At-a-Glance

- **Proposed Update to the Calculated PRA (CPRA)**

- **Affected/Proposed Policy:** No policy language will be affected; this will be a programming only effort

- **Histocompatibility Committee**

- The purpose of this proposal is to update CPRA so it can better reflect current laboratory practices as well as the current donor pool. These revisions include updating the HLA frequencies used to calculate CPRA, the addition of the antigen HLA-C to the calculation and the addition of a question to the waiting list to better interpret 0% default CPRA value.

- **Affected Groups**
  Lab Directors/Supervisors
  OPO Coordinators
  Transplant Data Coordinators
  Transplant Physicians/Surgeons
  PR/Public Education Staff
  Organ Recipients
  Organ Candidates
  General Public

- **Number of Potential Candidates Affected:**
  This could possibly affect all kidney, kidney/pancreas and pancreas candidates because it will change the order used for allocation. The most direct effect will be for those registrations that have at least one unacceptable antigen listed or approximately 37,000 kidney and more than 1,000 pancreas and kidney-pancreas registrations.

- **Key Goal advanced**:
  Increase access to transplants

Proposed Update to the Calculated PRA (CPRA)

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Histocompatibility Committee

Summary and Goals of the Proposal:

The purpose of this proposal is to update CPRA so it can better reflect current laboratory practices as well as the current donor pool. These revisions include updating the HLA frequencies used to calculate CPRA, the addition of the antigen C to the calculation and the addition of a question to the waiting list to better interpret 0% default CPRA value.

Background and Significance of the Proposal:

In October 2009, the OPTN implemented Policy 3.5.11.3, which effectively replaced a Panel Reactive Antibody (PRA) value with a Calculated Panel Reactive Antibody (CPRA) value for Kidney, Kidney/Pancreas and Pancreas and significantly changed kidney and pancreas allocation. The CPRA is simply the percentage of deceased donors that have HLA antigens listed as unacceptable for a candidate.

Based on post-implementation data analyzed by the Histocompatibility Committee, the policy has been very effective and has yielded many benefits. (Exhibit A) However, the CPRA as it is calculated today is based on older technology and HLA frequencies.

Policy Proposal:

In order to maximize the effectiveness of CPRA, the Committee is proposing major updates which include the following:

<u>Updating the HLA Frequencies Used to Calculate CPRA</u>

CPRA was fully implemented in October 2009 with HLA frequencies generated by M. Sue Leffell, Ph.D., from Johns Hopkins University in Maryland based on deceased kidney donors entered into OPTN registry from January 1, 2003 through December 31, 2004 and the ethnic frequencies are based on deceased kidney donors recovered from January 1, 2006 through June 30, 2007. CPRA continues to be calculated today using these data.

Because HLA typing methods have changed since 2003, these frequencies should be updated to a more recent time frame so that the CPRA truly reflects the probability of an incompatible match within the current donor pool. The Committee proposes that an update be done as soon as possible using frequencies calculated by Dr. Leffell using data from January 1, 2007 through December 31, 2008. This data has already been given to UNOS. These new frequencies will be added to the existing frequency tables used to calculate CPRA unchanged.

The Committee further proposes that the HLA and ethnicity frequencies be updated in two years (to reflect changes that may result from the implementation of the molecular typing proposal that went

into effect June 1, 2011) and then again in 5 years. The Committee will evaluate changes at that time and make a recommendation as to how often these updates should continue.

The Addition of HLA-C to the CPRA Algorithm

The current CPRA calculation uses the HLA frequencies for A, B, DR and DQ types. The addition of HLA antigen C (HLA-C) was considered at the time of implementation but ultimately not included because there was not enough data available on the frequency of HLA-C types in donors. That has since changed; updated frequencies using data from January 1, 2007 through December 31, 2008 contain enough data to generate the HLA-C frequencies.

Currently more than 10,000 kidney registrations are listed with at least one HLA-C antigen as unacceptable. These candidates are screened from lists but receive no CPRA value for their increased potential of a positive crossmatch because HLA-C is not included in CPRA calculation.

