At-a-Glance

- **Proposal to add the factors "current bilirubin" and "change in bilirubin" to the lung allocation score (LAS)**

- **Policy affected: Policy 3.7.6.1 (Candidates Age 12 and Older)**

- **Thoracic Organ Transplantation Committee**

  This proposal adds the following two factors to the LAS to better predict a lung transplant candidate's waiting list urgency: 1) current bilirubin (for a candidate in any diagnosis group); and 2) change in bilirubin of at least 50% (for a candidate in diagnosis Group B only). Analyses revealed the association between high bilirubin levels and waitlist mortality. The association between current bilirubin of at least 1.0 mg/dL and waiting list mortality has statistical significance. An increase in a lung transplant candidate's bilirubin level of 50% or more during a six-month period, when the higher bilirubin value is at least 1.0 mg/dL, increases a diagnosis Group B candidate's risk for dying on the waiting list. This association between change in bilirubin of at least 50% and waiting list mortality for candidates in diagnosis Group B (largely candidates diagnosed with pulmonary hypertension) has statistical significance.

  The Thoracic Committee anticipates that this policy modification will reduce waitlist mortality for a lung transplant candidate, and improve the ability of the LAS to predict a candidate's medical urgency for a lung transplant.

- **Affected Groups**

  - Lung transplant candidates, particularly candidates with pulmonary hypertension
  - Transplant pulmonologists
  - Lung transplant surgeons
  - Lung transplant coordinators
  - Transplant data coordinators
  - General public

Proposal to add the factors "current bilirubin" and "change in bilirubin" to the lung allocation score (LAS)

Policy affected: Policy 3.7.6.1 (Candidates Age 12 and Older)

Thoracic Organ Transplantation Committee

Summary and Goals of the Proposal:

The LAS prioritizes candidates who are 12 years of age or older on the lung transplant waiting list. This proposal adds the following two factors to the waitlist survival model in the LAS: 1) "current bilirubin[A] (for all candidates);" and 2) "change in bilirubin" (for candidates in diagnosis Group B[B] only).

Analyses revealed the association between high bilirubin levels and waitlist mortality. The association between current bilirubin of at least 1.0 mg/dL and waiting list mortality has statistical significance. An increase in a lung transplant candidate's bilirubin level of 50% or more during a six-month period, when the higher bilirubin value is at least 1.0 mg/dL, increases a diagnosis Group B candidate's risk for dying on the waiting list. This association between change in bilirubin of at least 50% and waiting list mortality for candidates in diagnosis Group B (largely candidates diagnosed with pulmonary hypertension (PH)) has statistical significance.

The Thoracic Committee (the Committee) anticipates that this policy modification will reduce lung transplant waitlist mortality, and create a more clinically comprehensive waitlist survival model that increases the sensitivity of the LAS in predicting a candidate's medical urgency for a lung transplant.

Problem Statement:

Since the implementation of the LAS, though the death rate has declined among lung transplant candidates who are at least 12 years of age, there continue to be waiting list deaths in this group. Further, the death rate in the diagnosis Group B population appears to have increased slightly. The continued occurrence of mortality on the waiting list necessitates this effort to enhance the ability of LAS to better predict waitlist urgency. The result of this effort has the potential to reduce deaths on the waiting list for lung transplant candidates in all diagnosis groups.

Significance of the Proposal:

OPTN data as of January 9, 2009 (see Table 1 on the next page) show that there continue to be deaths on the waiting list among lung transplant candidates who are 12 years of age or older. For all diagnosis groups, death rates per 100 patient-years decreased in the year following the implementation of the LAS

[A] The body's breakdown of hemoglobin results in the production of bilirubin. (Hemoglobin, a protein in red blood cells, contains iron and carries oxygen.) Bilirubin levels in the body help assess the health of the liver or gallbladder. For more information about bilirubin, visit the following website: http://www.nlm.nih.gov/medlineplus/ency/article/003479.htm

[B] The five LAS diagnosis groups are organized by the clinical characteristics of the various diagnoses for patients awaiting lung transplantation and existing data on survival behavior in these patients. Within each group are various illnesses that share similar clinical characteristics and similar risk factors for mortality on the waiting list and for post-transplant mortality. Group A includes chronic obstructive pulmonary disease, including alpha-1 antitrypsin deficiency and emphysema, lymphangioleiomyomatosis, bronchiectasis, sarcoidosis (with mean PA pressure $\leq$30 mmHg). Group B includes primary pulmonary hypertension, and pulmonary vascular disease. Group C includes cystic fibrosis and immunodeficiency disorders such as hypogammaglobulinemia. Group D includes idiopathic pulmonary fibrosis, pulmonary fibrosis (other causes), sarcoidosis (with mean PA pressure > 30 mmHg), and obliterative bronchiolitis (non-retransplant). Group E includes all patients aged 11 and under and will continue to be allocated lungs based on waitlist time and ABO type.

(May 4, 2005). However, with the exception of Group A, the death rates appear to have increased during the two most recent eras (5/4/06-5/3/07 and 5/4/07-5/3/08). These increases likely reflect a shift towards candidates being listed at later stages of lung disease as well as the listing of more medically urgent candidates who may not have been added to the waiting list in the pre-LAS era. Diagnosis Group B experienced the largest increase (5.5 deaths per 100 patient-years higher than during the 2006-2007 era): 12.9 deaths per 100 patient-years in the latest era as compared with 7.4 deaths per 100 patient-years between May 4, 2006 and May 3, 2007.

