OPTN Public Comment Proposal: Ethical Considerations of Normothermic Regional Perfusion

The International Society for Heart and Lung Transplantation (ISHLT) appreciates the opportunity to provide feedback on the "Ethical Analysis of Normothermic Regional Perfusion (NRP)" OPTN Public Comment proposal. Feedback was solicited from the ISHLT Advocacy Committee, the ISHLT Ethics Committee, the ISHLT Advanced Lung Failure and Transplant Interdisciplinary Network Steering Committee and the ISHLT Advanced Heart Failure and Transplant Interdisciplinary Network Steering Committee

ISHLT understands that the OPTN White paper is not meant to be a referendum on the topic of NRP, and not meant to solicit agreement on a single unified policy or position.

As you know, ISHLT represents many countries, in some of which the practice of NRP is considered illegal, therefore much of the paper may pertain only to the US and North America. However, ISHLT feels that the following were ethical issues that also have broader implications.

Overall, the document addresses the utilitarian arguments well, but these could be more closely linked to the respect for persons argument, with more emphasis on accomplishing the donor's final autonomous wish.

Specific Comments:

1) The fundamental question is whether one accepts the declaration of death in the donor. For the majority of DCD donation (Maastrict III), a protocol is followed – a decision is made to withdraw life sustaining treatment based on accepted medical standards and shared decision making between the family and the donor's clinical team that continued efforts to save the donor's life will not be effective. Once that decision is made, then it is ethical to proceed with DCD donation. For TA-NRP, this protocol is no different: the patient is declared dead in the same manner as all DCD. The ethical challenge arises when organ perfusion *in situ* with care not to restore neurologic circulation is interpreted as resuscitation. Once death has been declared, such efforts may be perceived as attempts to resuscitate the donor which would be an ethical violation of self-determination. Moreover, if the determination of death is conditional on avoiding resuscitative efforts, A-NRP and TA-NRP could risk undermining the practice of cDCD even without NRP.

   This question is at the core of the debate about NRP. It is possible to separate out the therapeutic intent for the patient as patient, vs the intent for the donor as recently dead patient.

   More discussion of the definition of death, particularly because the interpretation of the language of the law is such an important aspect. There is some reference to this

with the distinction between “cardiac” and “circulatory” but more discussion about this, particularly as it relates to the lawwould be helpful. In addition, recognition that the definitions of death with respect to permanent were made in a setting of very different life sustaining treatment technologies.

This would also have added value as we consider the other regulatory frameworks (legally and ethically) on the international stage.

2) The discussion of what information should be discussed with the surrogate stems from the question: are the surrogates providing authorization or informed consent?

   TA-NP started in the UK in 2015 and all donor families gave specific informed consent for NRP, and no family was recorded as declining NRP. This document argues for a similar approach. Certainly, good practice would be transparency with families and surrogates which should be documented, and it is not much further to achieve informed consent.

   A more comprehensive discussion of the difference, and the ramifications of this difference would help clarify some of the questions raised in this paper.

   It is difficult to determine what the reasonable person standard is for organ procurement of all manners. Having specific suggestions about what this might comprise, and how to achieve this would be important as the paper leans more towards informed consent rather than authorization.

   More research needs to be performed to understand donor family understanding of DCD TA-NRP when consenting for this process.

3) Although this OPTN white paper is focused on US activities, some discussion of the international differences should be acknowledged and discussed. This would also lend to more deliberation on the difference between TA-NRP and abdominal only NRP as they do have different ethical considerations.

   A-NRP is much more widely practiced worldwide than TA-NRP, frequently in the context of pre-mortem vessel cannulation. It does make lung procurement more challenging, and indeed heart procurement where direct thoracic organ procurement is to be performed alongside A-NRP. Although A-NRP is accepted to carry a lesser risk of cerebral perfusion than TA-NRP, the act of clamping the supra-celiac aorta is no different from the act of clamping the supra-aortic vessels. These issues should be addressed to avoid the situation where A-NRP becomes accepted and not TA-NRP.

4) In the context of DCD donation for thoracic organs, there is an alternative to TA-NRP which the paper mentions briefly, namely, the ex-vivo perfusion systems. ISHLT suggests that as this is an alternative procedure to TA-NRP, at least for donors weighing more than 40kg, that this should be further expanded upon in this paper,

   More concretely the OPTN might wish to consider whether ex vivo perfusion systems are uniformly accessible. While ex vivo may not have the ethical concern of death definition, the availability of these systems does squarely fall into ethics of justice and equity.

5) Finally, it is important to note that although there is good evidence pointing to better outcomes with NRP for liver and kidney transplantation, the evidence for improved outcomes with NRP in cDCD heart transplantation is currently weak and the data for data for lung transplant outcomes is unclear at best. In terms of beneficence and organ utilization in DCD TA-NRP, current experience with lung transplantation from TA-NRP is promising within the United States. As centers have gained experience with DCD TA-NRP, lung allograft utilization and function has been similar to standard DBD donors. The DCD TA-NRP system not only has allowed for good quality lung allografts, but has an advantage over ex-vivo perfusion systems as it allows for en-bloc heart-lung allograft usage as well. Though some people argue TA-NRP may have detrimental effects on lung allografts, the data arguing worse lung quality comes from porcine data recently presented at the AATS Mechanical Support and Thoracic Transplantation Summit – this model did not involve venting the left atrium which is likely cause of worse lung function and is not consistent with current procurement techniques. Further standardization of technique is necessary for more centers to reliably procure lung allografts utilizing DCD TA-NRP.

   In addition, the ability to perform a functional assessment of the heart and lungs *in situ* is likely to push the acceptance of extended criteria donors in this setting over ex-vivo perfusion systems which are less effective in this regard. Whether pursuing A-NRP or TA-NRP to improve outcomes of abdominal organs may come at the risk of poorer outcomes for thoracic organs remains to be fully elucidated.

   In summary, TA-NRP remains a promising technique to increase available lung allografts with good clinical outcomes. It also can best fulfill the wishes of the donor and donor family by increasing organ utilization and ensuring the best possible outcomes for organ recipients.

Minor specific issues with the text

1) Table 1: box 2
   The comment that “NRP is the only [technique] that perfuses the organs while they are in the body” is potentially misleading to the lay person. Every deceased donor organ procurement whether DBD or DCD currently involves a period of perfusion of the organs while they are in the body, prior to organ procurement. Perhaps the phrase could be that “NRP is the only technique that recirculates blood through the organs of a DCD donor following declaration of death and prior to organ procurement”. The distinction between circulation and perfusion is referred to in footnote 48 but then not really adhered to in Table 1. or line 71 of the text.
2) Line 169, a second Table, Box 1
   The last sentence where consent for NRP is mentioned is inappropriate in the same box as the decision to withdraw life support. It is better moved to the end of Box 2.”