

OPTN/UNOS Ad Hoc Disease Transmission Advisory Committee
Meeting Summary
April 21, 2016
Chicago, IL

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Discussions of the full committee on April 21, 2016 are summarized below. All committee meeting summaries are available at <https://optn.transplant.hrsa.gov>.

Committee Projects

1. Modifications to How New Donor Information Received Post-Transplant is Reported to Recipient Centers

The Committee conducted a final review of public comment on the proposed modifications to how new donor information received post-transplant is reported to recipient centers.

This proposal was well received and supported within the transplant community.

All eleven regions approved the proposal. Every region unanimously voted in favor except in region 2 where there was only one “no” vote. The Kidney, Living Donor, Membership and Professional Standards, OPO, Operations and Safety, Thoracic, Transplant Administrators, Transplant Coordinators, and Vascularized Composite Allograft (VCA) Committees all expressed support for the proposal. In addition, the American Society of Transplantation (AST), American Society for Transplant Surgeons (ASTS), American Society for Histocompatibility and Immunogenetics (ASHI), and NATCO all commented in support of the proposal. AOPO did not formally comment but has been a collaborator in the development of the proposal.

Several themes emerged during public comment and the DTAC made several post-public comment changes in response to comments.

1. Toxoplasmosis testing for all deceased donors

The DTAC sought specific public comment regarding toxoplasmosis testing on all deceased donors due to recent data showing morbidity and mortality in non-cardiac transplant recipients from this disease. The transplant community overall supported toxoplasmosis testing for all deceased donors. The DTAC has changed this proposal to require toxoplasmosis testing for all deceased donors.

Several commenters asked about testing when no specific tests have been approved, licensed, or cleared by the US Food and Drug Administration (FDA) specifically for donor screening. The FDA was consulted and responded that they had no concerns with this requirement. They provided a list of cleared FDA tests that can be used.

Some members in one region expressed concern about the cost of testing and another region commented that it might add roughly \$25,000 per year but that the cost could be absorbed. Multiple OPOs also indicated that they were already conducting toxoplasmosis testing in all donors.

The ASTS, ASHI, International Society for Heart and Lung Transplantation (ISHLT), and NATCO all supported routine toxoplasmosis testing. The AST requested more evidence to expand toxoplasmosis testing beyond donors involving heart allocation. The DTAC has an abstract being presented at the upcoming 2016 American Transplant Congress on a retrospective review of proven and probable toxoplasmosis reports from January 2008 through September 2015. The data show proven or probable transmissions in 11 recipients. Nearly half (45%) were in non-heart recipients (heart recipients = 6; non-heart recipients = 5). Five of the 11 recipients died. To exclude non-cardiac cases would miss an opportunity to prevent morbidity and mortality.

The MPSC, OPO, Operations and Safety, Thoracic, and VCA committees all expressed support for toxoplasmosis testing in all deceased donors.

Several commenters explained that the current system for either testing or sending a tube of blood to the transplant hospital for testing was problematic due to lost tubes, laboratories not accepting the specimens, and gaps in communicating results to all transplant hospitals.

2. VCA specific requirements

The DTAC sought specific feedback on the need for VCA specific requirements. In response to comments from the VCA Committee and the AST, the DTAC and VCA Committees will be forming a work group to explore specific testing and reporting needs regarding VCA donors.

The proposal was amended to require 24 hour reporting of positive results for genitourinary cultures, respiratory samples (bacterial or *Candida species*) to transplant programs receiving lungs or head and neck VCAs, and urine cultures (bacterial or *Candida species*) to transplant programs receiving kidneys or genitourinary VCAs.

3. Specific requirements for reporting positive results

In response to comments to concerns of potential over reporting regarding negative histopathology results, the DTAC amended this requirement to include only relevant findings.

In response to concern for including positive tissue cultures and the possibility of confusion with tissue recovery, the DTAC amended the language to exclude a specific statement on positive tissue cultures as the organ transplantation needs are actually covered in the requirement to report positive serologic, NAT, or antigen results indicating presence of parasites, virus, or fungi.

The DTAC also clarified language regarding reporting of bacterial, mycobacterial, and fungal results including requirements for reporting *Candida species*.

DTAC members discussed all public comments. There were areas discussed for which the Committee did not recommend making changes. These other themes included:

1. Patient safety contacts

The DTAC acknowledges issues with the patient safety contact system as identified in the FMEA and public comments. The DTAC agrees that improvements can be

made in this area. Standardization where feasible would improve the quality of communication processes including more agile processes for identifying and contacting patient safety contacts. The DTAC has not addressed this issue in the proposal because there is a pilot UNOS Customer Innovation project that should help with this issue and provide increased abilities to identify, amend, and contact designated patient safety contacts.

2. Information transfer and confirmation of receipt of information

The DTAC agrees that standardization of information transfer and documented receipt of information would improve the quality of communication processes. The DTAC has not addressed this issue in the proposal because there is a pilot UNOS Customer Innovation project that should help address this issue and provide more standardized processes including documentation of communication.