Table 1

Lung Death Rates by Era and Diagnosis Grouping for Candidates 12 Years or Older at Listing
[Ever listed: May 4, 2004 – Mary 3, 2008]

Diagnosis group	Waiting time period (era)	Number of candidates ever waiting	Deaths in era*	Patient years (PY) in group	Deaths/ 100 PY
A	05/04/2004 - 05/03/2005	2384	176	1646.7	10.7
	05/04/2005 - 05/03/2006	1984	91	1326.6	6.9
	05/04/2006 - 05/03/2007	1832	84	1160.8	7.2
	05/04/2007 - 05/03/2008	1740	59	974.5	**6.1**
B	05/04/2004 - 05/03/2005	644	39	531.1	7.3
	05/04/2005 - 05/03/2006	607	35	484.7	7.2
	05/04/2006 - 05/03/2007	523	30	405.3	7.4
	05/04/2007 - 05/03/2008	444	36	279.4	**12.9**
C	05/04/2004 - 05/03/2005	736	68	495.3	13.7
	05/04/2005 - 05/03/2006	705	39	453.7	8.6
	05/04/2006 - 05/03/2007	648	45	401.5	11.2
	05/04/2007 - 05/03/2008	579	47	325.1	**14.5**
D	05/04/2004 - 05/03/2005	1616	204	997.2	20.5
	05/04/2005 - 05/03/2006	1637	160	868.1	18.4
	05/04/2006 - 05/03/2007	1600	152	752.7	20.2
	05/04/2007 - 05/03/2008	1632	158	651.6	**24.2**

Note. Caution should be used in drawing conclusions based on death rates due to differences in patient populations and small number of deaths in some groups.
*Deaths include those reported to the OPTN or to the Social Security Death Master File (SSDMF) while on waiting list or within 7 days of non-transplant removal.

The death rates for diagnosis Groups B, C, and D appear to have increased since the implementation of the LAS. The LAS "…determines the order in which lung offers are made to candidates awaiting transplantation based on estimates of each candidate's medical urgency prior to transplant and his or her probability of success following a transplant" (p.1).[3] As such, the occurrence of deaths on the lung

transplant waiting list may indicate, in part, the need for a more sensitive LAS system (i.e., a system that enhances the identification of and lung allocation to candidates who are medically urgent). Therefore, the need to add bilirubin to the LAS is paramount as the proposed policy modification may reduce the number of deaths on the waiting list and improve the ability of the LAS to predict a candidate's medical urgency for a lung transplant.

Strengths of the Proposed Policy Modification

This modification: 1) will enhance the waitlist component of the lung allocation score system, thereby increasing the ability of the LAS to predict a candidate's medical urgency for a lung transplant; and, 2) will likely reduce deaths on the waiting list for all candidates.

Weaknesses of the Proposed Policy Modification

The addition of bilirubin, like the addition of PCO_2, is occurring after the implementation of the lung allocation score (2005). Current clinical observations and statistical analyses suggest that using bilirubin as a biological marker for lung candidates' waitlist mortality is appropriate and significant. However, the SRTR analyzed the inclusion of bilirubin, like PCO_2, using information gathered in the lung retrospective data collection project. An analysis of the factors in the waitlist model using data collected since the implementation of the LAS has not yet occurred, and cannot occur until more LAS data are collected. Once this analysis is performed, the results could indicate changes needed in the waitlist model, such as the removal of one or more of these variables. As such, in this future analysis, the current statistical rationale for including bilirubin in the waitlist model may not hold.

Intended Consequence of Modifying Policy 3.7.6.1

Adding current bilirubin to the lung allocation score will more accurately predict waiting list mortality of candidates who have experienced hyperbilirubinemia[C]. Further, diagnosis Group B candidates with change in bilirubin values that are at least 50% (when the highest value is at least 1.0 mg/dL) will likely experience a beneficial difference in their match-run positions. Since candidates with PH often experience hyperbilirubinemia, including change in bilirubin in the LAS may help to more accurately reflect the medical urgency of this population.

Unintended Consequence of Modifying Policy 3.7.6.1

The addition of the change in bilirubin parameter might prioritize the waitlist urgency for Group B candidates beyond the true medical urgency for this diagnosis group. Further, candidates in Groups A, C, and D – who may not receive the same prioritization as Group B candidates – might have received lung offers sooner if change in bilirubin was not included in the LAS for Group B candidates. At its future meetings, the Committee will continue to review data on waiting list mortality and transplant rates to assess the impact of these proposed policy modifications.

[C]Hyperbilirubinemia is the presence of too much bilirubin in the blood. Normal bilirubin levels are 0.3 mg/dL to 1.0 mg/dL.

History of the Development of the Policy Proposal:

At its October 30, 2006 meeting, the Committee met with a professional representative of the PH community to discuss the impact of the LAS on PH candidates on the lung transplant waiting list. Due to growing concerns that the LAS does not optimally prioritize lung candidates with PH, this professional representative encouraged the Committee to collect data to better predict waitlist mortality and post-transplant survival among PH candidates. The Committee supported this idea.

Separately, as part of its LAS monitoring efforts, the Committee began its examination of the impact of bilirubin on waiting list mortality. UNOS had collected bilirubin values during the Lung Retrospective Data Collection project (2003-2004)[D]. These bilirubin values were available for a large number of candidates whose clinical data the Committee used to develop the LAS. In February 2, 2007, the Committee began to examine whether bilirubin would be a predictor of waitlist mortality. The Committee suspected that this predictor would be especially relevant for diagnosis Group B candidates (includes those with PH). This initial SRTR analysis indicated that higher bilirubin values were statistically significant predictors of waitlist mortality among lung transplant candidates.

At the May 3, 2007 Committee meeting, the SRTR reported that for a diagnosis Group B candidate with a peak bilirubin value of at least 1.0 mg/dL, an increase in bilirubin of at least 50% in a six-month period is associated with an increased mortality risk for diagnosis Group B. This change in bilirubin factor is the first data element examined since the implementation of the LAS that benefits the scores of the PH candidate population. The Committee inquired about the association of bilirubin with post-transplant survival and tasked the Lung Subcommittee to discuss this analysis and make appropriate policy recommendations.

