

Ethical Analysis of Normothermic Regional Perfusion

Executive Summary

This white paper outlines conditions for ethical practice of donation in the United States, and implications for normothermic regional perfusion (NRP).¹ Many viewpoints exist on NRP, and while the analysis espoused here may not accord with the views of some, all were taken into account in the analysis. The purpose of this paper is to provide the transplant community and the OPTN Board of Directors with ethical analysis and guidance at the systems-level to support the sustainability of organ donation and transplantation in the United States and to maintain public trust. This analysis recognizes both the importance of increasing utility for candidates waiting for a transplant, and the importance of maintaining public trust and adhering to longstanding ethical and legal norms that underpin support and sustainability of the entire transplant system.

Importantly, this white paper is not a referendum on clinicians, centers, or OPOs that engage in the practice of NRP. The analysis assumes at the outset, that all stakeholders in the transplant community currently engaged in the practice of NRP have good intentions and engage in NRP responsibly, attempting to do so in accordance with their transplant center's stated protocols. Of the many protocols and testimonials reviewed in development of this white paper, none undertook the pursuit of NRP lightly: all were thoughtful, well-intended, and followed protocols that were well-developed.

NRP is a technique for perfusion either of abdominal organs (A-NRP) or thoracic and abdominal organs (TA-NRP) in a person's body after declaration of circulatory death, and includes occlusion of vessels to prevent brain perfusion.² This paper reviews the ethical implications of NRP according to established ethical principles guiding donation and transplantation, including: the principle of nonmaleficence (do no harm), respect for persons (which includes respect for autonomy), and utility. The principle of nonmaleficence is important for maintaining public trust and requires compliance with the Dead Donor Rule, which requires that patients must be dead at the time of organ procurement (i.e. meet criteria for brain or circulatory death) and that organ donation does not cause death.³ This paper concludes that:

¹ The analysis benefited from presentations and participation of European transplant leaders who routinely conduct both A- and TA-NRP. There are important differences in basic premises underlying differences between donation practices between the United States and some European contexts, which include: support for interventions related to donation, adherence to the Dead Donor Rule, determinations of death criteria, differences in policies regarding provision of analgesics as part of organ donation practices, and differences in public attitudes and expectations regarding donation practices.

² Perfusion is the act of providing flow of fluid, blood, or other substances into a blood vessel and/or organ. Occlusion, a blockage of a blood vessel or passageway in the body, can be complete or partial. The Appendix (page 30) includes relevant terms used throughout the paper.

³ The formulation of the Dead Donor Rule used in this paper is based on what the OPTN Ethics Committee has published in the past in its review of Imminent Death Donation. Upholding public trust in this context requires that NRP does not violate the Dead Donor Rule in the process of recovering organs.

- NRP has great potential to improve utility for candidates with end-stage organ disease awaiting organ transplantation, and as such should be strongly considered. Utility is necessary, but insufficient to demonstrate that a practice is ethical.
- It is unclear whether NRP complies with the Dead Donor Rule. Circulation⁴ is restored regionally in the person after circulatory death has been declared, giving rise to questions that are meaningful as to whether the person continues to meet criteria required for determination of death—in this case permanent⁵ cessation of circulation— at the time donation takes place. To clarify, this concern implies that a person legitimately meets criteria for determining death owing to permanent cessation of circulation at the time of death declaration, but that this criterion is violated subsequently when circulation is restored (at the time of donation).
 - There may be important differences in the degree to which the seriousness of these ethical concerns apply to A-NRP versus TA-NRP.
- NRP raises concerns about the potential for harm if the assumption that the donor is insensate is incorrect following restoration of circulation following occlusion of the arteries.⁶
 - Concern that the donor may still be sensate may be mitigated by studies demonstrating that blood flow to the brain during regional perfusion is minimal (e.g. using transcranial Doppler, angiogram studies, or tissue oxygenation measurement).
 - It may also be mitigated by the use of certain medications during NRP. However, use of such medications may further undermine compliance with the Dead Donor Rule.
- In the interest of public trust, respect for persons, and transparency, informed decision making for NRP should include disclosure of recirculation through the heart (TA-NRP) and the potential restoration of any cerebral perfusion (TA-NRP and A-NRP), as well as considerations of meaningful differences from other donation approaches.^{7,8}
 - Clear requirements and guidelines for disclosure, explanation of morally relevant components of NRP, and consistency within the authorization process are necessary components of informed decision making.

⁴ Circulation in this context refers to blood flow in the body through vessels and/or the heart. While circulation is a process, perfusion is a technique. Both terms are used in the paper where it makes sense – i.e. if the passage is about the protective effect on organs, ‘perfusion’ is used, if it is in context of post-circulatory death declaration then circulation may be used to highlight the potential concern of oxygenated blood flowing to the brain. Although circulation is regional, the descriptor is accurate to the action performed and highly relevant to the ethical implications. Description of circulation reference: InformedHealth.org [Internet]. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG); 2006-. How does the blood circulatory system work? 2010 Mar 12 [Updated 2019 Jan 31].

⁵ While the Uniform Declaration of Death Act identifies circulatory death as “irreversible cessation of circulatory and respiratory functions,” this paper uses “permanent” cessation as most medically relevant. As explained by James Bernat, “Physicians determining death test only for the permanent cessation of circulation and respiration because they know that irreversible cessation follows rapidly and inevitably once circulation no longer will restore itself spontaneously and will not be restored medically...Although most statutes of death stipulate irreversible cessation of circulatory and respiratory functions, the accepted medical standard is their permanent cessation because permanence is a perfect surrogate indicator for irreversibility, and using it permits a more timely declaration.” Reference: Bernat, J. “How the distinction between “irreversible” and “permanent” illuminates circulatory-respiratory death determination.” *The Journal of Medicine and Philosophy: A Forum for Bioethics and Philosophy of Medicine*, Volume 35, Issue 3, June 2010, Pages 242–255, <https://doi.org/10.1093/jmp/jhq018>.

