Interim Report

OPTN/UNOS Histocompatibility Committee Meeting
O'Hare Airport Hilton Hotel, Chicago, IL
July 14-15, 2009

J. Michael Cecka, Ph.D. opened the meeting by introducing himself as the chair of the Committee and Nancy Reinsmoen, Ph.D. as the vice chair. Lori Gore, Committee Liaison, then gave a brief orientation covering the Committee roles and responsibilities. She was followed by Anna Kucheryavaya, Committee Research Liaison who provided an outline for the processes of making data requests and analyses.

Orientation from the SRTR. Dr. Alan Leichtman began the second day of the meeting with an overview of the Scientific Registry of Transplant Recipients (SRTR).

Summary of the Meeting of the Board of Directors. Ms.Gore provided the Committee with a brief update on relevant actions from the June 2009 meeting of the OPTN/UNOS Board of Directors in Richmond, Virginia. The Committee's primary interest was the proposal to allow the Kidney Paired Donation (KPD) Pilot Program to be monitored by the Membership and Professional Standards Committee (MPSC). The Committee was very much in favor of this proposal.

OPTN/UNOS Strategic Planning. Ms. Gore updated the Committee on the development and identification of the OPTN/UNOS strategic planning goals for the Committee. The 2009-2010 goals for the Histocompatibility Committee are as follows:

1) Oversee implementation of CPRA into current kidney/pancreas allocation system

2) Develop technical guidelines for laboratories on appropriate definition of unacceptable antigens

3) Continue work with National Kidney Paired Donation Program (KPD) subcommittee to develop Histocompatibility guidelines for participating programs

4) Develop guidance for the Membership and Professional Standards Committee in its consideration of the maximum number of laboratories that may be appropriate for one person to direct. Consider revisions to the by-laws to better define a laboratory director's responsibilities and coverage

5) Review the operation of HLA Discrepant Typing Report as it is now functioning in Tiedi and decides whether current OPTN policy and bylaw references to the Discrepant Tying Report should be proposed in view of ongoing changes in the field of transplantation-related histocompatibility testing

The Committee was informed that these annual goals were developed by the incoming and outgoing president with staff input. They include previous Committee priority activities not yet completed as well as areas the OPTN leadership believes to be important for the coming year. The Committee was informed that the goals should continue to form the primary basis of Committee activity over the next year.

Discussion of Public Comment Proposals Distributed on June 30, 2008

Committee Comments on current public comment proposals:

1. "Proposal to Include Non-Directed Living Donors and Donor Chains in the Kidney Paired Donation Pilot Program (Affected Program: Kidney Paired Donation Pilot Program) (Kidney Transplantation Committee)." The Committee supports the expansion of KPD transplants to include open and closed chains. They noted the more UNOS limits the options for KPD, the less likely they will succeed. They also said the success of the pilot program will depend to a large extent on UNOS staff exposure to the special approaches and challenges of dealing with the multiple options for finding matches and moving these chains forward.

2. "Proposal to Improve the ABO Verification Process for Living Donors (Affected Policy: Policy 12.3.1 – ABO Identification; Policy 12.8.1. - Reporting Requirements) (Living Donor Committee)." The Committee supports the improvement of the ABO verification process for living donors. They opined the process should be at least as rigorous for living donors as it is for deceased donors.

7. "Proposal to Change Requirements for Labeling and Packaging Organs Procured by Visiting Transplant Center Teams and for OPO Labeling of Tissue Typing Materials (Affected Policy: Policy 5.0 – Standardized Packaging, Labeling and Transporting of Organs, Vessels and Tissue Typing Materials (Organ Procurement Organization) (OPO) Committee)." The Committee supports the proposal to require changes for labeling and packaging organs and the inclusion of two identifiers to be included. They said this will prevent sample mix-ups and speed testing.

The Committee had no comment on the other proposals.

Membership Issues and Report from the Membership and Professional Standards Committee (MPSC). The Committee reviewed key personnel changes within Histocompatibility laboratories and made recommendations to be presented to the Membership and Professional Standards Committee at its July 21, 2009 meeting. The Committee discussed the evaluation of directors with multiple laboratories and concluded (again) that this is an enormously complex issue best left to the accrediting agencies unless there are complaints or incidents that would require action by UNOS.

The Committee discussed two other MPSC-referred issues.