Therefore, candidates sensitized to only the HLA-C antigen appear in the UNet system as completely unsensitized because their CPRA value would be zero. Adding HLA-C to the CPRA calculation would denote these candidates as sensitized. For patients who currently have a CPRA that is greater than zero, the CPRA could potentially underestimate the percentage of donors who are incompatible. For those candidates, inclusion of HLA-C into the calculation could possibly raise their CPRA to over 80% and result in 4 additional sensitization points being awarded, thus elevating their priority on the match run list.

The Committee voted unanimously that HLA-C be incorporated into the CPRA algorithm in July 2010. The Committee believes this should be done as soon as possible because candidates who are sensitized to HLA-C are disadvantaged.

Removal of Zero (0) Default

The current CPRA value zero default in the UNet system does not differentiate between candidates in the following situations:

1) candidates who are truly unsensitized and have no donor specific antibodies,
2) candidates who have some donor specific antibodies, but none that warrant the listing as unacceptable
3) candidates who have antibody to HLA-C and/or DP HLA antigens, which are not part of the CPRA algorithm, and
4) candidates who have had no data entered into the system

Each one of the above scenarios describes a very different candidate; however, the system does not distinguish between the way the CPRA of these candidates is displayed.

Collaboration:

The Committee proposes to work with Dr. Mary S. Leffell from Johns Hopkins University in Baltimore MD (MDJH) in development of the proposed changes to CPRA. Dr. Leffell calculated the original frequencies that are being used now in her laboratory at MDJH. She has also supplied the Committee with new updated frequencies using data from January 1, 2007 through December 31, 2008. These new

frequencies Replace the older frequencies in the existing frequency tables which are used to calculate CPRA.

Alternatives considered:

To maximize the effectiveness of CPRA, it must reflect the current donor pool and current technology. Therefore, the Committee determined that the only viable option would be to make changes to HLA frequencies and to add HLA-C to the algorithm because to not to do so would have an adverse effect on candidates. The Committee considered the option to change the default at a later time, because it is not a critical matter. However, it believed that the ambiguity could lead to confusion and could confound data analyses. Since other changes are being made in the system, the Committee believed that it would be most efficient and prudent to correct this limitation now.

Strengths and weaknesses:

Update the HLA frequencies

Strengths:
By using more current HLA frequencies the CPRA will more accurately reflect the probability of an incompatible match with the current donor pool. The ethnic diversity of the deceased donor pool is dynamic and continues to change with the changing ethnic diversity of the population of individuals who reside in the U.S. Updating the HLA frequencies and ethnic frequencies will make the allocation process more accurate and more effective and thereby making it less likely that a candidate will receive a kidney offer that results in a positive crossmatch. CPRA has already increased allocation of organs to sensitized patients and reduced wasting of resources for crossmatches that have low likelihood of a compatible result; it should be more effective if the calculation more accurately reflects the percentage of donors who are excluded by unacceptable antigens.

Weaknesses:
There will be some financial cost to the contractor for required programming.

Inclusion of HLA-C in the CPRA calculation

Strengths:
By including the HLA antigen C to the CPRA, those candidates who are sensitized to HLA-C will be considered for allocation priority similar to those candidates who currently are sensitized to the antigens A, B, DR, and DQ. This removes an existing arbitrary inequity in the current allocation prioritization for candidates sensitized to HLA-C.

Weaknesses:
The committee identified two potential weaknesses in the proposal:

(1) This change will increase the CPRA for all candidates who are sensitized to HLA-C just as the current calculation process for CPRA increases the value for candidates who are sensitized to antigens A, B, DR, and DQ. The resulting changes will inevitably result in more candidates with a CPRA greater than 80 and eligible for 4 sensitization points allowing greater priority for a kidney match for these candidates.
(2) There will also be a financial cost to the contractor for required programming.

