INTERIM REPORT OF THE
OPTN/UNOS PEDIATRIC TRANSPLANTATION COMMITTEE

July 17, 2008
Chicago, Illinois

The OPTN/UNOS Pediatric Transplantation Committee met on July 17, 2008, and considered the following items:

Welcome and Orientation

New and returning committee members were welcomed by Drs. Simon Horslen and David Campbell. After introductions were complete, a series of orientation presentations were offered to provide members critical information regarding:

- general Pediatric Transplantation Committee membership details - roles and responsibilities, 2008-09 strategic initiatives;
- OPTN regulatory and contractual frameworks;
- policy development process;
- UNOS Research Department committee support;
- SRTR committee support;
- update on progress towards reaching the HHS Donor-Related Program Goals; and
- policy implementation and IT technology implications.

Update Regarding Actions from the June 19-20, 2008 Board of Directors Meeting

The Committee discussed actions from the June 2008 Board of Directors meeting. Of specific interest to this committee were its three proposals for broader sharing of pediatric donor hearts, livers, combined liver-intestines, and lungs. All three proposals were approved and are tentatively scheduled for implementation by third quarter, 2009. Members were urged to review the policy notice detailing all policy and bylaw changes approved during the Board meeting, which was released to members on July 18.

Review of Policies and Bylaws Currently Issued for Public Comment on June 30, 2008

The Committee reviewed the five proposals out for public comment, and provided the following feedback during its meeting:

1. *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) (Thoracic Organ Transplantation Committee)*

   After discussion, the Committee questioned whether such a change will negatively impact candidates without pulmonary hypertension. It was noted that while this is meant to help the adolescent and adult Group B candidates with hypertension, it is not expected to have negative effects on the other candidate diagnosis groups. The pulmonary hypertension candidates were recognized as being underserved in the current LAS system and this is an attempt to better serve the needs of these candidates.

It was suggested that retrospective bilirubin values should be also considered to ensure that a candidate is receiving the appropriate benefit. Members agreed that a candidate's historical bilirubin values should be entered at listing if this candidate has met this criterion before presenting to the transplant center.

A member also questioned whether this change would benefit candidates with intrinsic but not life threatening liver disease who may need a lung. The Thoracic Committee did not specifically consider this, but the Committee thought that monitoring may be required- especially in cases of candidates listed for combined liver-lung transplant. Concern was noted because there is a significant portion of the population with non-conjugated hyperbilirubin due to either low grade or drug-induced hemolysis or Gilbert's Disease that would also benefit, perhaps unfairly, with this new factor in place.

The Committee voted in favor of this proposal with the suggestions that (1) retrospective bilirubin values be included to ensure that all candidates with a significant increase are receiving the appropriate benefit; and (2) the Thoracic Committee consider the exclusion of candidates with intrinsic liver disease or modifications to the scoring system for candidates with this added diagnosis to avoid unfairly advantaging these candidates with a high LAS score based on bilirubin. (Committee vote: 16 in favor, 0 opposed, 1 abstention)

2. *Proposal to verify that foreign agencies importing organs to the United States, or receiving organs exported from the United States, are legitimate and test organs for transplant safety. Policy affected: 6.4.2 (Developmental Protocols in Organ Exchange) and 6.4.3 (Ad Hoc Organ Exchange) (Ad Hoc International Relations Committee)*

Upon review, members voiced concerns that the verification of these foreign organizations would be essentially left to the importing OPO. Members were concerned that OPO personnel would have no way of knowing whether the exporting OPO's accreditation process would be equivalent to the expectations for American quality criteria for organ procurement. Members were not aware of any documentation that requires foreign governments to approve their specific organ procurement systems in the same manner as OPOs in the United States are held responsible. A member questioned whether existing import/export relationships (i.e. Canada) would be in compliance with the proposed language, or whether such current relationships could be potentially damaged- potentially affecting organ offers on both sides of the border. A member questioned whether such changes may create pressure on OPOs to import organs from greater distances in order to find foreign programs that were able to meet specific criteria.