⁶ By “insensate” this paper means unable to feel pain.

⁷ All organ donation is based on Uniform Anatomical Gift Act (UAGA) but whether informed consent or authorization is more pertinent to NRP depends on one’s consideration of the validation of the initial declaration of death. This paper therefore refers to “informed decision making” to encompass the range of perspectives that may apply. If specifically addressing points related to authorization or informed consent processes then these terms are still used.

⁸ “Transparency” in this context implies that unique elements of NRP are communicated in a plain-language way to individuals impacted by the donation process.

- The paper emphasizes the importance of encouraging engagement with donor families to ensure the level of information shared reflects their individual preferences.
- Uncontrolled scenarios for NRP raise additional serious concerns for respect for persons and proceeding too quickly from therapeutic treatment to organ recovery.⁹

The table below provides a brief overview of the relevant uniqueness of NRP in relation to other forms of organ transplantation.

Uniqueness of NRP

NRP entails restoring blood flow through a portion of a person’s body after that person has been declared dead by loss of circulatory function, which by definition requires permanent cessation of circulation.¹⁰ By contrast, standard donation after circulatory death (DCD) does not entail introducing artificially induced localized blood circulation within the body after circulatory death is declared.¹¹

Unlike other machine perfusion techniques, NRP is the only one that perfuses the organs *in situ*, *i.e.* while they are in the body.¹²

While circulation may be present when a person is declared dead by neurological criteria, those donors must meet strict and specific criteria to be accepted as neurologically dead, criteria that are unable to be assessed when NRP is performed.¹³ In DCD, criteria for circulatory death are maintained, so neurological testing is not needed as this person already meets criteria for death determination. For NRP, neurological criteria are not demonstrated to have been met, while at the same time, criteria for circulatory death may not be demonstrated to be maintained following the process of reperfusion.

Scope of White Paper

The OPTN Ethics Committee “aims to guide the policies and practices of the OPTN related to organ donation, procurement, distribution, allocation and transplantation so they are consistent with ethical principles.”¹⁴ White papers are developed for informational purposes and are intended to guide OPTN operations. As such, it is beyond the scope of this paper to speculate regarding potential future changes to the Uniform Determination of Death Act (UDDA), and to opine on whether NRP complies with current

⁹ Uncontrolled scenarios are those in which circulatory death occurs unexpectedly, not after the planned withdrawal of life support. See: Dunne, Kathryn., Doherty, Pamela. “Donation after circulatory death.” *Continuing Education in Anaesthesia Critical Care & Pain*, Volume 11, Issue 3, June 2011, Pages 82–86, <https://doi.org/10.1093/bjaceaccp/mkr003>

¹⁰ Bernat, J. “How the distinction between “irreversible” and “permanent” illuminates circulatory-respiratory death determination.” *The Journal of Medicine and Philosophy: A Forum for Bioethics and Philosophy of Medicine*, Volume 35, Issue 3, June 2010, Pages 242–255, <https://doi.org/10.1093/jmp/jhq018>.

¹¹ Reich, D.J., et al. “ASTS Recommended Practice Guidelines for Controlled Donation after Cardiac Death Organ Procurement and Transplantation.” *American Journal of Transplantation* 9, no. 9 (2009), 2004-2011. doi:10.1111/j.1600-6143.2009.02739.x

¹² “Introduction to NRP and Perfusion in DCD: What Do These Concepts Mean?” The Organ Donation and Transplantation Alliance. Last modified February 28, 2023. <https://www.organdonationalliance.org/insight/introduction-to-nrp-and-perfusion-in-dcd-what-do-these-concepts-mean/>.

¹³ Glazier, Alexandra K., and Alexander M. Capron. “Normothermic regional perfusion and US legal standards for determining death are not aligned.” *American Journal of Transplantation* 22, no. 5 (2022), 1289-1290. doi:10.1111/ajt.17002.

¹⁴ “Ethics Committee.” OPTN: Organ Procurement and Transplantation Network - OPTN. Accessed April 7, 2023. <https://optn.transplant.hrsa.gov/about/committees/ethics-committee/>. Charter is listed at the top of this webpage.

law.^{15,16} The Addendum (page 25) provides background on the UDDA and its relevance for the NRP discussion. **This paper's scope does not include reviewing the ethical foundations of DCD, which have been considered extensively elsewhere.**^{17,18,19,20,21} The focus of this white paper is to fully explore and map the relevant ethical principles applied to NRP and the ensuing implications for the OPTN and broader transplant community.

Introduction

There has been an increasing interest in machine perfusion techniques to improve organ quality and utilization, and multiple machines that perfuse organs *ex vivo* (outside the body) have received FDA approval within the last five years.^{22,23} NRP is unique in perfusing organs *in situ* (in the body), which involves ligating the major blood vessels to the brain prior to restoration of circulatory blood flow; in contrast, other machine perfusion techniques are *ex vivo* (outside the body). While NRP has expanded significantly in the United States since 2020, no formal ethical analysis or guidance has been issued by the OPTN regarding the implications for *in situ* organ perfusion.²⁴ Many other countries that have pursued NRP or have decided against it have provided additional guidance and consideration of its

¹⁵ It is important to note that the UDDA is not itself legally binding. Each state may consider the UDDA in enacting its laws, which are legally binding. All states allow determinations of death by either neurological or circulatory criteria, and many have enacted the language of the UDDA. The Dead Donor Rule is also not legally binding but an underlying moral principle to organ transplantation.

¹⁶ The Uniform Law Commission has suspended its deliberations on the UDDA as of 9/22/23, indicating that the UDDA may not be updated at all for the foreseeable future.