Zero (0) Default of CPRA

Strengths:
This change will make it possible to distinguish the several types of candidates who are currently listed with a "zero" (O) value for CPRA but in fact have much different clinical characteristics. This will eliminate the ambiguities with the current reporting and display process. The resulting clarity will make organ allocation more accurate and more effective (for those organs that incorporate CPRA information in the prioritization algorithm) and will make the results of statistical analyses by UNOS and SRTR more meaningful and thereby more useful when required for making revisions to allocation policies.

Weaknesses:
This will require response to the new data field for each candidate registration ("Was this candidate tested for anti HLA antibodies?"). There will be a financial cost to the contractor for required programming

Description of intended and unintended consequences:

One of the possible unintended consequences is that changes in CPRA would need to be incorporated into systems that transplant programs use for managing their patients. This could cause increased costs to the transplant center but would also improve the accuracy of the CPRA and equity for sensitized patients.

Supporting Evidence and/or Modeling:

Update the HLA frequencies

CPRA has been used for the allocation of deceased donor kidneys since October 1, 2009. CPRA is the percentage of donors expected to have one or more of the unacceptable antigens indicated on the waiting list for the candidate. The CPRA is determined using an established algorithm_(1,2) and HLA frequencies were derived and verified by an OPTN/UNOS Histocompatibility subcommittee for different ethnic groups. HLA frequencies currently used for CPRA calculation (HLA-A, -B, -DR and -DQ) are based on the HLA phenotypes of deceased kidney donors recovered from January 1, 2003 through December 31, 2004. Ethnic frequencies are based on deceased kidney donors recovered from January 1, 2006 through June 30, 2007. (3) These frequencies should be updated to a more recent time frame so that the CPRA truly reflects the probability of an incompatible match with the current donor pool.

The Histocompatibility Committee formed an HLA Frequency Subcommittee to access whether using HLA frequencies based on a more recent cohort of donors would improve CPRA accuracy. On the January 24, 2011 call, the subcommittee reviewed the data. CPRA was recalculated based on HLA and ethnic frequencies derived from a more recent cohort of deceased kidney donors (2007-2008). It should be noted that the reporting of HLA-DQ 4, 5, 6, 7, 8, and 9 antigens increased in the past decade which would lead to a substantial CPRA increase for some kidney registrations if the current HLA frequencies were used. It was shown that if the recalculated CPRA were used for allocation of deceased donor kidneys, almost 500 kidney registrations with current CPRA of less than 80 would become eligible for 4 sensitization points. A large portion of this increase is due directly to the increased reporting of split DQ antigens in donors and more frequent reporting of subtypes rather than broad antigens. (Exhibit B)

Addition of HLA-C

At the July 13-14, 2010 meeting, the Histocompatibility Committee voted to propose the inclusion of HLA-C frequencies into the CPRA calculation. At the January 24, 2011 call, the HLA Frequencies Subcommittee discussed the data needed to support this proposal. The subcommittee requested recalculated CPRA based on HLA-A, -B, -DR, -DQ and -C frequencies for a subgroup of kidney registrations on the waiting list with antibodies to HLA-C antigens.

Current CPRA values were compared to recalculated CPRA for all kidney registrations on the kidney waiting list with antibodies to HLA-C antigens and 0% CPRA or 50-79% CPRA.

On February 28, 2011, there were 93,711 kidney registrations on the waiting list. Eleven percent (10,569) of these registrations had at least one unacceptable HLA-C antigen reported on the waiting list. As of June 2010 it is required that all standard criteria donors be typed for HLA-C. Therefore, candidates with HLA-C designated as an unacceptable antigen are currently screened from match runs but they do not receive a fair priority because their CPRA value is lower than it should be. Among all kidney registrations with unacceptable HLA-C antigens, 7% (728) only had antibodies to HLA-C antigens. These candidates are also being screened from match runs and have a CPRA of 0.