The Committee voted to support this proposal, suggesting that transparency in the process of accreditation for foreign organ procurement agencies should be considered if available. If such transparency exists, then this information could be evaluated to determine whether an exporting OPO is a legitimate and safe alternative organ source. Members agreed that this proposal should be amended to include specific language to address this suggestion. (Committee vote: 17 in favor, 0 opposed, 1 abstention)

3. *Proposal to improve the safety of living donors by restricting the acceptance and transplant of living donor organs to OPTN member institutions. Policy affected: Add OPTN Policy 3.3.7 (Center Acceptance of Organs from Living Donors) (Living Donor Committee)*

Committee members noted that the 22 recoveries completed at non-OPTN/UNOS member centers did not involve any stand-alone pediatric center transplants. Recognizing that it is possible that a living donor may benefit most from access to a specific hospital and acknowledging that this may become a larger issue when kidney paired donation is utilized more aggressively on a national level, the Committee supported this proposal with the suggestion that the procuring hospital should be expected to assist the transplant center in ensuring that adequate follow-up for the living donor is maintained. Members believe that until living donor follow-up is a requirement for the procuring center, this must be considered a shared responsibility. (Committee vote: 16 in favor, 0 opposed, 1 abstention)

4. *Proposal to modify the bylaws pertaining to conditional approval status for liver transplant programs that perform living donor transplants. Bylaw affected: Attachment I, Appendix B, Section D, (4) Liver Transplant Programs that Perform Living Donor Liver Transplants of the OPTN/UNOS Bylaws (Membership and Professional Standards Committee)*

   Upon review, the Committee was concerned that the number of required procedures is somewhat arbitrary, as there is no specific data to support it. Members noted that pediatric programs will be affected and that cutting down the number of living donor programs will make it harder for candidates to have access to technical variants. The Committee requested data on the number of pediatric centers that are currently performing living donor transplants but will not be able to meet the criteria (as evidenced by those who have requested conditional approval but are now withdrawing their applications). A member questioned whether the MPSC might entertain changes to its requirements based on the number of left lateral segment versus right lobe procedures completed by a center. Members agreed that relatively arbitrary standards may impair the pediatric community from offering living related donor transplant, a key component to both managing candidates and the waiting list.

   The Committee agreed to request the desired data from the MPSC for review by the Liver Working Group. A conference call will be held to review this data and determine whether pediatric programs with existing living donor programs will be negatively impacted and whether a compromise can be sought that will not impact living donor or living donor recipient safety.

   The Committee voted unanimously to authorize the Liver Working Group to submit a public comment response on its behalf before the September 24 deadline. (Committee vote: 16 in favor, 0 opposed, 0 abstentions)

5. *Proposal to change the OPTN/UNOS Bylaws to better define functional inactivity, voluntary inactive membership transplant program status, relinquishment of designated transplant program status, and termination of designated transplant program status. Bylaw affected: Appendix B, Section II, C of the OPTN/UNOS Bylaws (Membership and Professional Standards Committee)*

   After discussion, a member questioned whether small programs with a surgeon on vacation requiring temporary inactivation should even be transplant programs. Members felt strongly that small programs that could be in this situation must be very clear with candidates at the time of listing regarding coverage plans and the option of multiple listing to avoid inactivation on the wait list due to provider who is unavailable for up to 14 days.

Equally, members agreed that there must be protection for candidates hospitalized in a center that is inactivated. What should be done with a Status 1 candidate when a program must inactivate suddenly (i.e. the surgeon dies, etc.) and arrangements cannot be made for transfer, as noted in Appendix B, Section II, C, 3b (6) and (7)? A suggestion was made to revise the policy language to include initiate transfer to reflect that a program may be working in good faith to accomplish the transfer, but still be unsuccessful in its efforts due to patient volume or other issues. It was acknowledged that a candidate's lack of insurance, for example, may make transfer difficult if not impossible in some instances.

After discussion, the Committee supported the proposal in principle, including notification of all transplant candidates and recipients of temporary and/or permanent inactivation as well as good faith efforts to these patients in reasonable time and according to medical status. The Committee requested that the MPSC consider modifications to the proposed bylaw language to ensure that expectations regarding the transfer of candidates can be met. (Committee vote: 16 in favor, 0 opposed, 0 abstentions)

Discussion of the OPTN Final Rule Requirements for Organ Allocation Policy

- Status of Kidney Allocation Policy Review

Dr. Sharon Bartosh, the Kidney Working Group Chair, outlined this group's recent activities as well as its ongoing efforts to monitor the effects of Share 35 policy on pediatric candidates and to work with both the Kidney and Pancreas Transplantation Committees to determine how pediatric kidney and simultaneous kidney-pancreas candidates should be factored into the kidney allocation system (KAS) currently in development. Additionally, she noted that the Working Group will begin a Joint Subcommittee with the Kidney Committee to ensure that highly sensitized pediatric candidates receive priority in kidney allocation.

