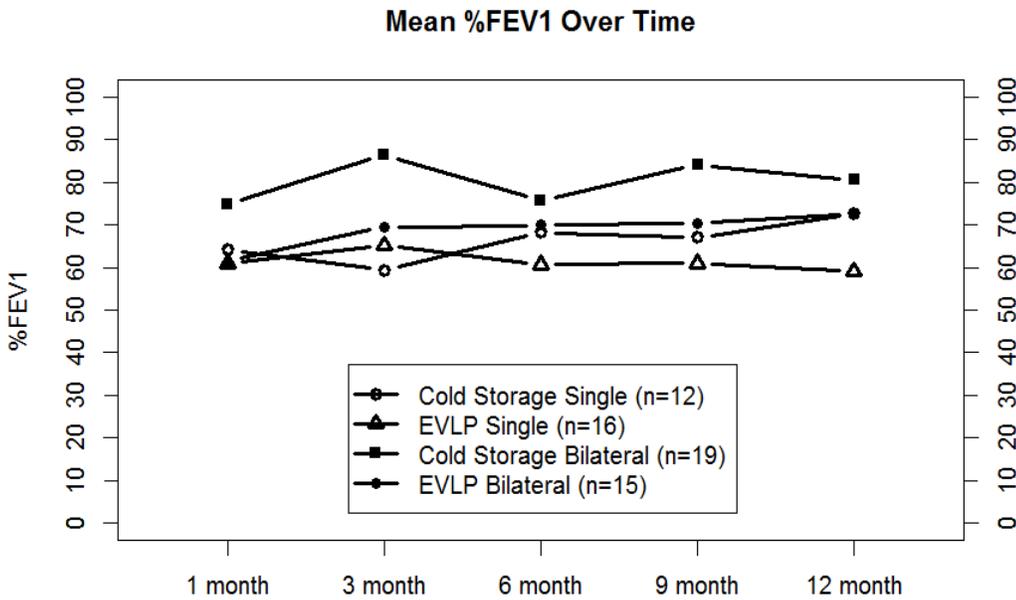


Figure 4 – Percent FEV1 Data at One Year



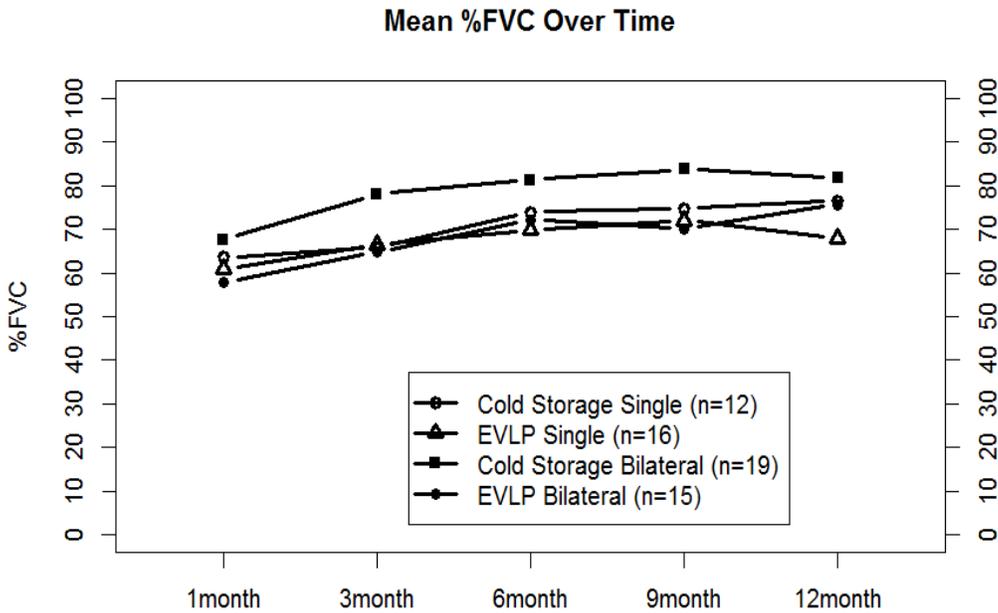
The Median FEV1 over time is shown below. Bilateral lung recipients had a higher FEV1 in both the EVLP and the control groups than had the single lung transplants.

Figure 5 – Mean Changes in % FEV1 Over Time



At 12 months after transplantation, the mean % FEV1 was 80.47 vs. 72.45 for cold storage vs. EVLP double lung transplants, respectively. In the single lung transplant arms, the mean % FEV1 was 72.64 vs. 59.07 for the control vs. EVLP lungs, respectively.