The Lung Subcommittee convened on September 20, 2007, and summarized its discussion to the Committee on October 2, 2007. Change in bilirubin was associated only with waitlist mortality, and not post-transplant survival. The incorporation of this biological marker in the lung transplant waitlist urgency model may help predict waitlist mortality for candidates with PH. A professional representative of the PH community reported that the Reveal Registry[E] is very new and does not have adequate data regarding bilirubin as a marker for candidates with PH. This representative reported that increases in bilirubin are predictive of poor health outcomes, such as right heart failure. At this October meeting, the Committee voted in favor of the following resolution to include change in bilirubin in the lung allocation score (20-Yes, 0-No, 0-Abstentions):

> **RESOLVED, that Policy 3.7.6.1 (Candidates Age 12 and Older) shall be modified to include change in bilirubin in the lung allocation score.

In 2008, the Lung Subcommittee determined that the language of the bilirubin policy would be similar to the PCO_2[F] policy (Policy 3.7.6.1.b -- http://www.optn.org/policiesAndBylaws/policies.asp). The Subcommittee set the normal clinical bilirubin value of 0.7 mg/dL, and determined that a candidate's

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[D]The goal of the retrospective data collection project was to obtain more detailed information regarding the disease progression and medical urgency for lung transplant waiting list registrations and transplants. These data are used in the ongoing refinement and improvement of the proposed lung allocation algorithm. The results of this project are also useful in specifying additional fields for collection either longitudinally on the waiting list or at the time of listing.

[E]As written on the Reveal Registry's web site, "the Reveal Registry is a multi-center, observational, US-based registry study of pulmonary arterial hypertension." For more information, visit the following website: http://www.revealregistry.com/

[F]PCO_2 is a blood gas – partial pressure of carbon dioxide. Previous analysis revealed that increases in PCO_2 increase a lung transplant candidate's waitlist mortality. The OPTN/UNOS Board of Directors approved the addition of PCO_2 in the LAS on March 23, 2007. On October 9, 2008, UNOS implemented the addition of PCO_2 in UNet^{SM}.

peak bilirubin value should be at least 1.0 mg/dL in order for a candidate's LAS to be altered. These decisions were based on clinical expertise and the results of additional SRTR analyses.

From June 30, 2008 through September 24, 2008, the Committee submitted for public comment a proposal to add change in bilirubin (50% or higher in a six-month period) to the LAS[G]. The Lung Subcommittee convened on October 16, 2008 to review comments on the proposal. The public, and the OPTN/UNOS committees and regions submitted largely favorable comments on the proposal. The Subcommittee, upon re-reviewing the statistical evidence supporting the addition of change in bilirubin to the LAS, questioned the inclusion of the creatinine[H] variable in some of the data published in the June, 2008 proposal. (This earlier proposal was based primarily on quantitative data that included creatinine as well as bilirubin; however, the Committee did not propose that creatinine be incorporated into the waiting list component of the LAS calculation.) The Subcommittee asserted that the creatinine variable made it difficult to discern whether the results shown were based on analyses that included both bilirubin and creatinine, or just bilirubin. As a result, the Lung Subcommittee requested the SRTR to analyze whether the impact of bilirubin on the waitlist component of the LAS was due to bilirubin and creatinine, or bilirubin only. The Committee then requested the SRTR to perform this analysis and deferred forwarding the change in bilirubin proposal for review by the OPTN/UNOS Board of Directors.

The Lung Subcommittee reviewed this SRTR analysis in late October, 2008 and again at its November 20, 2008 meeting. The Lung Subcommittee made the following recommendations to the Committee based on the data reviewed:

- Add current bilirubin values that is at least 1.0 mg/dL to the LAS for all diagnosis groups; and
- Add change in bilirubin that is at least 50% to the LAS for diagnosis Group B, provided that the highest value used in the change calculation is at least 1.0 mg/dL and the change occurs in a six-month period.

At its meeting on November 21, 2008, the Committee agreed with the Subcommittee's recommendations and voted in favor of the following resolution to include in the LAS current bilirubin (for all diagnosis groups) and change in bilirubin (for Group B only) (22-Yes, 0-No, 0-Abstentions):

> **RESOLVED, that Policy 3.7.6.1 (Candidates Age 12 and Older) shall be modified to include in the LAS the factors of current bilirubin for all diagnosis groups, and change in bilirubin for diagnosis Group B only.

The following section provides additional detail on the SRTR analyses referenced above.

Supporting Statistical Evidence:

The SRTR modeled the inclusion of current and change in bilirubin in the lung allocation score. Current bilirubin refers to the value with the most recent test date and time. Current bilirubin values lower than 0.7 mg/dL were substituted with the normal clinical value of 0.7 mg/dL. Change in bilirubin was based

[G] To review this change in bilirubin public comment proposal, please visit the following web site and click on the first pdf document to the right of the title, "Thoracic Organ Transplantation Committee - Proposal to add the factor 'change in bilirubin' to the lung allocation score (LAS) Policy affected: 3.7.6.1 - (Candidates Age 12 and Older):" http://www.optn.org/policiesAndBylaws/publicComment/proposals.asp.

[H] The initial statistical model that included bilirubin also analyzed the addition of "current" and "change in creatinine" in the lung allocation score. Both creatinine factors were statistically significant. However, the Committee sought additional analyses and will discuss again the inclusion of current and change in creatinine in the waiting list component of the LAS. The current LAS calculation does include creatinine, but only in the pos-transplant component.

on the percentage increase from any value in the six month period and prior to the current bilirubin value. In these analyses, change in bilirubin was limited to the pairs of values – minimum (or, "lowest") and maximum (or, "highest") – where the lower value was observed prior to the highest value. Also, the highest value was required to be at least 1.0 mg/dL.