1. Dr. Cecka reported that there continue to be complaints about insufficient amounts of tissue used for typing being sent with organs for transplant. As a history, this issue was first brought to the MPSC in January 2008. The MPSC suggested a policy change and passed this suggestion on to the Histocompatibility Committee for consideration. In response, the Histocompatibility Committee reviewed policy 2.5.5 which defines the minimum tissue typing material requirements. The Committee said the existing policy is adequate and the issue was one of compliance. Because the Committee was not sure how often or prevalent this problem actually is, it developed a survey that was given to fellow Committee members to fill out. (Most regional representatives to the Committee are also HLA Laboratory

Directors.) The Committee members tracked the amount of typing material received with all import organs for three months.

Preliminary results from this survey show that there may indeed be a compliance issue that should be addressed by the MPSC. The results suggested up to 6% of imported kidneys were shipped with inadequate typing materials or were improperly labeled. The Committee opined that there should be a way to track these findings and a mechanism should be developed for centers to report this problem to the Committee and ultimately the MPSC.

Lee Ann Baxter-Lowe, Ph.D. was unable to present the final assessment from the survey by our meeting date. However, Dawn Brims, the committee's OPO representative, suggested that such incidents could be reported On UNet under Patient Safety –Safety Issues. All incidents reported in this manner are investigated and could be reported to the MPSC. The Committee asked if it could send a blast email to all HLA laboratories to make them aware of this reporting mechanism. Ms. Gore said she would look into it and report back to the Committee.

2. The MPSC sent a letter to Dr. Cecka and the Committee asking assistance with the development of clear responsibilities and guidelines for individuals serving as a data coordinator in a HLA Laboratory. It was noted that current bylaws provide similar information for other positions. Dr. Cecka wrote an outline of the requirements which the Committee reviewed. The Committee developed the following:

Laboratory Data Coordinator. All laboratories should identify one or more staff members who will be responsible for coordinating data entry, checking and validation of histocompatibility information reported on UNET and DonorNet forms. The data coordinator will work with laboratory staff to insure complete and accurate data reporting to the OPTN. The data coordinator must be familiar with laboratory and transplant program information systems and other sources of patient and donor histocompatibility test results as needed to fulfill these functions.
Specific responsibilities should include, but are not limited, to:

1. *Waitlist form*
    a. *Assures the accuracy of HLA typing and sensitization data entered on the waitlist form, whether these data are entered by the laboratory, transplant program or other personnel.*
    b. *Assures unacceptable antigens and CPRA are updated when needed.*
2. *Donor histocompatibility form*
    a. *Completes donor histocompatibility forms within 30 days of donor testing if this is performed by the laboratory.*
    b. *Corrects HLA typing data when discrepancies are noted and resolved.*
    c. *Verifies donor histocompatibility data.*
3. *Recipient histocompatibility form:*
    a. *Completes recipient histocompatibility forms within 30 days of transplantation.*
    b. *Corrects HLA typing data when discrepancies are noted and resolved.*
    c. *Verifies donor histocompatibility data.*

Discrepancy report. As background, at the July 2007 meeting, the Committee discussed the UNet[SM] Discrepant HLA Typing report, as referenced in OPTN Policy Appendix 3C. This report will flag centers that provide HLA on the waitlist, the donor histocompatibility form (DHF) and/or the recipient histocompatibility form (RHF) if the typing provided differs. The policy goes on to say "The Laboratory Director(s) or their designee(s) shall contact the other Laboratory Director(s) or their designee(s) to resolve these discrepancies."

A brief OPTN analysis revealed that 2,787 donor records and 2,079 recipient records were unresolved at that time. It also showed that the report was not working as intended, and that it was not being used by many laboratories. Several Committee members said that they did not know the report existed. Given the high number of unresolved discrepancies shown, the Committee opined that the programming problems within the report should be resolved. The Committee also agreed that once the UNet[SM] report has been modified, laboratories should be notified that they are to resume using the report. UNOS IT staff corrected the report in May 2008. On May 9, 2008, a system notice was sent to all UNet[SM] users stating that "The OPTN/UNOS Histocompatibility Committee will be reviewing the Discrepancy Report for all OPTN member laboratories annually

Ms. Kucheryavaya gave the Committee an updated report using current data from the discrepant HLA typing report in UNet[SM.] The report showed, that over all, there continues to be an increase in the percentage of resolved cases from September 2007 to June 2009.

