

OPTN/UNOS Ad Hoc Disease Transmission Advisory Committee (DTAC)

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

*Prepared by:
Robert A. Hunter
UNOS Policy Department*

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Executive Summary

The HIV Organ Policy Equity Act (HOPE Act), enacted on November 21, 2013, allows research to be conducted on the transplantation of organs from donors infected with HIV into individuals who are infected with HIV before receiving such organ. The legislation required the OPTN to revise its policies “not later than 2 years after the enactment” to allow this research to begin. The HOPE Act also states that “not later than 4 years after the date of enactment and annually thereafter, the Secretary shall review the results of scientific research in conjunction with the Organ Procurement and Transplant Network to determine whether the results warrant revision of the standards of quality.”

Though the OPTN/UNOS policies went into effect on November 21, 2015, creating a variance to permit the research to be conducted, the policy does not explicitly address how the OPTN will work with the Secretary to review the results of the research. OPTN/UNOS leadership discussed the OPTN’s role in this review, and recommended modifying the variance to require members participating in a HOPE Act research study to provide periodic reports from their data safety monitoring boards to the OPTN. On October 19, 2015, under the authority granted by OPTN/UNOS Bylaw 11.7: *Emergency Actions*, the OPTN/UNOS Executive Committee approved this requirement to meet the statutory deadline outlined in the HOPE Act. Bylaw 11:7 requires policies adopted as an emergency action “to be distributed for public comment no more than 6 months after approval.”

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

Affected Policy: Policy 15.6: Open Variance for the Recovery and Transplantation of Organs from HIV Positive Donors

Sponsoring Committee: Ad Hoc Disease Transmission Advisory Committee (DTAC)

Public Comment Period: January 25, 2016 – March 25, 2016

What problem will this proposal solve?

This proposal solves two distinct problems:

1. Non-specific data submission requirements for the HOPE Act Variance
2. Absence of an expiration date for the HOPE Act Variance

The HIV Organ Policy Equity Act (HOPE Act), enacted on November 21, 2013, allows research to be conducted on the transplantation of organs from donors infected with HIV into individuals who are infected with HIV before receiving such organ. Under OPTN/UNOS policy, members can engage in a HOPE Act research study according to the HOPE Act variance in *Policy 15.6: Open Variance for the Recovery and Transplantation of Organs from HIV Positive Donors*. The HOPE Act states that “not later than 4 years after the date of enactment and annually thereafter, the Secretary shall review the results of scientific research in conjunction with the Organ Procurement and Transplant Network to determine whether the results warrant revision of the standards of quality,” and *Policy 1.3.D: Reporting Requirements for Variances* states, “members participating in a variance must submit data and status reports to the sponsoring Committee at least annually.” The HOPE Act variance in Policy 15.6, however, does not explicitly state what data must be submitted. Additionally, according to the *Policy 1.3.B: Application for a Variance*, variances must have “a defined expiration date or period of time when the variance will end.” The OPTN Final Rule also states that variances “shall be time limited.” When the Board adopted the HOPE Act variance, it did not contain a defined expiration date. Therefore, the Executive Committee adopted an expiration date of January 1, 2018.

To meet the statutory requirement and to clarify the data submission requirements of the HOPE Act variance, the OPTN/UNOS Executive Committee modified the variance to require members participating in a HOPE Act research study to provide periodic reports from their data safety monitoring boards to the OPTN. These changes were already adopted by the Executive Committee, but have a sunset date of September 1, 2016, and must be submitted for public comment and subsequent Board approval in order to make the changes permanent.

Why should you support this proposal?

This proposal aims to fulfill the OPTN’s requirement under the HOPE Act to review the results of the scientific research “to determine whether the results warrant revision of the standards of quality,” UNOS must work with HOPE Act researchers to monitor the safety of the transplants performed as part of the

research studies. Therefore, this proposal includes a requirement for researchers to submit periodic data safety monitoring board reports to the OPTN. This will allow UNOS to identify issues or trends across multiple research studies and proactively address potential problems.