¹⁷ The Madrid Resolution on Organ Donation and Transplantation. *Transplantation* 91():p: S29-S31, June 15, 2011. DOI: 10.1097/01.tp.0000399131.74618.a5. Of note: "The Third Global Consultation on Organ Donation and Transplantation was organized by the WHO in collaboration with the ONT and TTS and supported by the European Commission. The Consultation, held in Madrid on March 23 to 25, 2010, brought together 140 government officials, ethicists, and representatives of international scientific and medical bodies from 68 countries." The Resolution finds that "Donation after both brain death and circulatory death should be regarded as ethically proper."

¹⁸ "An Official American Thoracic Society/International Society for Heart and Lung Transplantation/Society of Critical Care Medicine/Association of Organ and Procurement Organizations/United Network of Organ Sharing Statement: Ethical and Policy Considerations in Organ Donation after Circulatory Determination of Death." *Am J Respir Crit Care Med* Vol 188, Iss. 1, pp 103–109, Jul 1, 2013 DOI: 10.1164/rccm.201304-0714ST.

¹⁹ Herdman R, Beauchamp TL, Potts JT. "The Institute of Medicine's report on non-heart-beating organ transplantation." *Kennedy Inst Ethics J* 1998;8(1):83-90, doi:10.1353/ken.1998.0003

²⁰ "Institute of Medicine (US) Committee on Non-Heart-Beating Transplantation II: The Scientific and Ethical Basis for Practice and Protocols. "Non-Heart-Beating Organ Transplantation." *Washington (DC): National Academies Press (US); 2000, 2000.* doi:10.17226/9700.

²¹ The extent to which, in deference to transparency, the public is made aware of transplant practices (including whether centers participate in NRP) varies on a case-by-case basis, an issue which is beyond the scope of this paper.

²² "OrganOx Metra® System - P200035." U.S. Food and Drug Administration. Last modified January 11, 2022. <https://www.fda.gov/medical-devices/recently-approved-devices/organox-mettra-system-p200035>.

²³ "FDA Approves Device to Help Increase Access to More Lungs for Transplant." U.S. Food and Drug Administration. Last modified April 26, 2019. <https://www.fda.gov/news-events/press-announcements/fda-approves-device-help-increase-access-more-lungs-transplant>.

²⁴ Croome, Kristopher P., et al. "American Society of Transplant Surgeons recommendations on best practices in donation after circulatory death organ procurement." *American Journal of Transplantation* 23, no. 2 (2023), 171-179. doi:10.1016/j.ajt.2022.10.009.

ethical implications.^{25,26,27} Transplant centers and OPOs have developed a patchwork of approaches and decisions related to NRP in the U.S., creating fragmentation and inconsistency in protocols for treatment of potential organ donors. Many questions remain at this time about the science of NRP as it relates to potential blood flow to the brain, particularly in a retrograde fashion through collateral flow to the spinal cord.²⁸ While some studies reflect rapid progress in identifying the potential for cerebral flow to be minimal during NRP when vessels are occluded,^{29,30} and although this paper acknowledges that the potential for a donor being sensate at the time of organ procurement may be low, more research is needed to confirm that the perfusion of the brain or brainstem during NRP does not occur.

Appendix A (page 31) provides an overview of all relevant terms and acronyms that are defined in this paper; it may be referenced throughout where technical terms are used. Finally, an overview of presenters and topics discussed by the Workgroup is included in Appendix B (page 35).

Overview of Ethical Findings

Ethical principles guiding transplantation provide a system of checks and balances.³¹ This is spelled out in the OPTN Final Rule according to which utility, justice, and respect for persons are “the major ethical principles to be balanced to achieve an equitable outcome in the allocation of organs for transplantation.”³² Another important cornerstone of organ transplantation is public trust, since no transplant would occur without the endorsement of society and the generosity of individual donors and their families.

The **Dead Donor Rule** states that donors must meet criteria for death at the time of donation, to ensure that persons donating organs do not die by or for donation.³³ The Dead Donor Rule is a fundamental tenet of trust in the organ donation system. Adherence to this is critical despite the need to reduce

²⁵ British Transplantation Society. *Transplantation from deceased donors after circulatory death*. British Transplantation Society, 2013. https://bts.org.uk/wp-content/uploads/2016/09/15_BTS_Donors_DCD-1.pdf.

²⁶ Manara, Alex, Sam D. Shemie, Stephen Large, Andrew Healey, Andrew Baker, Mitesh Badiwala, Marius Berman, et al.

"Maintaining the permanence principle for death during in situ normothermic regional perfusion for donation after circulatory death organ recovery: A United Kingdom and Canadian proposal." *American Journal of Transplantation* 20, no. 8 (2020), 2017-2025. doi:10.1111/ajt.15775.

²⁷ Dominguez-Gil. "Organ Donation and Transplantation: The Spanish Model." Lecture, The Committee on a Fairer and More Equitable, Cost-Effective, and Transparent System of Donor Organ Procurement, Allocation, and Distribution, The National Academies of Sciences, Engineering, and Medicine, April 16, 2021.

²⁸ Bernat, James., et al. "Understanding the Brain-based Determination of Death When Organ Recovery is Performed with DCDD In Situ Normothermic Regional Perfusion." *Transplantation* ():10.1097/TP.0000000000004642, May 12, 2023. | DOI: 10.1097/TP.0000000000004642

²⁹ Dalsgaard, Frederik F., et al. "Clamping of the Aortic Arch Vessels During Normothermic Regional Perfusion After Circulatory Death Prevents the Return of Brain Activity in a Porcine Model." *Transplantation* 106, no. 9 (2022), 1763-1769. doi:10.1097/tp.0000000000004047.

³⁰ Frontera J., Lewis A., James L., Melmed, K., Parent, B., Raz, E., Hussain, S., Smith, D., Moazami, N., "Thoracoabdominal Normothermic Regional Perfusion in Donation after Circulatory Death Does Not Restore Brain Blood Flow." *J Heart Lung Transplant*. 2023 May 19;S1053-2498(23)01862-4. doi: 10.1016/j.healun.2023.05.010. Online ahead of print.