Also of the kidney candidates on the waiting list that have antibodies to HLA-C antigens, only 63% have a CPRA of 80% or higher and are eligible for 4 additional sensitization points during allocation of deceased donor kidneys. Inclusion of HLA-C frequencies into CPRA calculation would result in a higher CPRA value for most registrations. For those listed with HLA-C antibodies, almost 644 registrations had a recalculated CPRA value increased to 80%. The Committee said that 644 out of 93,711 represented a small change but it would be very important to those 644 registrations. (Exhibit C) Members of the also pointed out that it is likely that the incidence of HLA-C antibodies is underestimated because some programs do not currently list HLA-C as an unacceptable because it is not part of the CPRA calculation and it has only recently been added to the requirements for deceased donors. It is expected that the number of reported instances of HLA-C antibody will soon increase.

Based on these observations the inclusion of HLA-C frequencies into CPRA calculation would benefit a relatively large number of kidney registrations who have antibodies to HLA-C.

Zero (0) default of CPRA:

A CPRA value of zero could reflect many scenarios. It could mean that the candidate had not been tested yet or that the candidate is truly unsensitized and has no HLA antibodies. Alternatively, it could mean that the candidate does have some HLA antibodies, but none that warrants listing as an unacceptable antigen based on the judgment of the transplant center. It could mean that the candidate has antibody to HLA-C and/or DP HLA antigens, which are not part of the CPRA algorithm, even though the candidate may be truly sensitized. Finally, it could mean that the unacceptable antigens listed are so rare that the CPRA is less than .5%.

Each one of the above scenarios describes a very different candidate but all would be shown to have a CPRA value of 0.

Data reviewed by the committee at the July 11, 2011 meeting showed the following:

The Committee asked how many kidney candidates were directly impacted by having a CPRA of 0 yet may indeed be sensitized.

On 03/31/2011, 56,669 of adult kidney alone registrations had 0% CPRA. Out of these registrations:

- 974 had antibodies to HLA-C antigens
- 1,490 had antibodies to non HLA-C antigens
- 226 had antibodies to both HLA-C and non HLA-C antigens

The Committee explored several ways to distinguish between these candidates on the waitlist. UNOS IT informed the Committee that the CPRA field on waitlist must be filled a whole number (no letter or symbol could be used), and could not remain blank if untested. They also said the field would not accept 00 as an option.

Therefore, the Histocompatibility Committee is proposing that a mandatory field be added to the waitlist form for all kidney, kidney/pancreas and pancreas candidates. They are also requesting that this field be added to other organ allocation systems, such as the Thoracic waitlist form, if that group decides to utilize CPRA within their system. This field would ask, "Was this candidate tested for anti HLA antibodies?" with the drop down box that gave the following options; yes, antibodies detected, yes, no antibodies detected, or no, not tested. This information would distinguish between the various circumstances underlying a CPRA equal to zero.

Expected Impact on Living Donors or Living Donation:

Not applicable.

Expected Impact on Specific Patient Populations:

These updates will diminish systematic limitations that affect management of and allocation to many sensitized patients**.**

<u>Update HLA Frequencies</u>

Recalculation of CPRA using updated (and more accurate) HLA frequencies results in increase for almost 500 kidney registrations with current CPRA of less than 80% such that the recalculated CPRA would be greater than 80% and therefore these candidates would be eligible for 4 sensitization points. This represents a very small percent of total kidney registrations (0.53%).

<u>Addition of Antigen C to CPRA Algorithm</u>

This will increase the CPRA for those candidates sensitized to HLA-C. Currently 63% of these candidates already have a CPRA of 80% or greater and are eligible for 4 additional sensitization points. For those who do not currently have a CPRA of equal to or greater than 80%, almost half (524 individuals) will increase above the 80% threshold for assignment of 4 sensitization points. This represents a very small percent of total kidney registrations (524 out of 93,711 or about 0.56%).

Zero (0) Default of CPRA

This change will not have any impact on specific patient populations. However, it will help transplant professionals throughout the field. Currently, when confronted with a candidate with a CPRA of 0, transplant surgeons, physicians, coordinators and lab personnel can not tell if that candidate is truly unsensitized, sensitized, or not been tested. This is important information especially given the increased use of a prospective virtual crossmatch.