Additionally, to comply with *Policy 1.3.B: Application for a Variance*, which states that variances must have “a defined expiration date or period of time when the variance will end,” the Executive Committee adopted an expiration date for the HOPE Act variance of January 1, 2018.

As of May 5, 2016, four transplant hospitals have joined the open variance. Each of the transplant hospitals provided all the information required in *Policy 15.6: Open Variance for the Recovery and Transplantation of Organs from HIV Positive Donors*, including the additional requirements as outlined in this proposal.

How was this proposal developed?

- **Data Submission Requirements:** UNOS staff discussed the OPTN’s role in reviewing the results of scientific research as outlined in the HOPE Act. The OPTN will review published peer-review literature detailing the results of HOPE Act research as well as OPTN data to determine if additional policy changes are warranted.
In order to conduct ongoing review of research studies, the DTAC is proposing an additional requirement for transplant hospitals participating in HOPE Act research to provide a detailed schedule of institutional review board (IRB) data safety monitoring report deadlines and submit copies of the reports according to the schedule. UNOS staff consulted with members of the HOPE Act work group to determine if these additional requirements would result in a burden for researchers. The members agreed that it was a reasonable requirement since the information will already be required for IRB approval. This information, along with data and patient safety information collected by the OPTN, will allow the OPTN to identify issues or trends across multiple research studies and proactively address potential problems. UNOS will also monitor transplant volume, waitlist registrations, HIV positive match runs, and waitlist removals for HIV positive donors.
- **Expiration Date:** When the Board approved the original HOPE Act variance, staff planned to use the statutory review period of “not later than 4 years after the date of enactment” of the HOPE Act as the review period for this variance. However, the expiration date for the variance was not explicitly included in policy. Four years after the date of the enactment of the HOPE Act would be November 2017. Since the Board will meet in December 2017, the Executive Committee adopted an expiration date that would fall soon after the Board meeting: January 1, 2018.
- **Procedure:** The Executive Committee adopted these changes on October 19, 2015 under OPTN *Bylaw 11.7: Emergency Actions*, which permits the Board of Directors to adopt a proposal prior to public comment if it is “necessitated by a pending statutory or regulatory change,” but the modification must be “distributed for public comment no more than 6 months after approval.” The Bylaw also requires that a proposal “designates a future date upon which the policy will expire, not more than 12 months beyond the policy’s effective date.” Therefore, the changes adopted by the Executive Committee (clarification of the data submission requirements for the HOPE Act variance and the expiration date for the HOPE Act variance) have a sunset date of September 1, 2016, and will expire if not adopted by the Board in June 2016.

How well does this proposal address the problem statement?

By establishing data submission requirements for transplant hospitals participating in the HOPE Act variance, the OPTN Contractor will be able to monitor the research studies to ensure patient safety and fulfill the data submission requirements in *Policy 1.3.D: Reporting Requirements for Variances*.

Additionally, this proposal addresses the requirements in *Policy 1.3.B: Application for a Variance*, which states that variances must have “a defined expiration date or period of time when the variance will end.”

Was this proposal changed in response to public comment?

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 and the American Society of Transplantation supported the proposal. The American Society of Transplant Surgeons 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.

The DTAC appreciates the comments received from the ASTS. However, the committee does not agree with several of the concerns raised 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 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.

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

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 approved the language for submission to the Board of Directors in June 2016.

Which populations are impacted by this proposal?

This proposal will impact transplant programs engaged in the HOPE Act variance by clarifying its data submission requirements. The proposal will also impact transplant candidates and recipients participating in the HOPE Act variance by allowing the OPTN to identify issues or trends across multiple research studies and proactively address potential patient safety problems.

How does this proposal support the OPTN Strategic Plan?