³¹ OPTN Ethics Committee. "Ethical Principles in the Allocation of Human Organs." *OPTN*, 2015.

<https://optn.transplant.hrsa.gov/professionals/by-topic/ethical-considerations/ethical-principles-in-the-allocation-of-human-organs/>.

³² "Final Rule." OPTN: Organ Procurement and Transplantation Network - OPTN. <https://optn.transplant.hrsa.gov/about/final-rule/>.

³³ Truog, Robert D., and Walter M. Robinson. "Role of brain death and the dead-donor rule in the ethics of organ transplantation." *Critical Care Medicine*. Last modified 2003, 10.1097/01.ccm.0000090869.19410.3c.

ischemic time and optimize perfusion to improve transplant outcomes. NRP raises questions about whether the act of ligating the arteries or using an occluding balloon prior to perfusion with the knowledge and intent of restarting regional circulation constitutes a violation of the Dead Donor Rule, as well as a violation of the UDDA, by rendering the initial determination of death by circulatory criteria invalid (as circulation was restarted successfully), and without a determination of death by brain death criteria.³⁴

To provide assurance, the following question should be asked: Does regional postmortem circulatory restoration imply that the criteria for meeting death, legitimately established at the time death was declared according to accepted DCD practices, is overturned following that restoration?³⁵ Has adequate brain monitoring been conducted to examine brain function in circumstances where the carotid and vertebral arteries cannot be perfused? Would such function be restored, or even somewhat improved, if these arteries were not occluded?³⁶ Evidence demonstrating lack of blood flow to the brain would be instructive to address concerns about harm, but may not address the larger question about whether the act of occluding the arteries itself violates the Dead Donor Rule. While there are differing ethical opinions regarding the implications of NRP and the Dead Donor Rule, assurance that the Dead Donor Rule has not been violated must be met to be consistent with current ethical practice.

NRP has further implications on the requirement of non-maleficence, or do no harm. It is currently unclear if NRP results in collateral blood flow to the brain, including the brainstem. Also, it is not fully clear if collateral blood flow, if it does exist, poses any risk to the donor in the form of experiencing pain. The detection of brain or brainstem flow may be tested through transcranial Dopplers, angiograms, or tissue oxygenation measurements as a step to clarify the nature of collateral blood flow, but at the moment there is a lack of good data for these measurements, certainly precluding any possibility of arriving at consensus in the transplantation community that in NRP non-maleficence is not violated.

Another important ethical consideration is whether and how NRP upholds **respect for persons** (which includes respect for autonomy). This entails demonstrating a proactive and transparent process of informed decision-making. The principle of respect for autonomy refers to one's capacity to self-determine and have a say over what happens to oneself.³⁷ In order for NRP to adhere to the principle of autonomy, clearer guidelines and standards are needed to ensure that patients, health care agents, and families approached about organ donation understand and can opt to, or not to, proceed with NRP.³⁸

³⁴ National Conference of Commissioners on Uniform State Laws. *Uniform Determination of Death Act*. 1980.

³⁵This paragraph has been highly informed by the contributions to the discussion on the part of Robert Truog and Jim Bernat. OPTN Ethics Committee NRP Workgroup, *Meeting Summary*, September 22, 2022. Available at: https://optn.transplant.hrsa.gov/media/ri5dahru/20220922_ethics_nrp_meeting-summary_draft.pdf; OPTN Ethics Committee, *Meeting Summary*, October 21, 2022. Available at: https://optn.transplant.hrsa.gov/media/l1cfcmv3/20221021_ethics_meeting-summary_draft.pdf.

³⁶ Initial research seems to indicate – “yes.” Dalsgaard, Frederik F., et al. "Clamping of the Aortic Arch Vessels During Normothermic Regional Perfusion After Circulatory Death Prevents the Return of Brain Activity in a Porcine Model." *Transplantation* 106, no. 9 (2022), 1763-1769. doi:10.1097/tp.0000000000004047

³⁷ OPTN Ethics Committee. *Ethical Principles in the Allocation of Human Organs*. OPTN, 2015.

<https://optn.transplant.hrsa.gov/professionals/by-topic/ethical-considerations/ethical-principles-in-the-allocation-of-human-organs/>.

³⁸That full consent would take place with NRP should not be taken for granted. Some countries, such as Spain and France, permit cannulation maneuvers to begin in NRP scenarios in when first-person consent has not been procured. See: J. Hessheimer, Amelia, and Constantino Fondevila. "Normothermic Regional Perfusion in Solid Organ Transplantation." *Advances in Extracorporeal Membrane Oxygenation - Volume 3*, 2019. doi:10.5772/intechopen.84771.

The paper also acknowledges the potential benefit to demonstrating respect for the principle of autonomy in that NRP facilitates the fulfillment of potential donor wishes to give the gift of life.

Lastly, the principle of **utility** is a highly relevant consideration to any ethical analysis of NRP. The principle of utility takes into account all possible goods and harms that can be envisioned, considering the quantity and probability of the various outcomes. Current evidence suggests that the *in situ* manner in which NRP organs are acquired yields optimal results for the recipient by maximizing the number of organs procured, as well as the quality and longevity of these organs.³⁹ The alternative methods of *ex vivo* machine perfusion also have positive impacts on organ utilization while avoiding the central controversy of perfusing organs and creating blood flow in the body of someone who was declared dead by circulatory criteria, but the utility benefits for hearts may be lessened by increased post-transplant graft failure.⁴⁰ In developing this paper, the available attestations on the part of transplant professionals working in, and intimately familiar with, NRP were considered.⁴¹ It is of central importance to consider potential recipients whose lives stand to be improved for the better as a result of NRP, and this mattered a great deal in the overall ethical analysis.