3. Active seeking and posting of negative results by OPOs

The DTAC discussed comments requesting that OPOs actively seek results. The proposed language does require OPOs to have a protocol to obtain and report all results. Due to the variability in result reporting timeframes, a specific time period was not proposed. OPOs, however, should develop their protocols to include a specific process to obtain all results within a timely period. This will be highlighted in educational efforts.

4. Duplicative reporting

Some commenters asked for ways to receive feedback on cases or have search abilities to identify previously reported cases in order to avoid unnecessary duplicative reporting. The DTAC did not change the current policy that requires both OPOs and transplant hospitals to report to avoid the greater harm and potential for missing reports.

The Committee voted unanimously (13-0) to send the proposed policy language as amended at the in-person meeting for OPTN/UNOS Board of Directors consideration at their June 2016 meeting.

One DTAC member who serves on the UNOS Customer Council shared the latest development in a pilot IT solution to communicate results through UNetsm.

2. Modifications to the Open Variance for the Recovery and Transplantation of Organs from HIV Positive Donors

The Committee conducted a final review of public comment on the proposed modifications to the open variance for the recovery and transplantation of organs from HIV positive donors. This proposal was assigned to DTAC later in the proposal development process.

There were minimal public comments received on this proposal. The proposal was part of the non-discussion agenda for the regional meetings and received unanimous support with no comments. The OPTN/UNOS Kidney Transplantation Committee and OPTN/UNOS Operations and Safety Committee reviewed and supported the proposal with no comments. The American Society for Histocompatibility and Immunogenetics (ASHI) and the American Society of Transplantation (AST) supported the proposal. The American Society of Transplant Surgeons (ASTS) provided the following comments:

“The American Society of Transplant Surgeons supports this proposal in general; however, the proposal assumes each center's IRB will require a Data Safety and Monitoring Board (DSMB), which is actually not necessarily the case (DSMB's are only required for randomized trials, which this is not one). Specifying a DSMB requirement is practicing medicine and interfering with IRB judgment, and will make the eventual data confusingly heterogeneous. ASTS recommends that OPTN/UNOS remove all references to a DSMB and think carefully about what data should be collected”

DTAC members reviewed the following points that were developed in conjunction with the UNOS Chief Medical Officer and DTAC leadership to address concerns brought up by the ASTS.

- 1) *DSMBs are only required for randomized trials.* The FDA does not mandate the use of a DSMB for any particular type of trial; the need for a DSMB is related to the degree of participant risk, not the study design. In the FDA guidance document on Data Monitoring Committees¹, a committee is recommended for “any controlled trial of any size that will compare rates of mortality or major morbidity.” While the HOPE Act transplant protocols that centers are devising are not controlled trials and are more observational in nature, the OPTN will be comparing rates of mortality and major morbidity.
- 2) *The DSMB requirement is practicing medicine and interfering with IRB judgment.* The DSMB requirement is not practicing medicine or interfering with IRB judgement. The system established by the OPTN keeps the OPTN out of the role of directing the collection or analysis of primary research or safety data. This is best done by the local principal investigator (PI) and by a local DSMB. Each participating center has the option of developing its own unique protocol. So far the four centers that have active HOPE Act programs approved by their IRBs have all utilized the DSMB approach and have not had an issue with this requirement. DSMBs can take many forms and can be internal to the institution. The only requirement for DSMB membership is relevant subject matter expertise and absence of serious conflicts of interest. There is no specified size for a DSMB. Transplant centers and PIs have a fair amount of latitude in how their DSMBs are constituted and what the reporting schedule is.
- 3) *Heterogeneous data collection.* Requiring all transplant centers to use a DSMB approach will actually decrease heterogeneity and make the submitted safety analyses within the HOPE Act more uniform and interpretable. Part of the controversy is perhaps related to the unusual establishment of the HOPE Act by an act of Congress. It was defined as research to address the subsequently issued National Institutes of Health (NIH) guidelines. The OPTN is charged with assessing safety of participants and the transplant system as a whole in conjunction with the Secretary of HHS. There were initial discussions related to the OPTN providing the primary data collection for HOPE Act transplants. This would have been extremely

¹ <http://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm>

difficult as there is no uniform protocol used by all hospitals and some of the data elements in the NIH criteria do not have clear clinical definitions.

Finally, because this is an allocation variance and thus defined as research under OPTN policy, the OPTN can make reporting of study safety data a condition of participation. All IRB approved clinical protocols are required to have a safety assessment component according to the NIH requirements. DSMBs are required to provide their IRBs with written assessments so this approach makes it easier for the PIs. All participating centers need to do is follow their own protocol and provide those reports to the OPTN Contractor. UNOS will assess the DSMB reports from various institutions in conjunction with the currently collected recipient outcome data. UNOS has not mandated any additional specific HOPE Act data collection; however, participating centers are required by the statute to address the NIH requirements² in their research protocols, including a number of safety and outcome issues. In assessing the outcomes of the HOPE Act research, UNOS will review peer reviewed research publications that arise from these protocols and any additional research from other countries.