1. *Increase the number of transplants:* This specific proposal does not impact this strategic goal but the previously approved proposal supports the goal by allowing HIV positive recipients to utilize kidneys or livers from HIV positive donors, thus increasing the pool of organs available for transplant.
2. *Improve equity in access to transplants:* There is no impact to this goal
3. *Improve waitlisted patient, living donor, and transplant recipient outcomes:* There is no impact to this goal
4. *Promote living donor and transplant recipient safety:* This proposal will promote transplant recipient safety by allowing the OPTN to review IRB data safety monitoring reports to identify issues or trends across multiple research studies.
5. *Promote the efficient management of the OPTN:* This proposal promotes the efficient management of the OPTN by setting an expiration date for the HOPE Act variance.

How will the sponsoring Committee evaluate whether this proposal was successful post implementation?

The OPTN has a statutory requirement to review the results of HOPE Act research studies. This proposal is meant, in part, to help it better review the results of the previously approved HOPE Act variance. In order to “review the results of scientific research to determine whether the results warrant revision of the standards of quality,” the OPTN/UNOS will review:

- OPTN data, including short-term patient and graft survival.

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>

- Published peer-review literature.

In order to monitor patient safety concerns that might require changes to the variance, the OPTN/UNOS will review:

- OPTN data, including reported patient safety events and unexpected disease transmissions.
- IRB data safety monitoring reports in order to identify national trends.

How will the OPTN implement this proposal?

This proposal was implemented on November 21, 2015. Programming requirements included updates to the membership database to identify those transplant centers with institutional review board approval to participate in a HOPE Act research study and changes in UNetSM to address donor and candidate screening. The OPTN created a standard request form for members to join the open variance and the form has been modified to include information in this proposal. The OPTN plans to form an ad hoc work group to review the data safety monitoring reports from IRB approved studies as well as outcomes based on standard recipient data collected by the OPTN. This new proposal will not require any additional programming.

How will members implement this proposal?

Transplant hospitals participating in a HOPE Act IRB approved research study must provide the OPTN with a schedule of deadlines for data safety monitoring reports and provide reports to the OPTN according to the schedule.

Will this proposal require members to submit additional data?

Members participating in the HOPE Act variance will be required to submit IRB data safety monitoring reports to the OPTN to allow for ongoing review of research studies to ensure patient safety. Collecting data for this purpose is consistent with the OPTN Principles of Data Collection.

How will members be evaluated for compliance with this proposal?

Before a transplant hospital can have HIV positive organs allocated to their candidates, the hospital must submit a request for an open variance that will include: 1. A detailed schedule of required deadlines for IRB data safety monitoring board reports. 2. A copy of the IRB approval letter.

Policy or Bylaw Language

Proposed new language is underlined (example) and language that is proposed for removal is struck through (~~example~~).

1 **RESOLVED, that modifications to Policy 15.6 (Open Variance for the Recovery and**
2 **Transplantation of Organs from HIV Positive Donors), as set forth below and**
3 **implemented on November 21, 2015, are hereby approved, effective September 1, 2016.**

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5 **FURTHER RESOLVED, Policy 15.6 (Open Variance for the Recovery and**
6 **Transplantation of Organs from HIV Positive Donors), will expire on January 1, 2018.**
7 **15.6 Open Variance for the Recovery and Transplantation of Organs from HIV**
8 **Positive Donors**

9
10 This variance applies to members participating in an institutional review board (IRB) approved research
11 protocol that meets the requirements in the OPTN Final Rule regarding the recovery of organs from
12 donors that test positive for human immunodeficiency virus (HIV) and the transplantation of these organs
13 into HIV positive recipients, including Health and Human Services (HHS) research criteria pertaining to
14 the transplantation of organs from HIV positive donors, as applicable.

15
16 Transplant hospitals participating in this variance must submit *all* of the following to the OPTN Contractor:

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18 1. A detailed schedule of required deadlines for IRB data safety monitoring reports that addresses the
19 requirements in the HHS research criteria.
20 2. IRB data safety monitoring reports at each deadline in the schedule.

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