Statistical Study Population and Methods

The SRTR analyzed data for lung transplant candidates who were at least 12 years of age from the retrospective dataset. The analysis described the effect of current bilirubin and change in bilirubin on waiting list mortality when current bilirubin values were observed to be at least 1.0 mg/dL. The SRTR did not consider the effect of current bilirubin or change in bilirubin for candidates who did not reach a current bilirubin value of at least 1.0 mg/dL. The analysis provided lung allocation scores and corresponding rankings for patients with complete LAS data. The analysis included a comparison of LAS calculated without bilirubin (as is done today) and with bilirubin to consider its effect on waitlist mortality. The SRTR analyzed data from candidates in the retrospective dataset[I]. If data were not found in the patient charts for the retrospective review, data in the OPTN database (at listing) were used.

The waitlist model predicted mortality based on measures of serial bilirubin, adjusted for the current LAS factors[J]. The SRTR also examined interactions between change in bilirubin and diagnosis group. The factors in the waitlist model were:

- Current bilirubin (required to be at least 1.0 mg/dL; defined above)
- A yes/no indicator for increase in bilirubin (at least 50 %) for Group B.
  (i.e., did the candidate in diagnosis group B have at least a 50% increase in bilirubin: yes/no?).
  The current bilirubin is required to be at least 1.0 mg/dL for change to be considered as "yes".
- All other approved LAS factors (including PCO_2)

The SRTR used Cox proportional hazard regression models to examine mortality on the lung transplant waiting list (N=2042). There were 376 candidates available with an observed current bilirubin of at least 1.0 mg/dL. Of these, 33 candidates were available for analysis from diagnosis Group B that reached the 50% change threshold.

Results: Waitlist Mortality Statistical Modeling

There was a statistically significant increased risk for waiting list mortality associated with higher bilirubin levels among candidates in any diagnosis group who had current bilirubin values of at least 1.0 mg/dL (p-value is 0.0027; see Table 2). Among diagnosis Group B candidates with peak bilirubin values of at least 1.0 mg/dL, a change in bilirubin of at least 50%, as defined above, was significantly associated with increased risk for mortality on the lung transplant waiting list (p-value is less than 0.0001; see Table 2). The impact of change in bilirubin was not statistically significant for diagnosis Groups A, C, and D.

Table 2, on the next page, describes the effect on waiting list mortality when the current bilirubin value is 1.0 mg/dL or higher. Analyses showed that in the Group B candidate population, a change in bilirubin

[I]The retrospective dataset included lung transplant waitlist candidates added to the waiting list with diagnoses other than primary PH between January 1, 1999 and December 31, 2000. For candidates with a diagnosis of primary PH in the retrospective dataset, the addition to the lung transplant waiting list occurred between January 1, 1998 and December 31, 2003.

[J]The current, implemented, waiting list factors are forced vital capacity, pulmonary artery systolic, oxygen required at rest, age, body mass index, diabetes, NYHA, six-minute walk distance, continuous mechanical ventilation, diagnosis, and PCO_2.

of at least 50% was associated with an increased risk for death on the waiting list. The Committee proposed to incorporate in the LAS the hazard ratios presented in Table 2. These hazard ratios are based on the lower bound of the 90% confidence intervals for current bilirubin and change in bilirubin. These conservative estimates of the bilirubin effect are appropriate to use given that the results are based on data from the retrospective data collection project, rather than the current OPTN database. Further, the use of the lower bound of the 90% confidence interval is consistent with the prior analysis of serial PCO_2 and the Committee's decision to include current and change in PCO_2 in the LAS.

Table 2

Waitlist Mortality Model Results

Parameter	N	Hazard ratio*	P-value	90% Confidence interval
Current bilirubin (continuous) when current bilirubin is at least 1.0 mg/dL	376	1.22**	0.0027	(1.09, 1.35)
Highest bilirubin of at least 1.0 mg/dL and increase from minimum to maximum bilirubin of at least 50% within six-months of minimum bilirubin for Group B	33	3.85	<.0001	(2.31, 6.43)

*Hazard Ratio = A hazard ratio that is greater than 1.0 indicates an increased risk for waiting list mortality due to the given parameter, whereas a value less than 1.0 indicates a decreased risk for waiting list mortality due to the given parameter.
**1.22 = The hazard ratio for current bilirubin represents the increase in hazard per 1 mg/dL increase in bilirubin above 1.

Because the 90% lower confidence bound for both factors is greater than 1: (i) Group B candidates that meet either condition (current bilirubin value of at least 1.0 mg/dL or change in bilirubin of 50% or more); and (ii) Group A, C and D candidates with current bilirubin values of at least 1.0 mg/dL will experience an increase in their LAS.

The analysis examined the effect of including current bilirubin (all diagnosis groups) and change in bilirubin (diagnosis Group B only) on lung allocation scores. LAS calculation occurred only for candidates with complete data, that is with serial bilirubin and all other existing LAS parameters (including serial PCO_2) available in the retrospective data (N=98). The modified algorithm with bilirubin effects utilized the lower bound of the 90% confidence intervals for current bilirubin and change in bilirubin in the calculation. The mean, median, minimum, and maximum lung allocation scores were at least as high as scores without bilirubin for each diagnosis group, and, overall, were higher.

Table 3, on the next page, shows the relationship between the LAS algorithm currently in place and one modified to include bilirubin effects for each of the four diagnosis groupings.