The discussion on this topic included a number of possible explanations for discrepant typings and revealed some of the difficulties that may bias the report. An example cited was a situation where the antigen order was identified as a discrepancy, or it was pointed out that correct typing might be technique specific. Dr. Cecka said he thought this is not in the spirit of discrepancy resolution. He said that if one technique provides a more accurate type, that type should be the one recorded in UNet. Ms. Kucheryavaya also showed data that suggested a major source of discrepant types were transcription errors. The committee discussed the possibility of developing a threshold for these types of errors, and suggested that laboratories that went over this threshold should be reported to accrediting agencies as alerts for inspection. Ms. Gore said she would look into this possibility.

Dr. Cecka went on to say the primary goal of the discrepancy report is to provide UNOS with accurate data. He said the report alerts laboratories that there are conflicting data that has been recorded and that these discrepancies need to be resolved with the data corrected. Regional representatives were urged to relay this information to the laboratory directors in their regions. Ms. Kucheryavaya said she would provide her PowerPoint presentation on the discrepancy report to the Committee so that representatives could illustrate the scope of the problem and discuss its implications for allocation, data accuracy and possibly laboratory performance. Ms. Kucheryavaya also said she could develop a laboratory-specific report that would give each laboratory the number and frequency of discrepancies it had and a compare it with the national data. The Committee felt strongly that laboratories with high levels of unresolved discrepancies should be made aware that they have a high percentage of discrepant typings and that they may be held accountable.

The Committee also opined that discrepancies between match run and donor forms may be a key measures of laboratory performance. A subcommittee (Char Hubbell M.T., Steve Geier, Ph.D., and Paula Wetzsteon) was appointed to review and evaluate the specific discrepancies between

the donor match run and DH form to determine whether this is a good indicator of laboratory performance or merely reflects sloppy reporting.

As part of the discussion, Dr. Cecka voiced the concern that if one technique provides a more accurate type, that type should be the one recorded in UNet. At this point in the discussion the Committee opined that the time had come to require a level of testing for all deceased donors that was uniform and therefore would eliminate many discrepancies.

> **POLICY PROPOSAL: Deceased donor typing, must be performed by DNA methods and must identify splits of HLA-A,-B,-Cw,-DR and -DQ antigens. (As listed in appendix 3A) prior to the match run.**

A subcommittee was formed to update appendix 3a (equivalence tables) as required by policy. Char Hubbell M.T., Karen Sullivan Ph.D., Jerry Morrisey volunteered to work on this subcommittee. The Committee asked Ms. Kucheryavaya for supporting data that it will need to update the table; specifically they wanted antigen counts for A, B, Bw4/6, Cw, DR, DR51, DR52, DR53 and DQ for deceased donors and candidates during 2007-2008 by DNA and serology separately.

> **POLICY PROPSAL: Update Appendix 3a as required by policy**

Report from the Kidney Committee/ Kidney Allocation Review Subcommittee Guidelines for Paired Kidney Donation (PKD) .The PKD guidelines for histocompatibility laboratories were reviewed including changes in the document to replace unacceptable and undesirable antigens with high and low stringency pairings.

- Low Stringency Antigens: those antigens to which the patient is sensitized and would preclude transplantation at the candidate's center with a donor having any one of those antigens (previously called "unacceptable antigens").
- High Stringency Antigens: additional, lower level antibodies against HLA-A,-B, -Bw4, 6, -Cw,-DR,-DQ and DP antigens listed that may result in a positive or negative crossmatch. The rate of positive crossmatches would be expected to be higher against donors who express these antigens. (These antigens were previously called "undesirable antigens").

There was also discussion about subdividing the antibodies reported for sensitized candidates into identified unacceptable antigens, recognized antigens that were identified by antibodies that did not qualify as unacceptable and those that were safe (with no antibodies identified).

Dr. Baxter-Lowe suggested the Committee request data to help evaluate outcomes for patients transplanted through the KPD program. A subcommittee was formed to develop specific data elements and outline research questions (Dr. Baxter-Lowe, A. Bradley Eisenbrey M.D., Ph.D. and Karen A Sullivan Ph.D.).