Dr. Wida Cherikh presented an ongoing evaluation of modifications to OPTN/UNOS policy on pediatric priority for kidneys from deceased donors under the age of 35. This presentation specifically focused on the number of pediatric living donor kidney transplants across regions and the number of inactive pediatric candidates on the waiting list by age group.

Dr. Cherikh noted that the trends of living donor kidney transplants in pediatric recipients seemed to vary by age group and region. In summary, Dr. Bartosh noted that for younger 0-5 and 6-10 year-old recipients, there have not been substantial changes. Adolescents appear to have an increase in deceased donor transplants and a decrease in living donor transplants. These changes are more prominent in certain regions. Alternatively, some regions have maintained a stable number of living donor transplants.

When considering the number and percentage of registrations on the waiting list at the end of each from January 2005 through May 2008, the data illustrated:

- Although the number of inactive candidates aged 0-5 was less than the number of active candidates in the beginning of the study period, this number started to increase even before Share 35 implementation, and since October 2007, the number of inactive candidates exceeded the number of active candidates. For example, in October 2005,

there were 35 (34%) inactive and 69 (66%) active candidates, whereas in May 2008, there were 91 (59%) inactive and 64 (41%) active candidates.

- The number of inactive candidates aged 6-10 also started out less than the number of active candidates and it seemed to increase around Share 35 implementation. The number of inactive candidates exceeded the number of active candidates during June 2007 – September 2007. In the more recent months, however, the number of inactive candidates was slightly less than the number of active candidates. For example, in October 2005, there were 43 (36%) inactive and 77 (64%) active candidates, whereas in May 2008, there were 64 (49%) inactive and 67 (51%) active candidates.
- The number of inactive candidates aged 11-17 was less than the number of active candidates, and this number seemed to increase before Share 35 implementation. The gap between active and inactive candidates has narrowed in the more recent months. For example, in September 2005, there were 159 (27%) inactive and 426 (73%) active candidates, and in May 2008, there were 258 (49%) inactive and 272 (51%) active candidates.

Dr. Cherikh then presented a brief slide set of work done by former Committee Chair and member, Dr. Ruth McDonald, considering whether younger deceased donor kidneys had better graft survival rates than older living donor kidneys. The cohort reviewed was from 1994 through 2005, prior to Share 35 implementation. A multivariate analysis of allograft survival comparing living donor and deceased donor groups to the 18-34 year-old deceased donor group in all recipients indicated that three of the living donor kidneys age groups had a higher graft survival rate than deceased donor kidneys from any age group.

Donor Group (yrs)	Number of Transplants	Adjusted RR*	95% CI
LD 18-34	1655	0.70	0.60-0.82
LD 35-49	2431	0.66	0.58-0.77
LD 50-54	180	0.65	0.45-0.92
LD ≥ 55	72	1.09	0.73-1.63
DD 10-17	667	1.06	0.90-1.26
DD 18 – 34	1373	1.00	
DD 35-49	728	1.19	1.01-1.41
DD ≥ 50	185	1.19	0.92-1.54

*Adjusted for: donor race, gender, HLA MM, CIT, and cause of death and recipient race, age, gender, %PRA, primary renal pathology, and year of transplantation

Members noted that living donation is going down in general. Potential donors are frequently not even worked up because they do not qualify due to the increase in adult diabetes, hypertension and obesity. Anecdotally, the demographics are changing and the ability to access a parent as a living donor is going done. The 2007 rate for living donor kidney dropped 6% overall. In many cases, living donor selection is much more stringent as well for pediatric candidates because practitioners know that they will have quicker access to deceased donor kidneys from donors less than 35 years of age.

Members also recognized that not all candidates who receive living donor kidney transplant appeared on the waitlist. Some centers list all living donor candidates and some don't list any. This makes it difficult to truly survey the situation. Additionally, some insurance companies are requiring that recipients be evaluated and listed (but marked as inactive) prior to working up any potential donors. Dr. Bartosh questioned whether this could be related the higher than expected number of inactive pediatric candidates on the waiting list. The Working Group will request more data and look at the inactive candidate population and how it relates to Share 35 and the decrease in living donation more closely.