Table 3

LAS by Scoring Algorithm and Diagnosis Group for Candidates with Maximum Bilirubin Values of 1.0 mg/dL or Greater

Diagnosis group	Scoring algorithm	N	Mean	Median	(Min, max)
Group A	Current	15	30.5	30.2	(29.5, 31.9)
	Modified	15	30.6	30.3	(29.5, 32.0)
Group B	Current	39	30.2	29.4	(27.2, 42.8)
	Modified	39	31.2	30.0	(27.3, 43.4)
Group C	Current	4	32.6	32.6	(31.4, 33.8)
	Modified	4	32.7	32.8	(31.4, 33.9)
Group D	Current	40	32.2	31.7	(28.6, 44.5)
	Modified	40	32.3	31.7	(28.6, 44.6)

Each LAS diagnosis group experienced a slight increase in its average LAS (mean or median) when including bilirubin. Because diagnosis Group B was the only group that had change in bilirubin incorporated into the score, the lung allocation scores for this group increased by the greatest amount in the modified LAS algorithm. Table 4 below provides summary measures for both the LAS as it is currently calculated and a score that includes bilirubin effects for 13 PH candidates in the retrospective dataset. These 13 candidates experienced at least a 50% change in bilirubin and had current bilirubin values of at least 1.0 mg/dL. These 13 candidates also had non-missing values for each of the other LAS parameters.

Table 4

LAS by Scoring Algorithm for Diagnosis Group B Candidates with Maximum Bilirubin of 1.0 mg/dL or More, and a 50% Change in Bilirubin (from Minimum to Maximum)

Diagnosis group	Scoring algorithm	N	Mean	Median	(Min, max)
Group B	Current	13	29.4	29.1	(27.5, 31.4)
	Modified	13	32.3	31.0	(28.4, 37.2)

Figure 1, on the next page, shows lung allocation scores based on factors in the current policy ("Current LAS"). It also shows scores based on the proposed policy factors, current bilirubin when it is at least 1.0 mg/dL, and change in bilirubin of at least 50% ("Modified LAS"). To provide a larger sample size, candidates with missing PCO_2 were given a value of 40 mmHg for current PCO_2 and a value of no change for change in PCO_2. These imputations followed policy and were due to the large number of missing PCO_2 values in the retrospective dataset. Other than to provide a larger number of candidates for whom the effects of bilirubin can be assessed, the imputation of default values for missing values has no impact on the results discussed in this section. In Figure 1, values along the diagonal line indicate that there is no or very little change in the LAS due to the modified algorithm. While most candidates are on

or very near the no-change line, there are several candidates, particularly those in Group B, that experience substantial increases in their lung allocation scores in the modified algorithm.

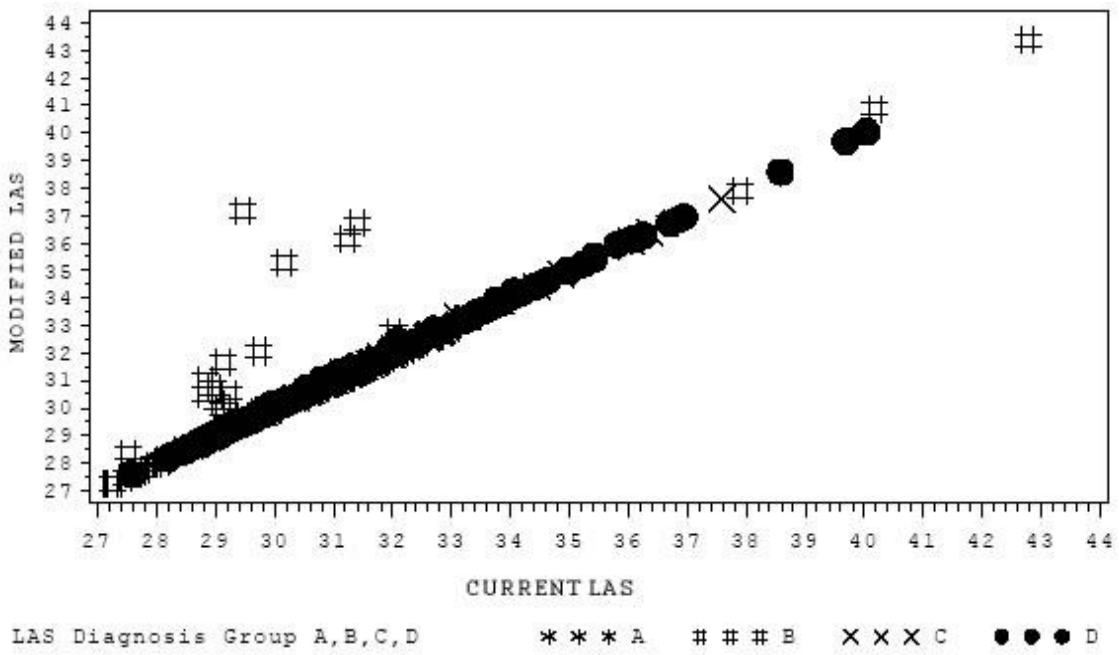

Figure 1. LAS Based on Current Policy (3.7.6.1) and LAS Based on the Addition of Bilirubin for Candidates with Complete* LAS Parameters

*Complete values were required for all LAS factors other than PCO_2.

Figure 2, on the next page, shows the corresponding change in allocation rankings between the current algorithm and the modified algorithm. Candidates with small changes in lung allocation scores can still experience substantial change in allocation ranks. (A candidate with an allocation rank of 1 will have the highest priority for an organ offer.) Candidates with elevated bilirubin, and more so Group B candidates with at least a 50% change in bilirubin, will likely see a decrease in their ranks, thereby increasing their priority for transplant offers.