Calculated Panel Reactive Antibody (CPRA). Ms. Gore updated the Histocompatibility Committee on the implementation schedule for CPRA. As a review, in December 2006, the OPTN/UNOS Board of Directors (BOD) approved modifications to Policies 3.5.11.3 (Panel Reactive Antibody) and 3.8 (Pancreas Allocation) to replace current and peak Panel Reactive Antibody (PRA) with calculated Panel Reactive Antibody (CPRA) for kidney, kidney-pancreas,

and pancreas allocations. Due to the complexity of these changes, they will be introduced in three phases.

- Phase One: Allocation will continue to be based on traditional PRA; however, OPOs, transplant centers, and HLA laboratories will be able to calculate and see CPRA on the Waitlist℠. Members can access the CPRA calculator on the OPTN and UNOS Web sites.
- Phase Two: Allocation based on CPRA will be initiated, although OPOs, transplants centers, and HLA laboratories will be able to enter and see traditional PRA on the Waitlist℠ if desired.
- Phase Three: Allocation will be based on CPRA. Traditional PRA information will no longer appear on the Waitlist℠.

Phase one was implemented in December 2007. On the March 2008 conference call, Ms. Gore announced the delay of phase two due to programming difficulties at UNOS. This pushed implementation of phase two back to the second quarter of 2009.

Initial analyses were presented to the Committee during conference calls held on January 29, 2008, and March 20, 2008. The Committee requested ongoing updates of these analyses until phase two of CPRA is implemented.

At this meeting, Ms. Kucheryavaya reported to the Committee on CPRA data analyzed from the kidney waiting list registrations as of June 12, 2009 and compared it to the PRA data. She gave the percentage of registrations with a CPRA and the number of registrations who could potentially lose their sensitization points if CPRA were implemented today.

She reported as of June 12, 2009, 27,503 registrations (32.4%) on the kidney waiting list have at least one unacceptable antigen entered, allowing the calculation of a CPRA. This is an increase from the number observed on June 13, 2008 (23,009). A small number of centers (11/256) have not entered any unacceptable antigens for their candidates. Most of these centers (8/11) have less than 10 kidney candidates.

The Committee was pleased with the progress in the listing of unacceptable antigens. Ms. Gore told the Committee that the planned implementation of phase two of CPRA should go as scheduled at the end of September 2009. She also said that because of the long delay in implementation, phase three will also be executed at this time.

Dr. Cecka then asked the Committee to discuss a potential problem that may surface with this implementation. He asked if there should be a way to show if a candidate was sensitized to HLA antigens, but has a CPRA of 0. He asked if a check box could be added on the waitlist that would signify that the candidate did indeed have HLA antibody, but not at levels high enough to list them as unacceptables. Ms. Gore told the Committee that such a revision at this time would delay execution of the CPRA policy. The Committee therefore agreed to let implementation go on as scheduled. Dr. Baxter-Lowe would like to propose the addition of a field to capture acceptable antigens (low level antibodies) that would not screen candidates from donor matches.

The Committee may propose this addition for the candidate waitlist form depending on whether or not the need becomes evident with the implementation of phase two of CPRA.

> PROPOSAL FOR WAITLIST FORM: Add a check box query to waitlist form…"Were any anti-HLA antibodies detected? Yes/No/Not done/blank", the CPRA would default to 0 if yes or no is indicated. If the CPRA field is blank, that would indicate that the test was not done.

The Committee also asked Ms. Gore to send an "are you aware?" letter to centers where 20+% of patients who would lose sensitization points when phase two of CPRA is implemented. They requested that the letter be addressed to the program director and lab director.

Sliding scale for Sensitization points- Current policy grants four points to those kidney candidates with a PRA of 80% or higher. When CPRA is implemented, policy will grant kidney candidates with a CPRA of 80% or higher 4 points. Policy does not grant any points to those candidates with a PRA/CPRA level of 79% and lower. The members of the Histocompatibility Committee, as well as those from the Kidney Committee, have voiced a concern that this policy was not fair because all sensitized candidates are disadvantaged to some degree.

At the July 2009 meeting the Committee discussed proposing a change to policy that would grant the number of points received by sensitized candidates on the waiting list during deceased kidney allocation process based on a sliding scale. The Committee realized that the points granted should not follow a linear progression because that is not how candidates are disadvantaged. . Therefore, the Committee requested the following data on transplant rates by sensitization level to be presented during next meeting.