Next, Ms. Kathryn Meyer, an analysts for the SRTR, presented the calculated adjusted living donor graft outcomes pre- and post-Share 35. Living donor characteristics were examined to look for changes since Share 35 was implemented when a difference was observed in the adjusted analysis. Ms. Meyer noted that the characteristics of the pediatric recipients of living donor kidneys are similar between pre- and post-Share 35 policy periods. Adjusted survival among recipients before and after the policy implementation does not show decreased survival among living donor recipients in the later period, although with reporting lag it is too soon to draw any firm conclusions based on these results.

Ms. Meyer later presented the consequences of increased pediatric priority. The Committee requested that the SRTR use KPSAM to assess the impact of the following changes to the existing allocation policy on the number of transplants in pediatrics:

- Prioritize highly sensitized pediatric patients (PRA≥80%) over highly sensitized adults (PRA≥80%) in the kidney allocation algorithm for all deceased kidney donors, regardless of age.
- Regional sharing for highly sensitized pediatric kidney patients (PRA≥80%) for all deceased kidney donors, regardless of donor age.

The total number of pediatric kidney transplants in the first simulation run was larger in the first allocation change than under the current rules, but could be attributed to random variation. It was noted that the number of sensitized pediatric transplants was similar when comparing the current rules versus this first simulation.

In the second simulation with regional sharing, the increases in pediatric transplant (as compared to the first simulation run) were less explainable by random variation. The increase in priority for sensitized candidates resulted in 18 more transplants to PRA≥80% candidates and 17 more transplants to candidates with a PRA<80. A possible explanation for the additional 17 transplants in the PRA<80 group was that sensitized non-0MM adults only outrank pediatric candidates if they have more kidney points than the highest pediatric (whether sensitized or not) candidate. With regional sharing of sensitized pediatric candidates, it became harder for non-0MM adults to have more points than any pediatric candidate, and thus they would tend to rank below all pediatric (even non-sensitized) candidates.

Members discussed these results. It is difficult to tell the significance of this modeling. The number of transplants went up for sensitized pediatric candidates, by 20 out of 6000 total transplants. The Kidney Committee also reviewed this data, and was willing to work as a Joint Subcommittee to consider this information further and discuss changing priority for highly sensitized children. Concern must be given to sensitized adults as well, who frequently wait many years for appropriate transplant.

- Status of Liver and Intestinal Organ Allocation Policy Review

  Dr. Horslen, Chair of the Liver and Intestine Working Group, outlined this group's recent activities as well as its ongoing efforts to work with the Liver and Intestinal Organ Transplantation Committee to consider broader sharing for adolescent donor livers and intestines, allocation based on net benefit, multi-organ transplantation concerns (i.e. liver-lung, liver-kidney) and advancing the number of split liver transplants. Dr. Horslen will be attending the July 29, 2008 Liver and Intestinal Organ Transplantation Committee to continue to build consensus and momentum on these joint projects.

  Members were made aware of a concern that will also be shared informally with the Liver and Intestinal Organ Transplantation Committee. UNOS Regional Administration has been contacted regarding several incidents were adolescent donor livers were offered to candidates less than 5 years-old where a split was agreed upon, but did not occur. The two programs willing to share the liver have run into conflict because the center accepting the original offer has repeatedly refused to travel to the donor hospital to split the liver. This center has requested that the whole liver be sent to its location to be split ex vivo. From there, the remaining segment would be flown to the center accepting the remaining segment. None of the local centers have been willing to do this due to significant amount of cold ischemia time added with transport back and forth for the liver. Ultimately, this accepting center is cutting down the graft and discarding the other side.

  As the Working Group prepares to continue its efforts to promote and incentivize split liver transplant in conjunction with the Liver and Intestinal Organ Transplantation Committee, members were asked to think about ways to address this and similar concerns.

- Status of Thoracic Organ Allocation Policy Review

  Dr. Stuart Sweet, Chair of the Heart and Lung Working Group, outlined this group's recent activities as well as its ongoing efforts. This group will continue to focus on doing more with the donors we have and increasing access to transplant. The reporting of pediatric donor outcomes is being also being considered in light of the Collaborative, and the Committee hopes to see OPOs being held accountable for pediatric metrics for conversion rates. Pediatric rates were higher than that for adults prior to the Collaborative, but did not enjoy the same increase that was seen in the adult donor population as a result of the Collaborative's efforts. The Working Group will also explore opportunities for facilitating organ procurement and recovery. It may be unnecessary for the transplant surgeon to go out to procure organs. Dr. Sweet suggested the opportunity of a regional pilot program to see if this might be a practical and acceptable change in practice. It was also noted that this group will need to be involved in the Thoracic Committee's upcoming project to consider net benefit for heart allocation, and its effects on the pediatric population