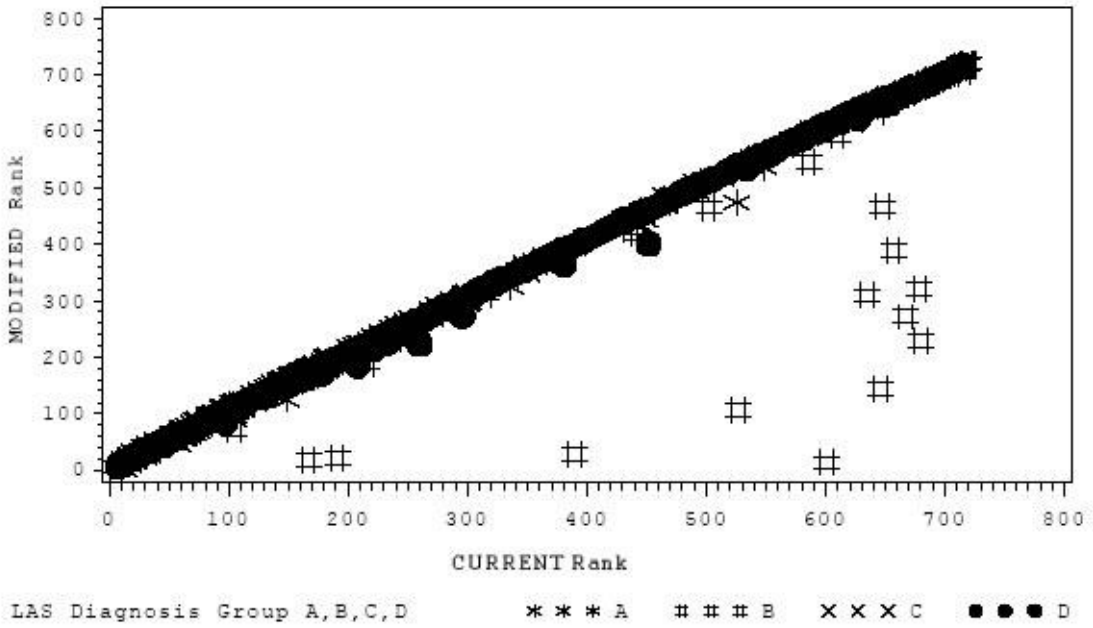

Figure 2. Allocation Rank* Based on Current Policy (3.7.6.1) (Current Rank) and Allocation Rank Based (Modified Rank) on the Addition of Bilirubin for Candidates with Complete** LAS Parameters

*Rank = "Rank" does not refer to an actual match-run position for any given candidate. The ranks displayed are hypothetical positions of candidates, and these candidates represent a combination of all blood types and geographic distributions. This figure does not account for individual candidate screening criteria that help determine actual match-run positions.

**Complete = Complete values were required for all LAS factors other than PCO_2.

The Committee set a normal clinical bilirubin value of 0.7 mg/dL for current bilirubin. The value of 0.7 mg/dL is the midrange of normal bilirubin levels (0.3 mg/dL to 1.0 mg/dL). Therefore, the proposed policy language states that UNet^{SM} will substitute 0.7 mg/dL for values reported that are less than the normal clinical value. Therefore, the lowest value that would be considered in the change calculation is this normal value of 0.7 mg/dL. To experience a 50% increase from the normal value would result in a high value of 1.05 mg/dL, which is greater than the required high value of 1.0 mg/dL. Therefore, this condition, though explicitly stated, is implicitly always true.

Results: Post-Transplant Survival Statistical Modeling

Current and change in bilirubin were not statistically significant predictors of post-transplant mortality. Thus, the Committee did not consider either factor for inclusion in the post-transplant survival component of the LAS.

Summary of Statistical Evidence

Across all diagnosis groups, an increased risk for waiting list mortality is associated with higher current bilirubin values when they are 1.0 mg/dL or more. Group B is the only LAS diagnosis group to demonstrate a statistically significant relationship between change in bilirubin and increased waitlist mortality. The LAS data shown in Table 4 and Figure 2 suggest that Group B lung transplant candidates

with elevated bilirubin will likely receive lung transplants sooner, than they do currently, upon the addition of change in bilirubin to the lung allocation score. Further, clinical observations of Committee members and the literature (see next section) support the inclusion of current bilirubin in the LAS for all diagnosis groups: hepatic health can have an impact on lung health.

The data described in this section provided the following statistical evidence for the Committee's decision to propose the inclusion of current and change in bilirubin in the waiting list urgency model of the LAS:

- A higher value of current bilirubin that is at least 1.0 mg/dL increases a lung transplant candidate's mortality on the waiting list, and this association is statistically significant for a candidate in any diagnosis group; and,
- A 50% or higher increase in bilirubin during a six-month period, when the highest bilirubin value is at least 1.0 mg/dL, increases a lung transplant candidate's mortality on the waiting list. This finding is statistically significant for diagnosis Group B only. The proposed policy language incorporates change in bilirubin of at least 50% for only candidates in diagnosis Group B.

Supporting Evidence in the Literature:

A search of the literature (completed in early June, 2008) on the impact of hyperbilirubinemia on lung transplant waiting list mortality (published in the English language; available in PubMed[K]) did not yield any studies that directly addressed the impact of high bilirubin levels on the waitlist mortality of lung transplant candidates. A few articles did discuss the relationship between hepatic function and lung health, as well as factors that contribute to waitlist or post-transplant mortality among candidates with PH. The existing literature supports the statistical analysis presented in the previous section as well as the clinical observations of pulmonologists and lung surgeons who are on the Thoracic Committee. A brief review of the literature relevant to this public comment proposal is presented below.

Worsening liver health is a marker for worsening lung health.[2] Schwartz et al.[2] examined 24 candidates diagnosed with adult respiratory distress syndrome (ARDS) to assess what factors are related to a clinical outcome. In this study, 14 of the 24 candidates died. A significant difference between the ARDS survivors and non-survivors was hepatic function: hepatic dysfunction as indicated by higher levels of bilirubin was associated with non-survivors. Schwartz et al. concluded that "hyperbilirubinemia was associated with a poor outcome" (p. 873) among ARDS candidates in the study.[2]

Hyperbilirubinemia is known to occur with right ventricular failure and is a common clinical occurrence among candidates with PH. Kramer et al. explored the relationship between pre-transplant bilirubin levels and post-transplant survival among heart-lung transplant candidates.[1] The study evaluated 62 cases of PH; of these 62 cases, 31 candidates had PH due to congenital heart disease and 31 due to Eisenmengers's syndrome. Mild elevations in bilirubin levels in heart-lung transplant candidates were indicative of the need for a transplant as very high levels of bilirubin in this population may lead to post-transplant (post-operative) mortality. Kramer et al. don't define what constitutes "mild" elevations in bilirubin; however, they recommend the following treatment in the population studied: "Maximal