Figure 6 – Mean Changes in %FVC Over Time



At 12 months after transplantation, the mean % FVC was 81.67 vs. 75.64 for CS vs. EVLP double lung transplants, respectively. In the single lung transplant arms, the mean % FVC was 76.45 vs. 67.86 for the CS vs. EVLP groups, respectively.

In this study, the incidence of Bronchiolitis Obliterans Syndrome (BOS) was not evaluated; therefore, the differences in FEV1 and FVC values are difficult to interpret for prognostic purposes. Due to the fact that only one-year data were available, long term safety outcomes concerning BOS were not assessed.

## MORTALITY

Seven deaths were observed in the NOVEL study. Five occurred in the EVLP group, and two in the cold storage, control group. One early death occurred at Day 10 post-transplant (EVLP group), due to an anti-thymocyte globulin (ATG) reaction post-transplant. Six deaths occurred beyond the fourth month after transplantation.

The five (\*three) EVLP deaths occurred in protocol deviation cases in patients who did not meet the EVLP transplantability criteria, as per the original protocol (please see Table 16 below). All five EVLP deaths were determined to be unrelated to the EVLP procedure, both by the investigators and by the safety review committee. Five EVLP deaths occurred in recipients with a primary lung diagnosis of idiopathic lung fibrosis (IPF), which has a greater risk of mortality post-transplant. \*After correction of PaO<sub>2</sub> delta for high altitude, three (3) of them met the delta PaO<sub>2</sub> criterion (and were no longer protocol deviations once corrected for altitude) and were transplanted.

Thirty-day mortality was the primary endpoint in the NOVEL trial. Clinical studies in lung transplantation have used 30-day mortality as a useful parameter to evaluate lung preservation. In this study, one patient died within the first 30 days post-transplant. This patient, who received a lung after EVLP evaluation, developed a serious complication after administration of ATG, which was part of the immunosuppression regimen used at that institution.

There are no statistically significant differences in one-year survival between the control and EVLP groups transplanted for IPF (e.g., 76% (EVLP) and 75% (control)), with no significant differences between the two arms.

## PROTOCOL DEVIATIONS

Table 16 includes 13 (\*10) protocol deviation in EVLP donor lungs that did not meet the two consecutive delta

PO<sub>2</sub> > 350mm Hg transplantability criterion, according to the original NOVEL protocol. All the protocol deviation EVLP donor lungs were transplanted, based on the totality of the parameter assessments and the surgeons' clinical judgment. Table 16 below also lists the clinical rationale for transplanting donor lungs not meeting transplantability criteria. \*Includes the three cases that underwent correction of delta PaO<sub>2</sub> for high altitude; these three met the delta PaO<sub>2</sub> criterion after correction and were transplanted.

Table 15 - Mortality Summary, NOVEL Study

Tx Arm	Donor Type	Recipient Dx	PGD at 72 Hrs	LAS	Hospital Stay (Days)	Survival (Days)	Cause
Control	BD	IPF	0	47	10	160	Airway Stenosis Respiratory Failure
Control	BD	IPF	2	39	250	250	Renal Failure
EVLP	BD	IPF	3	32	10	10	Reperfusion injury /diffuse alveolar hemorrhage due to Cytokine Release Syndrome associated to Thymoglobuline use
EVLP	BD	IPF	2*	49	13	141	Acute Rejection Respiratory Failure
EVLP	DCD	IPF	3	43	198	198	Complications from Aortic Injury
EVLP	BD	IPF	1	71	67	203	Airway Stenosis
EVLP	BD	COPD	0	33	13	272	Leukemia resulting in Bronchiolitis Obliterans Syndrome

Table 16 – NOVEL Study Protocol Deviations

Subject	Deviation	At Least one Delta> 350	At least one absolute PO2>400	Stable or decreased PVR	Stable or Improved Compliance	Clinical Decision	Out come	Cause of Death
0114	Post EVLP- One delta PaO <sub>2</sub> was not greater than 350 mmHg	YES	YES	YES	YES	Improvement trend, absolute PaO <sub>2</sub> greater than 400 mm Hg, PVR decrease/stability and stable/improved compliance	ALIVE	
0301	Post EVLP- One delta PaO <sub>2</sub> was not greater than 350 mmHg.	YES	YES	YES	NO	Improvement trend, absolute PaO <sub>2</sub> greater than 400 mm Hg, PVR decrease/stability, Improved/stable compliance	DEAD at 10 days	Reperfusion Injury due to Cytokine Release Syndrome from ATG
0402	Post EVLP- One delta PaO <sub>2</sub> was not greater than 350 mmHg - <b>not a true deviation after conversion due to Colorado altitude difference.</b> Converted Delta PaO <sub>2</sub> Time period 1: 412 mm Hg, Time period 2: 350 mm Hg EVLP run ended at 2 hrs and 45 minutes (needed to end at 3 hrs if transplant suitable) therefore second EVLP chest xray was not done	YES, BOTH WHEN CONVERTED FOR ALTITUDE	YES	YES (1F 15% used not 10%)	YES	Yes, based on Improvement. Both delta PaO <sub>2</sub> met criteria after altitude adjustment	ALIVE	
0404	Post EVLP- One delta PaO <sub>2</sub> was not greater than 350 mmHg. Converted Delta PaO <sub>2</sub> Time period 1: 279 mm Hg, Time period 2: 377 mm Hg	YES	YES	YES	YES	Improvement trend, absolute PaO <sub>2</sub> greater than 400 mm Hg, stable/improved compliance, PVR decrease/stable	ALIVE	