  The Working Group worked most recently with the MPSC's Data Subcommittee regarding post-transplant outcomes for lung recipients aged 12-17 years. The Lung Allocation Score (LAS) System created an artificial divide in the pediatric population as outcomes assessment process used by the MPSC. After a review of data requested to determine the impact of changing the age cutoff for pediatric programs, it was determined that when the adult cutoff was changed to

18 years of age, adult programs that transplanted adolescents were being flagged for poor outcomes. A review of a larger cohort group indicated that there was significantly increased hazard ratio (2.2 with a significant p value) for adolescents transplanted in adult transplant programs. For the first time, there is data to indicate that transplanting children in adult programs may not warrant as successful an outcome as transplant at a pediatric program.

The Joint Subcommittee agreed that the MPSC should consider how it looks at lung programs for outcomes review. The Joint Subcommittee suggested that pediatrics be considered from birth up to 18 years of age and adults are considered as 18 years and older. The Joint Subcommittee was disbanded, but the MPSC will contact the Committee should it need any suggestions or guidelines for a new review process.

Dr. Cherikh presented data on the evaluation of waiting list outcomes for adolescent cystic fibrosis (CF) patients after implementation of the LAS System, stratified by age (<12 versus 12-17 years of age). This data request was initiated after reviewing public comment feedback from the Committee's proposal for broader sharing of lungs. A commenter raised concerns that adolescent CF candidates may be disadvantaged by the broader sharing of 0-10 year old donor lungs to candidates aged 11 and under. The cumulative probabilities for transplant and death for patients with a primary diagnosis of CF at 3, 6, and 12 months after listing, stratified by listing period (pre- and post-LAS) and age group (<12, 12-17, and 18+ years of age):

- The cumulative probability of receiving a transplant at 12 months increased in the <12 candidates from 27.8% to 31.8% after the LAS system, while the probability of death on the waiting list increased from 11.1% to 27.3%.
- The cumulative probability of receiving a transplant at 12 months increased in the 12-17 candidates from 28.9% to 52.2% after the LAS system, whereas the probability of death on the waiting list increased from 10.3% to 13.9%.
- The cumulative probability of receiving a transplant at 12 months increased in the 18+ candidates from 31.9% to 61.9% after the LAS system, while the probability of death on the waiting list decreased from 14.7% to 9.4%.

Dr. Sweet suggested that these results indicate that, at least in the short term, the adolescent concerns should be monitored but are not significant at this time.

Committee members were asked to review the heart and lung allocation system update slide sets independently due to time constraints during the meeting.

- <u>Status of Pancreas Allocation Policy Review</u>

The Pancreas Transplantation Committee was scheduled to meet on July 18. The Committee received a brief update on the modeling that was requested during a joint subcommittee call to consider how both pediatric and combined kidney-pancreas allocation (SPK) should be handled in the new kidney allocation system. Modeling was not available for review at this time, but the joint subcommittee will reconvene prior to the November 2009 meeting to review this data and agree upon a request to take to the Kidney Committee for consideration.

The Committee also received a brief overview of the Pancreas Committee's survey results. The Committee was interested in learning more about barriers to pancreas placement- specifically

how OPOs determine whether to offer a combined SPK or allocate the pancreas and/or kidneys separately. This was an informational item for committee members.

Joint Pediatric-OPO Subcommittee Update

The Committee's ongoing efforts to determine if the community might benefit from best practices for donor management (as related to concerns related to the committee regarding thoracic organ quality being damaged due to pre-recovery drugs administered to prepare the intestine for recovery) were reviewed briefly for the benefit of new members. A Joint Pediatric-OPO Subcommittee met in January 2008 to discuss this issue. The OPO Committee discussed this matter during its June 26, 2008 meeting. A report was not available on the outcome of this discussion at the time of this committee's meeting. Details will be shared with the committee during its November 20, 2008 meeting.

Multi-organ transplant continues to be an issue. It was recognized that in most cases, OPOs are left to decide how they want to approach allocation of multiple organs because there is no policy in place to require placement, only a recommendation that OPOs are encouraged to allow other requested organs to follow a lifesaving organ if requested. The OPO Committee is currently addressing these concerns, and this Committee will receive feedback on this process.

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