As previously mentioned, all of the ethical principles considered are important to consider in tandem, to which end the analysis has taken the approach that fulfilling the expectations for normative justification for any one principle is *necessary, but not sufficient*, for arriving at a conclusion about NRP.

Background

*NRP Procedure*⁴²

Currently, there are two major classifications of NRP, abdominal (A-NRP) and thoraco-abdominal NRP (TA-NRP). A-NRP involves perfusing the liver, kidney and pancreas and other tissue in the lower part of the body using cannulas inserted below the diaphragm, either into the iliac artery and vein or into the abdominal aorta.⁴³ TA-NRP involves perfusing the thoracic organs in addition to abdominal ones, and also implies blood flow through the heart; both forms of NRP involve occlusion of arteries to the brain, although it is less likely that blood flow reach the brain due to A-NRP perfusing organs further from the brain and not perfusing the heart.⁴⁴ A distinction between TA-NRP and A-NRP is that regional perfusion is localized for A-NRP and does not include perfusion to the heart. In A-NRP, cross-clamp or ligation of the aorta eliminates perfusion to the upper body, and not specifically to the carotid vessels or the brain. However, considerations about restoration of circulation are still present in both TA- and A- NRP, and

³⁹Jochmans, Ina., et al. "Consensus statement on normothermic regional perfusion in donation after circulatory death: Report from the European Society for Organ Transplantation's Transplant Learning Journey." *Transplant International* 34, no. 11 (2021), 2019-2030. doi:10.1111/tri.13951.

⁴⁰Langmuur, Sanne J., et al. "Normothermic Ex Situ Heart Perfusion With the Organ Care System for Cardiac Transplantation: A Meta-analysis." *Transplantation* 106, no. 9 (2022), 1745-1753. doi:10.1097/tp.0000000000004167.

⁴¹Summaries of the Committee's deliberations are available here: <https://optn.transplant.hrsa.gov/about/committees/ethics-committee/>

⁴²A note that portions of this section are highly technical and a reminder that all relevant terms are defined in Appendix A, page 30.

⁴³Basmaji, John, et al. "Paving the Road for the Adoption of Normothermic Regional Perfusion in Canada." *Critical Care Explorations* 3, no. 11 (2021), e0553. doi:10.1097/cce.0000000000000553.

⁴⁴Manara, Alex., et al. "Maintaining the permanence principle for death during in situ normothermic regional perfusion for donation after circulatory death organ recovery: A United Kingdom and Canadian proposal." *American Journal of Transplantation* 20, no. 8 (2020), 2017-2025. doi:10.1111/ajt.15775.

the potential for blood flow to the brain with A-NRP still exists. Plausibly, A-NRP may be less of a concern, but more data is still needed to demonstrate blood flow to the brain does not occur.

The development of NRP in the U.S. emerged as a patchwork, with each center/OPO adopting different approaches, some with rigorous ethical oversight through institutional review boards (IRBs) and formal ethics consultations, others with more informal oversight. No objective, formal ethical evaluations have occurred, similar to prior reports issued by the Institute of Medicine with DCD donation.⁴⁵ It is important to note that any actions taken prior to and including declaration of death are those taken solely by the non-OPO, critical care team. Details of how NRP is performed vary but typically reflect utilization of standard DCD protocols. The ethically salient elements are as follows:⁴⁶

Elements of NRP that apply to both TA- and A-NRP:

| | |
|---|--|
| 1 | A decision is made to withdraw life-support from a patient based on the patient’s prognosis, the recommendations of the clinical team, and with the agreement of patient or surrogate decision-makers. This is consistent with practices and does not pose a unique ethical concern. |
| 2 | The patient has given authorization to be an organ donor (e.g., first person authorization or driver’s license) or permission has been given by an authorized surrogate. |
| 3 | The patient’s clinical condition is such that cardiopulmonary arrest is reasonably expected to occur within 1-3 hours of the withdrawal of life support. |
| 4 | Any interventions that are performed before the death of the patient (e.g., liver biopsy, bronchoscopy, placement of vascular catheters, administration of heparin) are done with the authorization of the patient or patient’s surrogate. |
| 5 | Life support is withdrawn, and standard end-of-life comfort measures are initiated. |
| 6 | When and if the patient becomes pulseless, the patient is monitored for a period of time (typically 5 minutes in the US), and if autoresuscitation does not occur in that time, death is declared by a physician independent of the transplant team based on determination of death by circulatory criteria. ⁴⁷ |

⁴⁵ Institute of Medicine (US) Committee on Non-Heart-Beating Transplantation II: The Scientific and Ethical Basis for Practice and Protocols. "Non-Heart-Beating Organ Transplantation." *Washington (DC): National Academies Press (US); 2000, 2000.* doi:10.17226/9700.

⁴⁶ Wall, Anji E., et al. "Applying the ethical framework for donation after circulatory death to thoracic normothermic regional perfusion procedures." *American Journal of Transplantation* 22, no. 5 (2022), 1311-1315. doi:10.1111/ajt.16959.

⁴⁷ Institute of Medicine (US) Committee on Non-Heart-Beating Transplantation II: The Scientific and Ethical Basis for Practice and Protocols. "Non-Heart-Beating Organ Transplantation." *Washington (DC): National Academies Press (US); 2000, 2000.* doi:10.17226/9700.