- Percentage of kidney registrations added to the waiting list in 2005-2006 who received deceased donor transplant within 3 years after listing stratified by allocation PRA group and candidate's blood group. Allocation PRA will be defined as the first current PRA reported for registration if the waiting list record indicates that the current PRA is to be used and first entered peak PRA if peak is indicated.
- Transplant rate per 1,000 active patient-years for kidney registrations on the waiting list during 2008 stratified by allocation PRA, blood group and measure of OPO waiting time.

The Committee asked that the results be stratified by the following allocation PRA groups: 0, 1-20, 21-30, 31-40, 41-50, 51-60, 61-70, 71-80, 81-85, 86-90, 91-95, 96-99, and 100.

The Committee will review the data at their next meeting and make a proposal.

> **POLICY PROPOSAL- Sensitization points would be awarded to sensitized candidates on a sliding scale (to be determined.)**

Desensitization protocol-Committee sponsored variance

Dr. Reinsmoen expressed concern that kidney candidates on a desensitization protocol would be disadvantaged with the implementation of CPRA. She said this is because the CPRA is directly linked to the unacceptables listed. If a candidate took part in a desensitization protocol, that candidate could receive a kidney from a donor to which he had previously had donor specific antibody (DSA) listed as unacceptable. If these unacceptable antigens were removed so the candidate would not be screened from the list from those donors, their CPRA level would fall, and potentially so could their place on the list. Therefore she proposed and the Committee supported the following Committee sponsored variance.

> **PROPOSAL FOR VARIANCE: Programs that submit an IRG-approved desensitization protocol can apply for a variance that will permit a desensitized patient's CPRA to remain at pre-desensitization levels for one year after reactivation even though unacceptable antigens may be removed.**

Thoracic Committee The Thoracic Committee has asked the Histocompatibility Committee to cosponsor a proposal to require HLA typing of deceased donors prior to the match run. The Committee supports this proposal and agreed to form a subcommittee that would work jointly with the Thoracic Committee toward that end. Dr. Baxter-Lowe and Dr. Reinsmoen volunteered to serve on this subcommittee.

Request from Tennessee Transplant Society. The Committee considered a request from the Tennessee Transplant Society (TTS) to modify its alternative system for kidney allocation. TTS presently uses the standard kidney distribution and allocation system with the following exceptions: a common, state-wide waiting list; with an alternate allocation for high PRA patients, critical status patients, and patients for whom there is a high quality match. Currently, if a candidate is not in one of these categories, they follow those who do, on the statewide list. This in essence creates two tiers on the waiting list ,first a" mandatory list" which includes high PRA patients, critical status patients; and patients for whom there is a high quality match, followed by a "voluntary list" which includes all other candidates. TTS requested that this portion of their variance for kidney allocation be eliminated. The Committee voted to support this request.

OMB forms- The Committee discussed concerns voiced by UNOS staff about Committee changes suggested on the OMB forms specifically the donor histocompatibility form (DHF) and the recipient histocompatibility form (RHF).

Most of the questions centered on the removal of a field that recorded the final cross match result. The Committee said it may want to collect data on survival rates in relation to positive crossmatches. After discussion the Committee decided to wait and see what criticisms were made in the public comment phase of the forms.

Members who were present:

J. Michael Cecka, Ph.D.	Chair
Nancy Reinsmoen, Ph.D.	Vice Chair
Dean Sylvaria, BS, CHS	Region 1
William Ward. Ph.D.	Region 2
Karen Sullivan, PhD	Region 3
Jerry Morrisey, Ph.D.	Region 4
Lee Ann Baxter-Lowe, Ph.D.	Region 5
Paula Wetzsteon	Region 6

David Maurer, Ph.D.	Region 7
Steve Geier, Ph.D.,	Region 8
Char Hubbell, M.T.	Region 9
A. Bradley Eisenbrey, M.D.	Region 10
John Schmitz, Ph.D.	Region 11
Dawn Brims, B.S.N., RN	At Large
Sister Michelle O'Brien	At Large
Douglas Keith, M.D.	At Large

UNOS Staff

Lori Gore	Committee Liaison
Anna Kucheryavaya	Data Liaison

SRTR

Alan Leichtman, M.D.
Emily Messersmith

Members unable to attend

Brad Kornfeld	At large