[K]PubMed is a free, electronic portal that allows users to search its database for biomedical articles. PubMed is a product of the National Library of Medicine. For more information, visit the following web site: http://www.ncbi.nlm.nih.gov/pubmed/ .

diuretic therapy should be attempted to decrease liver congestion, and serious consideration for transplantation should be given at this point" (p. 320).[1]

High bilirubin level in a thoracic transplant candidate is a marker for right heart failure. Further, candidates with PH frequently suffer from hyperbilirubinemia, and have poor lung transplant waitlist survival. Therefore, the addition of change in bilirubin as a factor in the LAS is necessary and will likely decrease the occurrence of waitlist mortality in the PH population.

Expected Impact on Program Goals and Strategic Plan:

This proposal will contribute to the following HHS Program Goal: *increase life years gained.* With the incorporation of current bilirubin and change in bilirubin in the LAS, the intended candidates will receive a higher priority on the match-run for receiving lung offers. As a result, these candidates are less likely to die on the waiting list because they will be identified for transplants sooner. The addition of change in bilirubin in the LAS may allow Group B candidates to receive higher priority for transplants than other lung diagnosis groups.

Plan for Evaluating the Proposal:

During its meetings, the Committee will evaluate the impact of the addition of current and change in bilirubin in the LAS through OPTN data analyses of the LAS. The Committee will refer to the following questions when evaluating the impact of bilirubin on the LAS:

- Has there been a reduction in waitlist mortality as a result of the addition of current bilirubin?
- Are Group B candidates with elevated bilirubin values receiving transplants at a rate higher than before the addition of change in bilirubin in the LAS?
- Are Groups A, C, and D with elevated bilirubin values receiving transplants at a rate higher than before the addition of current bilirubin in the LAS?
- Has the LAS system become more sensitive as a result of adding current and change in bilirubin to the LAS?

Additional Data Collection:

Currently, UNet^{SM} does not provide a mechanism for collecting bilirubin values of lung candidates. This data collection is justified by the following data collection principle: *Develop transplant, donation, and allocation policies*.

An approval of this proposal by the OPTN/UNOS Board of Directors would necessitate the collection of bilirubin values in electronic lung transplant waitlist records for adult and pediatric candidates. This proposal will require the inclusion of the current bilirubin and change in bilirubin as parameters in the LAS calculation. This addition will require the following of UNet^{SM}:

- Identification of current bilirubin value for all candidates;
- monitoring expiration of current bilirubin value for all candidates;
- application of current bilirubin of at least 1.0 mg/dL in the LAS for all candidates;
- calculation of percent change in bilirubin for Group B candidates;
- evaluation of highest and lowest bilirubin values for use in the change equation (Group B only);

- determining whether the Group B candidate receives the impact from change;
- determining when a Group B candidate may maintain benefit from change of at least 50%; and,
- enabling the UNOS Organ Center to modify archived values.

A data element asking whether the candidate is on a certain class of drugs will also be programmed. The purpose of this medication field is to learn whether medication is confounding the bilirubin values reported. (In this current proposal, the medication information will have no impact on the LAS.)

Expected Implementation Plan:

This proposal will require programming in UNet[SM], and this programming will impact the allocation of lungs to transplant candidates who are at least 12 years of age. Upon this programming, transplant centers should enter current bilirubin values in UNet[SM] for all lung candidates. (Though only candidates 12 years of age or older receive a lung allocation score, UNOS will enable the entry of bilirubin data for all lung transplant candidates.) This proposed policy, were it to be approved by the OPTN/UNOS Board of Directors, would be effective upon its technological implementation. Transplant professionals should become familiar with the bilirubin policy language. UNOS will notify transplant professionals when it has programmed the policy and an implementation date is available.

Communication and Education Plan:

If the OPTN/UNOS Board of Directors approves this proposed policy modification, Table 5 below proposes Committee's plan to communicate the addition of current and change in bilirubin to the LAS.

Table 5

Communication Activities

Type of communication	Audience	Delivery method	Timeframe
Policy notice (informs community that the proposed policy was approved by the OPTN/UNOS Board of Directors)	Transplant administrators, coordinators, program directors, surgeons, physicians, social workers, data coordinators	Email	Distributed 30 days after Board approval
UNet[SM] system notice (informs the community about policy implementation)	Transplant coordinators, administrators, directors, and data coordinators	Email	Four weeks before implementation and on the date of implementation
Notice to the thoracic community (informs group about policy implementation)	Transplant administrators, coordinators, program directors, surgeons, physicians, social workers, and data coordinators	Email	Four weeks before implementation and on the date of implementation

Monitoring and Evaluation:

The UNOS Department of Evaluation and Quality (DEQ) staff conducts routine site surveys of transplant centers to evaluate member compliance with OPTN/UNOS Policies and Bylaws. More specific details about OPTN/UNOS monitoring efforts will be available in the OPTN Evaluation Plan[L] following approval and implementation of these policy changes. Some general information is provided below.

During site surveys of lung transplant programs, UNOS staff currently verifies clinical data entered into UNet[SM] for lung transplant candidates for accuracy and compliance with applicable Policies and Bylaws. For example, to verify clinical data used to calculate a lung candidate's LAS (candidates who are at least 12 years old), UNOS staff compares the information entered into UNet[SM] to the medical record documentation. UNOS staff reports any discrepancies or potential policy violations that are identified during the site survey process to the transplant program. After receiving a response and corrective action plan (if applicable), UNOS staff forwards the survey results to the OPTN/UNOS Membership and Professional Standards Committee for confidential medical peer review.