At this point in the process of NRP organ procurement, TA-NRP and A-NRP procedures diverge. The relevant elements are noted below:⁴⁸

Elements of NRP: comparing TA- and A- NRP

| TA-NRP | A-NRP |
|--|--|
| A laparotomy and sternotomy are performed, an atrial cannula is placed to decompress the heart, the brachiocephalic arteries are occluded by clamping, the aorta is cannulated , and warm perfusion and circulation of oxygenated blood are initiated with an extracorporeal membrane oxygenation (ECMO) or bypass machine. | A laparotomy and sternotomy are performed, the iliac artery and vein or the suprahepatic abdominal aorta and the inferior vena cava are occluded (preventing blood flow through the thoracic aorta), the aorta is cannulated, normothermic perfusion to the abdominal organs is initiated. |
| Once ECMO perfusion is established, and the patient has been reintubated, the heart may resume beating inside the donor's chest and warm oxygenated blood circulates to the lungs and abdominal organs. Perfusion to the brain is prevented by the occlusion of the brachiocephalic arteries , ⁴⁹ allowing neuronal hypoxemia and ischemia to progress. An attempt is made to wean the patient off of ECMO or bypass when cardiac function has been restored. | The procurement team proceeds with warm dissection, abdominal cannulation, cold perfusion, and abdominal organ removal. This process is similar to ECMO, just applied to a more limited portion of circulation . In A-NRP, aortic occlusion occurs distally, therefore minimizing the risk of cephalic collateral blood flow . |
| At this point, organ procurement proceeds in the same way as it does for an organ donor who has been declared dead by neurologic criteria, with thoracoabdominal organs that are functioning and being perfused with oxygenated blood. Criteria for brain death are not assessed or confirmed. | At this point, organ procurement proceeds in the same way as it does for an organ donor who has been declared dead by neurologic criteria, with abdominal organs that are functioning and being perfused with oxygenated blood. The criteria for brain death are not assessed or confirmed. ⁵⁰ |

⁴⁸ Basmaji, John, et al. "Paving the Road..." *Critical Care Explorations* 3, no. 11 (2021), e0553. doi:10.1097/cce.0000000000000553.

⁴⁹ An abstract describing NRP in pigs (following an 8 minute no-touch interval) found that, when the aortic arch vessels were not clamped, some pigs had resumption of EEG activity, SSEPs, and resumption of spontaneous respiratory activity, suggesting that clamping is essential to the procedure and not merely precautionary: Dalsgaard, Frederik F., et al. "Clamping of the Aortic Arch Vessels During Normothermic Regional Perfusion After Circulatory Death Prevents the Return of Brain Activity in a Porcine Model." *Transplantation* 106, no. 9 (2022), 1763-1769. doi:10.1097/tp.0000000000004047.

⁵⁰ The American Academy of Neurology (AAN) identifies brain death determination by "demonstration of complete loss of consciousness (coma), brainstem reflexes, and the independent capacity for the ventilatory drive (apnea), in the absence of any factors that imply possible reversibility." Reference: Russell, James A. Epstein, Leon G., Greer, David M., Kirschen, Matthew., Rubin, Michael, A., Lewis, Ariane. "Brain death, the determination of brain death, and member guidance for brain death accommodation requests: AAN position statement." *American Academy of Neurology*, January 2, 2019, DOI: <https://doi.org/10.1212/WNL.0000000000006750>

Historical Perspective⁵¹

To appreciate the current ethical discussions regarding NRP, it is helpful to understand the context from which it arose. In 1993, the University of Pittsburgh developed a protocol that provided a path to obtain organs from individuals deemed dead by cessation of circulation or donors after circulatory death (DCD) to address a growing need for transplantation.⁵² The growth of DCD donors, and its subsequent acceptance by the medical community and society, was promoted in two Institute of Medicine reports that outlined the ethical and medical issues of non-heart beating donors.^{53,54} One report identified that the demand for organ transplantation had increased by 212% in the prior decade and that organs from DCD donors could increase organ transplantation by 25%.⁵⁵ Important contributions outlined the practice of separating the organ procurement teams from physicians charged with the management of the terminally ill patients and their death declaration.⁵⁶ They also defined the 5 minute “standoff” period from death declaration to procurement, that would minimize the chances of spontaneous cardiac restoration.⁵⁷ Early experience with DCD liver and kidney transplants demonstrated that these transplants were safe and had a significant survival benefit for recipients compared to remaining on the waitlist.⁵⁸

The ethical underpinning of DCD transplantation relies on the fact that it adheres to the Dead Donor Rule, in that the donation itself was not the cause of death, and that it was consistent with the UDDA definition that the donor had irreversible cessation of circulatory and respiratory function, interpreted in this case as “permanent” cessation of circulatory function.⁵⁹ An essential corollary is the implicit understanding that no attempts would be made to resuscitate the donor and as such, the lack of circulation to the brain also causes irreversible cessation of all functions of the brain, including the brainstem.^{60,61}

⁵¹ A note that portions of this section are highly technical and a reminder that all relevant terms are defined in Appendix A, page 30.

⁵² DeVita MA, Snyder JV. “Development of the University of Pittsburgh Medical Center policy for the care of terminally ill patients who may become organ donors after death following the removal of life support.” *Kennedy Inst Ethics J* 1993;3(2):131-43, doi:10.1353/ken.0.0175

⁵³ Herdman R, Beauchamp TL, Potts JT. “The Institute of Medicine's report on non-heart-beating organ transplantation.” *Kennedy Inst Ethics J* 1998;8(1):83-90, doi:10.1353/ken.1998.0003

⁵⁴ Institute of Medicine (US) Committee on Non-Heart-Beating Transplantation II: The Scientific and Ethical Basis for Practice and Protocols. “Non-Heart-Beating Organ Transplantation.” *Washington (DC): National Academies Press (US); 2000*, 2000. doi:10.17226/9700.

⁵⁵ Herdman R, Beauchamp TL, Potts JT. The Institute of Medicine's report on non-heart-beating organ transplantation. *Kennedy Inst Ethics J* 1998;8(1):83-90, doi:10.1353/ken.1998.0003

⁵⁶ Ibid.

⁵⁷ Ibid.