<b>0406</b>	Post EVLP- Two delta PaO <sub>2</sub> readings were not greater than 350 mmHg. Converted Delta PaO <sub>2</sub> Time period 1: 318 mm Hg Time period 2: 328 mm Hg	NO	YES	YES	YES	Improvement trend, absolute PaO <sub>2</sub> greater than 400 mm Hg, PVR decrease/stability and stable/improved compliance	ALIVE	
<b>0409</b>	Post EVLP- One delta PaO <sub>2</sub> was not greater than 350 mmHg - <b>not a true deviation after conversion due to Colorado altitude difference.</b> Converted Delta PaO <sub>2</sub> Time period 1: 390 mm Hg, Time period 2: 418 mm Hg	YES	YES	YES	YES	Yes, based on Improvement, adjusted delta PaO <sub>2</sub> meets the greater than 350 mmHg criterion	DIED AT 203 DAYS	AIRWAY STENOSIS AND RESPIRATORY FAILURE
<b>0412</b>	Post EVLP- One delta PaO <sub>2</sub> was not greater than 350 mmHg. <b>not a true deviation after conversion due to Colorado altitude difference.</b> Converted Delta PaO <sub>2</sub> Time period 1: 385 mmHg, Time period 2: 367 mm Hg	YES	NO	YES	YES	Yes, based on Improvement in compliance and decrease adjusted delta PaO <sub>2</sub> meets the greater than 350 mmHg criterion	DIED 141 DAYS	ACUTE REJECTION AND RESPIRATORY FAILURE
<b>0502</b>	Post EVLP- One delta PaO <sub>2</sub> was not greater than 350 mmHg	YES	YES	NO	YES	Improvement trend, absolute PaO <sub>2</sub> greater than 400 mm Hg, and stable/improved compliance	ALIVE	
<b>0503</b>	Post EVLP- Both delta PaO <sub>2</sub> were not greater than 350 mmHg	NO	YES	YES	YES	Improvement trend, absolute PaO <sub>2</sub> greater than 400 mm Hg, PVR decrease/stability and stable/improved compliance	ALIVE	
<b>0513/ 0514</b>	Post EVLP- Both delta PaO <sub>2</sub> were not greater than 350 mmHg	NO	YES	YES	YES	Improvement trend, absolute PaO <sub>2</sub> greater than 400 mm Hg, PVR decrease/stability and stable/improved	513 DIED AT 198 DAYS 514	COMPLICATIONS FROM INTRA-OP AORTIC INJURY

						compliance	ALIVE	
<b>0533</b>	Post EVLP- One delta PaO <sub>2</sub> was not greater than 350 mmHg	YES	YES	NO	YES	Improvement trend, absolute PaO <sub>2</sub> greater than 400 mm Hg, PVR decrease/stability and stable/improved compliance	ALIVE	
<b>0534</b>	Post EVLP- One delta PaO <sub>2</sub> was not greater than 350 mmHg	YES	YES	YES	YES	Improvement trend, absolute PaO <sub>2</sub> greater than 400 mm Hg, PVR decrease/stability and stable/improved compliance	ALIVE	
<b>0602</b>	Post EVLP- Both delta PaO <sub>2</sub> was not greater than 350 mmHg - center notified sponsor for approval prior to transplant based on all parameters improving and PO <sub>2</sub> at 400 mm Hg	NO	YES	YES	YES	Improvement trend, absolute PaO <sub>2</sub> greater than 400 mm Hg, PVR decrease/stability and stable/improved compliance	ALIVE	

## ADVERSE EVENTS

Below is a list of adverse events that occurred in the NOVEL trial (12-month analysis).