The DTAC did not recommend post public comment changes to the policy language and unanimously voted (13-0) to send the language for consideration by the Board of Directors in June 2016.

3. Developing Education and Guidance on Explaining Risk Related to Use of Increased Risk Donor Organs When Considering Organ Offers

The Committee received an update on this project that was selected to be a Joint Societies Work Group (JSWG) project.

The liaison leading this project reviewed how this affects the structure and process associated with the project. JSWG projects include representatives from ASTS, AST, and NATCO. In November 2015, the JSWG notified the OPTN that they desired to make this a JSWG project. In December 2015, the project was formally approved by the OPTN/UNOS Executive Committee. In March 2016, member representatives were chosen by the ASTS, AST, and NATCO and these names were provided to the OPTN to form the working group. The analyst reviewed the extra steps that will be incorporated. The next step will be to set up an initial meeting with all representatives.

Other Significant Items

4. Zika Virus Webinar

The DTAC and CDC are collaborating to broadcast a webinar on the Zika virus and transplantation on April 28, 2016. The webinar slides were presented to DTAC members for comment and information purposes. Members shared how Zika was impacting their day to day operations. Guidance developed jointly in February 2016 between the DTAC, AST, and ASTS is available at <https://optn.transplant.hrsa.gov/news/guidance-for-organ-donation-and-transplantation-professionals-regarding-the-zika-virus/>.

The guidance provides information, resources, and discussed the need to consider all pertinent information regarding Zika risk and weigh the risks and benefits regarding

² <https://www.federalregister.gov/articles/2015/11/25/2015-30172/final-human-immunodeficiency-virus-hiv-organ-policy-equity-hope-act-safeguards-and-research-criteria>

donation. At this time, DTAC members did not recommend consideration of any revisions but will continue to closely monitor the situation.

5. Data Requests

DTAC members received an update on DTAC data requests. Members received an analysis performed on PHS increased risk organ use. A synopsis of the findings follows. The full report can be requested as well. Standard criteria deceased donors recovered between January 1, 2010 and December 31, 2013 were analyzed.

Utilization rates were significantly higher for non-PHS Increased Risk donor organs as compared to PHS Increased Risk donor organs. For pediatric donors, there was no difference in heart. For adult donors, there was no difference in liver. Regardless of donor age, for PHS increased risk donor organs, kidney was utilized the most frequently, followed by liver and then thoracic organs. Regardless of organ, there were less PHS increased risk than non-PHS increased risk donors.

When adjusting for other factors, the data showed that for adult donors, a large number of kidneys, hearts, and lungs could be transplanted per year when ignoring the PHS increased risk label that otherwise may not be transplanted. For pediatric donors, the PHS increased risk label does not have the same magnitude of an effect on organ utilization for pediatric donors as it does for adult donors (likely due to smaller sample size).

Utilization rates of PHS increased risk donor kidneys varied by DSA. For PHS increased risk donors, more of the variability in utilization rates is accounted for by DSA as compared to non-PHS increased risk donor organs, thus suggesting variations in practice. This was not true, however, for adult hearts and lungs.

Export rates were higher for PHS increased risk donor organs as compared to non-PHS increased risk donor organs, with the exception of pediatric liver donor organs. Only kidney was significantly higher for pediatrics, while almost all organs for adults were significantly higher (lung was marginally significant). Regardless of donor age, PHS increased risk thoracic donor organs were exported the most frequently.

DTAC members also received a presentation on donor related malignancies as part of a standing request. This review encompassed post-transplant malignancies reported as "Donor Related" through recipient follow-up forms with diagnosis date of January 1, 2007 through December 31, 2015. About 40% of malignancy cases diagnosed and reported on follow-up forms (PTM) were also reported to the patient safety system (PSS). Many of these are not reported to PSS system because they are donor derived, diagnosed many years after transplant. The median time to diagnosis was 328 days (<1 year) for those reviewed by DTAC, and 2,128 days (<6 years) for those not reported to the PSS.

From the 137 donors with at least one report of donor-related malignancy on the PTM form, there were 401 recipients. Of these 401 recipients, 163 (or 41%) recipients died from 96 donors. There were 56 deaths (14% of the total 401 recipients) from 48 donors with case of death listed as malignancy related (excluded PTLD). Additional deaths may have been attributed to the malignancy but the specific cause was attributed elsewhere (e.g. infection, cardiovascular).

The DTAC plans to form a subcommittee to continue discussions over the best ways to review, analyze, and disseminate findings related to malignancy reports received by the OPTN.

6. Case Review

DTAC members and CDC representatives reviewed potential donor-derived transmission event (PDDTE) cases from 2015 and 2016.

Upcoming Meeting

- May 10, 2016 (Monthly case review teleconference call)