If this change is approved, UNet[SM] would be modified to collect the information described in the proposal. UNOS staff would modify monitoring efforts to incorporate a review of bilirubin data into the routine site survey process for lung transplant programs.

Proposed OPTN/UNOS Policy Proposal:

3.7.6.1 <u>Candidates Age 12 and Older</u>. Candidates age 12 and older are assigned priority for lung offers based upon Lung Allocation Score, which is calculated using the following measures: (i) waitlist urgency measure (expected number of days lived without a transplant during an additional year on the waitlist), (ii) post-transplant survival measure (expected number of days lived during the first year post-transplant), and (iii) transplant benefit measure (post-transplant survival measure minus waitlist urgency measure). Waitlist urgency measure and post-transplant survival measure (used in the calculation of transplant benefit measure) are developed using Cox proportional hazards models. Factors determined to be important predictors of waitlist mortality and post-transplant survival are listed below in Tables 1 and 2. It is expected that these factors will change over time as new data are available and added to the models. The Thoracic Organ Transplantation Committee will review these data in regular intervals of approximately six months and will propose changes to Tables 1 and 2 as appropriate.

[L] To read the OPTN Evaluation Plans, please visit the following website: http://www.optn.org/content/policiesAndBylaws/evaluation_plan.asp

Table 1
Factors Used to Predict Risk of Death on the Lung Transplant Waitlist

1.	Forced vital capacity (FVC)
2.	Pulmonary artery (PA) systolic (Groups A, C, and D – see 3.7.6.1.a)
3.	O_2 required at rest (Groups A, C, and D – see 3.7.6.1.a)
4.	Age
5.	Body mass index (BMI)
6.	Diabetes
7.	Functional status
8.	Six-minute walk distance
9.	Continuous mechanical ventilation
10.	Diagnosis
11.	PCO_2 (see 3.7.6.1.b)
12.	Bilirubin (current bilirubin – all groups; change in bilirubin – Group B; see 3.7.6.1.c)

[No further changes are proposed to this section of Policy 3.7.6.1.]

a. Lung Disease Diagnosis Groups

[No changes are proposed to this section of Policy 3.7.6.1.]

b. PCO_2 in the Lung Allocation Score

[No changes are proposed to this section of Policy 3.7.6.1.]

c. Bilirubin in the Lung Allocation Score

UNet℠ will use two measures of bilirubin in a candidate's lung allocation score calculation: current bilirubin (for all candidates), and change in bilirubin (for Group B only). There are two types of bilirubin change calculations: "threshold change" and "threshold change maintenance." This section of Policy 3.7.6.1 explains how UNet℠ uses bilirubin in the lung allocation score.

(i) *Definition of Current Bilirubin*
Current bilirubin is the bilirubin value with the most recent test date and time entered in UNet℠. UNet℠ will include in the lung allocation score calculation a current bilirubin value that is at least 1.0 mg/dL.

(ii) *Expiration of Current Bilirubin Value*
UNet℠ will evaluate a current bilirubin value as expired according to Policy 3.7.6.3.2.

(iii) *Use of Normal Clinical Value for Current Bilirubin*
The normal clinical value of current bilirubin is 0.7 mg/dL. UNet℠ will substitute this normal clinical value in the lung

allocation score calculation when the value of current bilirubin is less than 0.7 mg/dL, missing, or expired.

(iv) *Bilirubin Values Used in the Change Calculations (Group B Only)*
There are two types of bilirubin change calculations: threshold change and threshold change maintenance.

The threshold change calculation evaluates whether the bilirubin change is 50% or higher. In this calculation, UNet^{SM} will use highest and lowest values of bilirubin. The test date of the lowest value must be earlier than the test date of the highest value. The highest value must be at least 1.0 mg/dL. Test dates of these highest and lowest values cannot be more than 6 months apart. If necessary, UNet^{SM} will use an expired lowest value, but not an expired highest value. If a value is less than 0.7 mg/dL, UNet^{SM} will substitute the normal clinical value of 0.7 mg/dL before calculating change. The equation for threshold change is **[(highest bilirubin – lowest bilirubin)/lowest bilirubin].**

The threshold change maintenance calculation occurs *after* the candidate receives the impact from threshold change in the lung allocation score. This maintenance calculation determines the candidate's eligibility for retaining the impact from threshold change in the lung allocation score. To maintain the impact from threshold change in the lung allocation score, the current bilirubin value must be at least 50% higher than the lowest value used in the threshold change calculation. The equation for threshold change maintenance is **[(current bilirubin – lowest bilirubin)/lowest bilirubin]**.

UNet^{SM} will perform the threshold change maintenance calculation either when the current bilirubin value expires (Policy 3.7.6.3.2) or a new current bilirubin value is entered. For this calculation, the lowest and highest values that were used in the threshold change calculation can be expired. The current bilirubin value can be the highest one that was used in the threshold change calculation. If a current bilirubin value expires, the candidate's lung allocation score will lose the impact from threshold change. The reason for this loss is that when a current bilirubin value expires, UNet^{SM} will substitute that expired value with the normal clinical value of 0.7 mg/dL. This normal value, therefore, cannot be 50% *higher* than the lowest value in the threshold change calculation.

If a center enters a new current bilirubin value for a candidate who has lost the impact from threshold change, UNet^{SM} will perform the threshold change maintenance calculation. If the

new current bilirubin value is at least 50% higher than the lowest value used in the threshold change calculation, UNet[SM] will *reapply* the impact from threshold change to the candidate's lung allocation score.

(v) *Impact of Bilirubin Threshold Change in the Lung Allocation Score (Group B only)*
A change in bilirubin that is 50% or higher, or threshold change, will impact a candidate's lung allocation score. The candidate will not lose the lung allocation score impact from threshold change provided that the current bilirubin is at least 50% higher than the lowest value used in the threshold change calculation.

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