⁵⁸ D'Alessandro AM, et al. Donation after cardiac death: the University of Wisconsin experience. *Ann Transplant* 2004;9(1):68-71

⁵⁹ See footnote 5.

⁶⁰ Dalle Ave AL, Bernat JL. Using the brain criterion in organ donation after the circulatory determination of death. *J Crit Care* 2016;33(114-8, doi:10.1016/j.jcrc.2016.01.005

⁶¹ OPTN Ethics Committee NRP Workgroup, *Meeting Summary*, September 22, 2022. Available here:

https://optn.transplant.hrsa.gov/media/ri5dahru/20220922_ethics_nrp_meeting-summary_draft.pdf From Jim Bernat's presentation to NRP Workgroup: “Brain electrical activity as measured from skull surface electrodes ceases within one minute of complete circulatory cessation and will not resume in the absence of brain reperfusion. But brain electrical activity can be re-established with normothermic resuscitations within 20 minutes or so.”

The first challenge to the irreversibility clause of the UDDA came from the use of DCD hearts in three pediatric heart transplant recipients.⁶² If circulatory cessation is irreversible, then how is restarting cardiac function in the recipient permissible?⁶³ Although ethical debates continue regarding DCD heart transplantation, its expansion has been allowed by the notion that despite challenging the irreversibility of asystole, no attempts were made to resuscitate the donor and thus progressive deterioration of brain function proceeded consistent with the UDDA definition of brain death.⁶⁴ In response to this concern, terminology was modified to reflect the currently accepted terminology of “Donation after Circulatory Death” instead of “Donation after Cardiac Death.”⁶⁵ Indisputable in this debate was the agreement that attempts at reversing asystole in the donor, even after death declaration, were not consistent with the process of withdrawing support in a terminally ill patient.⁶⁶

The use of ECMO in a DCD donor was protocolized in the U.S. by the University of Michigan and was originally performed for intra-abdominal organs only.⁶⁷ The use of an intra-aortic occlusion balloon above the diaphragm eliminated cardiopulmonary resuscitation and thus the NRP procedure was deemed “regional” and reportedly consistent with the principle that there were no attempts to resuscitate a donor following the death declaration. During TA-NRP, the aortic arch vessels are ligated to address concerns that ECMO or cardio-pulmonary bypass may result in cerebral circulation.⁶⁸ Some protocols in Europe use a venting procedure to expose arch vessels to atmospheric pressure to further reduce the chances of collateral cerebral perfusion.⁶⁹ TA-NRP protocols in Spain use Bispectral index (BIS) monitoring to confirm lack of frontal lobe brain activity following the initiation of ECMO.⁷⁰

NRP poses significant questions, and its use has not had an *a priori* consensus in terms of its legality, ethical foundation, or societal acceptance. This is critical, as its further expansion may lead to improved survival for many patients waiting for transplant. However, a lack of transparency and failure to address gaps in knowledge have the potential to impact societal credibility in the overall transplant system. Spontaneous cardiac restoration has been observed in TA-NRP when cardio-pulmonary bypass was used, which then directly calls into question the defined event of death declaration prior to the standoff

⁶² Boucek, Mark M., et al. "Pediatric Heart Transplantation after Declaration of Cardiocirculatory Death." *New England Journal of Medicine* 359, no. 7 (2008), 709-714. doi:10.1056/nejmoa0800660.

⁶³ Bernat, James L. "The Boundaries of Organ Donation after Circulatory Death." *New England Journal of Medicine* 359, no. 7 (2008), 669-671. doi:10.1056/nejmp0804161.

⁶⁴ Lizza, John P. "Why DCD Donors Are Dead." *The Journal of Medicine and Philosophy: A Forum for Bioethics and Philosophy of Medicine* 45, no. 1 (2019), 42-60. doi:10.1093/jmp/jhz030.

⁶⁵ "Donation after circulatory death." *NHS: Blood and Transplant*. <https://www.odt.nhs.uk/deceased-donation/best-practice-guidance/donation-after-circulatory-death/>. Accessed May 24, 2023.

⁶⁶ Lizza, John P. "Why DCD Donors Are Dead." *The Journal of Medicine and Philosophy: A Forum for Bioethics and Philosophy of Medicine* 45, no. 1 (2019), 42-60. doi:10.1093/jmp/jhz030.

⁶⁷ Magliocca, Joseph F., et al. "Extracorporeal Support for Organ Donation after Cardiac Death Effectively Expands the Donor Pool." *The Journal of Trauma: Injury, Infection, and Critical Care* 58, no. 6 (2005), 1095-1102. doi:10.1097/01.ta.0000169949.82778.df.

⁶⁸ Dalsgaard, Frederik F., et al. "Clamping of the Aortic Arch Vessels..." *Transplantation* 106, no. 9 (2022), 1763-1769. doi:10.1097/tp.0000000000004047.

⁶⁹ Manara, Alex, et al. "Maintaining the permanence principle for death during in situ normothermic regional perfusion for donation after circulatory death organ recovery: A United Kingdom and Canadian proposal." *American Journal of Transplantation* 20, no. 8 (2020), 2017-2025. doi:10.1111/ajt.15775.