To see the proposed CPRA frequencies, please go to http://communication.unos.org/2011/08/optn-public-comment-proposal-offers-alternate-cpra-calculation-method/.

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

These updates to CPRA are important to achieving the "Best Use" program goal. Maximizing the use of deceased donor kidneys and reducing wastage of these organs is dependent on the timely and efficient placement of organs. The time the histocompatibility laboratory and the OPO spend crossmatching patients who have a predictably positive crossmatch add significantly to the overall time to allocate deceased donor kidneys. This can result in organs that are not used because the cold ischemic time is too long. (Exhibit E)

The application CPRA is also critical to "Patient Safety". Accurate unacceptable antigen equivalents reduce the chance that a sensitized patient might receive a graft that is at risk for hyperacute or early antibody-mediated rejection.

It has also been shown that the use of CPRA has increased the transplant rate of sensitized candidates which is not only mentioned within the Final rule but is addressed in the strategic goal of assuring equitable access. (Exhibit F)

HHS Program Goals	*Strategic Plan Goals*
Patient Safety	The OPTN will promote safe, high-quality care for transplant candidates, transplant recipients, and living donors
Best Use	To achieve the best use of donated organs, the OPTN will refine allocation policies by incorporating objective, measurable criteria related to concepts of donor risk/quality and recipient benefit
Equitable Access	To achieve equitable organ allocation, the OPTN will refine allocation policies to reduce geographic variation in waiting list deaths and access to transplantation
Maximum Capacity	The OPTN will support the HHS Program Goals and maximize the number of donors and transplants
Operational Effectiveness	The OPTN will identify process and system improvements that best support critical network functions, and work to disseminate them to all members who could benefit

Plan for Evaluating the Proposal:

The Committee will continue monitoring the use of CPRA, including blinded center and lab related differences and transplantation of sensitized patients, as well as offers declined because of a positive crossmatch.

Additional Data Collection:

The Committee is proposing the addition of a question to the Waiting list. This field would ask, "Was this candidate tested for anti HLA antibodies?" with a drop down box displaying the following options:

- Yes, antibodies detected,
- Yes, no antibodies detected, or
- No, not tested

This would require additional data collection**.**

Expected Implementation Plan:

The updates to CPRA will be to programming only**.**

Communication and Education Plan:

We will inform the transplant community of the updates to CPRA through the UNOS *Update* Magazine, the UNOS member electronic newsletter and the ASHI Quarterly.

Communication Activities			
Type of Communication	**Audience(s)**	**Deliver Method(s)**	**Timeframe**
UNOS magazine	Transplant community	mail	At the time of implementation
UNOS electronic news letter	Transplant community	Electronic delivery	When it is passed by the BOD and implementation
ASHI Quarterly	ASHI MEMBERS		

Education/Training Activities			
Education/Training Description	**Audience(s)**	**Deliver Method(s)**	**Timeframe and Frequency**
Not applicable			

Monitoring and Evaluation:

The Committee will continue monitoring the use of CPRA, including blinded center and lab related differences and transplantation of sensitized patients, as well as offers declined because of a positive crossmatch.

References:

1. Zachary AA and Braun WE. Calculation of a predictive value for transplantation. Transplantation 1985;39:316-8.
2. Zachary AA and Steinberg AG. Statistical Analysis and Applications of HLA Population Data. In, NR Rose, EC de Marcario, JD Folds, HC Lane, and RM Nakamura, Eds., Manual of Clinical Laboratory Immunology, 5th Edition, Washington, DC, ASM Press, 1997:132-40.
3. Leffell MS, Cherikh W S, Land GA, Zachary AA. Improved definition of HLA frequencies among minorities: applicability to estimates of transplant compatibility. Abstract #2135. World Transplant Congress 2006. Blackwell Publishing, Malden, MA, page 773-774.