Table 17 - Adverse Events /Infections by Preservation Method (12-month analysis)

	<b>EVLP (n=31 patients)</b>	<b>Control (n=31 patients)</b>
<b>AE System Organ Class</b>	<b># of Patients with Event</b>	<b># of Patients with Event</b>
<b>Non-Resp Infections and infestations</b>	<b>5 (16%)</b>	<b>3 (10%)</b>
Fungal infection	0	1 (3%)
Viral infection	1 (3%)	0
Bacterial infection	4 (13%)	2 (6%)
Infection, other	0	0
<b>Respiratory, thoracic and Mediastinal disorders</b>	<b>22 (71%)*</b>	<b>16 (52%)*</b>
Pneumonia	6 (19%)	8 (26%)
Pneumothorax/ Hemothorax/ Hydropneumothorax	11(35%)	3 (10%)
Dyspnea/Respiratory Distress	8 (26%)	3 (10%)
Pleural effusion/ Pseudomembrane	6 (19%)	5 (16%)
Chest pain	1 (3%)	0
Viral/URI/Fungal	5(16%)	2(6%)
Other	4 (13%)	2(6%)

\* Twenty-two EVLP subjects and 16 controls experienced at least one event categorized as “respiratory, thoracic and mediastinal disorders,” and some experienced multiple events. There were a total of 41 incidences of “respiratory, thoracic and mediastinal” disorders in EVLP subjects and 23 incidences in control subjects.

Adverse events were collected on an ongoing basis for the first 12 months post-transplant. The primary investigators or co-investigators at each site determined the rating of severity and causality.

An independent safety monitor reviewed each of the serious adverse events (SAEs) reported during the course of the NOVEL study. A safety committee appointed for purposes of the study also reviewed SAEs. All of the reported adverse events summarized below were deemed unrelated to the EVLP procedure and consistent with anticipated adverse events for patients undergoing lung transplant, which include:

- Death
- Renal failure or dysfunction
- Respiratory dysfunction/Infection

- Primary Graft Dysfunction
- Acute rejection
- Cardiac Arrhythmias
- Bronchiolitis Obliterans Syndrome (BOS)/ CLAD
- Bronchiole Stenosis/Dehiscence

In addition, risks due to the implantation procedure or anesthesia may also occur. The subjects received standard of care bronchoscopy with the protocol requiring specific findings as reportable, including clinically significant dehiscence, A2B2 rejection, stenosis, and bronchial infections treated with antibiotics. Any other bronchial disorders could also be reported under the “other” category. The EVLP and control arms did not experience any incidences of dehiscence. Four EVLP subjects experienced stenosis and three have recovered. The EVLP subject who died seven months after transplantation sustained an aortic injury prior to the lung transplant, leading to a cascade of events such as sepsis, pneumonia, PGD Grade 3, acute rejection, bronchial stenosis and skin infections. The control arm had two subjects with stenosis: one who recovered and the other who died five months post-transplant.

It is expected in this study population post-transplant to have positive BALs, dyspnea, pneumonia, gastric reflux, electrolyte imbalance, pneumothorax post bronchoscopy, and skin or hospital acquired infections. The types of events reported are consistent within this study population. In addition, complications due to the procedure can lead to post operative complications. In reviewing the events between the two treatment arms there was no clinically significant difference between the two arms. Some EVLP subjects had post operative complications due to the surgical procedure (i.e., aortic injury).

Cardiac disorders classify the different types of arrhythmias and heart failure. The vascular disorders capture ischemic injury, pulmonary emboli, deep vein thrombosis, hypertension, and cardiac arrest. Acute rejection was reported in the bronchial AEs at a Grade A2B2. Some centers also reported rejection as an AE, which has been listed under immune system disorders. Primary graft dysfunction is being reported at 0, 24, and 72 hours and has also been reported by some sites as an AE and is listed under injury, poisoning, and procedural complications. Under this system organ class are also any post-operative complications (i.e., hematoma, delay wound closure).

The infections and infestations system organ class includes skin infections, nosocomial infections, upper respiratory viral infections, ear, nose and throat infections. All pneumonia (viral and/or bacterial) are reported under the respiratory, thoracic and mediastinal disorders. If the pneumonia had a positive culture it was not reported under the infection system organ class.

### ***Potential Adverse Effects with Lung Transplant***

The outcome post-transplant is also dependent on the primary lung diagnosis.

Based on a review of the published literature on lung transplants, the following adverse events are typically associated with this study population:

- Death
- Renal failure or dysfunction
- Respiratory dysfunction/infection
- Primary graft dysfunction
- Acute rejection
- Cardiac arrhythmias
- BOS/CLAD
- Bronchiole stenosis/dehiscence

In addition, risks due to the implantation procedure or anesthesia or preservation method may also occur.