⁷⁰ Miñambres, Eduardo., et al. "Spanish experience with heart transplants from controlled donation after the circulatory determination of death using thoraco-abdominal normothermic regional perfusion and cold storage." *American Journal of Transplantation* 21, no. 4 (2021), 1597-1602. doi:10.1111/ajt.16446.

period.⁷¹ From a physiological perspective it is also unknown to what extent collateral circulation results in perfusion of the posterior brain and brainstem.⁷² Anatomically, there is substantial variability in how the spinal cord receives circulation and our current knowledge challenges the assertion that ligation of aortic arch vessels is sufficient to eliminate perfusion of the entire brain and brainstem, as required by the UDDA.⁷³

The ethical integrity of DCD donation is highly dependent on the societal acceptance that imminently dying individuals may have cardiopulmonary support withdrawn and, following the act of dying, they could donate organs to help others. Implicit is that the individual is not experiencing harm from the organ procurement as they are declared dead by accepted definitions. Unknown in NRP is if the issues regarding brain/brainstem circulation have been scientifically investigated, if organ resuscitation practices conducted in NRP result in inadvertent harm, and if there are in fact potential violations of the Dead Donor Rule.⁷⁴

Need for Ethical Review

As the use of NRP has expanded, so have concerns that its pursuit may violate ethical principles governing organ transplantation and legal boundaries.⁷⁵ The UDDA, which provides part of the legal framework for organ transplantation in the United States, defines death as **“An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem.”**⁷⁶ A 2021 statement by the American College of Physicians (ACP) expressed concern that NRP does not comply with the UDDA because it entails recirculation of blood in the body after death is declared, violating irreversibility, and potentially the Dead Donor Rule.⁷⁷ Additional concerns related to nonmaleficence include unknown implications of circulation and potential blood flow to the brain.

Those in favor of NRP consider that the procedure does not violate irreversibility because the circulation is localized, or “regional.” Under this view, the UDDA may need to be clarified to expand the interpretation of irreversibility understood as permanence to allow for regional recirculation.⁷⁸ However, proponents argue that no ethical norm is violated and this may be merely a legal

⁷¹ James L, LaSala VR, Hill F, Ngai JY, Reyentovich A, Hussain ST, Gidea C, Piper GL, Galloway AC, Smith DE, Moazami N. “Donation after circulatory death heart transplantation using normothermic regional perfusion: The NYU Protocol.” *JTCVS Tech*. 2022 Dec 13;17:111-120. doi: 10.1016/j.xjtc.2022.11.014. PMID: 36820336; PMCID: PMC9938390.

⁷² Peled, Harry, et al. “Normothermic Regional Perfusion Requires Careful Ethical Analysis Before Adoption Into Donation After Circulatory Determination of Death.” *Critical Care Medicine* 50, no. 11 (2022), 1644-1648. doi:10.1097/ccm.0000000000005632.

⁷³ Griep, Randall B., and Eva B. Griep. “Spinal Cord Perfusion and Protection During Descending Thoracic and Thoracoabdominal Aortic Surgery: The Collateral Network Concept.” *The Annals of Thoracic Surgery* 83, no. 2 (2007), S865-S869. doi:10.1016/j.athoracsur.2006.10.092.; Griep, Eva B., et al. “The anatomy of the spinal cord collateral circulation.” *The Annals of Thoracic Surgery* 1, no. 3 (2012), 350-357. doi: [10.3978/j.issn.2225-319X.2012.09.03](https://doi.org/10.3978/j.issn.2225-319X.2012.09.03)

⁷⁴ Dalle Ave, Anne L., Daniel P. Sulmasy, and James L. Bernat. “The ethical obligation of the dead donor rule.” *Medicine, Health Care and Philosophy* 23, no. 1 (2019), 43-50. doi:10.1007/s11019-019-09904-8.

⁷⁵ Glazier, A., Capron, A., “Normothermic regional perfusion and US legal standards for determining death are not aligned.” *American Journal of Transplantation* 22, no. 5 (2022), 1289-1290. Doi: <https://doi.org/10.1111/ajt.17002>

⁷⁶ National Conference of Commissioners on Uniform State Laws. *Uniform Determination of Death Act*. 1980.

⁷⁷ American College of Physicians. Ethics, Determination of Death, and Organ Transplantation in Normothermic Regional Perfusion (NRP) with Controlled Donation after Circulatory Determination of Death (cDCD): American College of Physicians Statement of Concern. American College of Physicians, 2021.

⁷⁸ Wall, Anji E., et al. “Applying the ethical framework for donation after circulatory death to thoracic normothermic regional perfusion procedures.” *American Journal of Transplantation* 22, no. 5 (2022), 1311-1315. doi:10.1111/ajt.16959.

clarification.⁷⁹ Proponents of NRP consider respect for persons (patient autonomy in choosing to donate) and utility (increased use of organs and improved outcomes for recipients) as strong ethical reasons to pursue NRP.⁸⁰ While still considering it necessary to have appropriate protocols and informed decision making, supporters of NRP do not consider that the Dead Donor Rule is violated or that harm is being done to donors because the procedure occurs after circulatory death has been declared.⁸¹ Given the varying perspectives within the community, a workgroup was convened of experts with diverse and diverging opinions and backgrounds to conduct a robust and balanced review of ethical implications, as described in the “Deliberative Process section” below.

Deliberative Process

In *circumstances* where no *a priori* agreement exists on the hierarchy of principles or values governing ethical decision-making, people turn to a procedural justice approach. This type of approach (in contrast to distributive justice approaches) stems from the following: if diverse stakeholders are engaged and the process is transparent, and if stakeholders can agree at the outset on the terms for a fair deliberative process, then the outcome arising from the deliberation must be seen and accepted as fair.⁸²

For such a new technology as NRP, with its complexity and potential for controversy, it was considered imperative to create a deliberative process for review that was thorough and inclusive of all relevant perspectives. To that end, a diverse workgroup was formed with expertise on NRP, organ donation, ethics, donor family experience, organ procurement, and transplantation to assess the ethical justification for NRP. The Workgroup included supporters and skeptics of NRP, as well as representatives from all key transplant communities, and diverse medical specialties.⁸³ Guest presentations included proponents and critics of NRP.

The Ethics Committee started its deliberation with presentations from both European surgical teams engaged in the practice of NRP and the American College of Physicians (ACP), which had recently issued a position statement critical of NRP.⁸⁴ The Workgroup reviewed protocols presented by U.S. transplant programs engaged in the practice, and sought out the perspectives of intensivists, neurological experts, anesthesiologists, researchers and clinical experts in determination of death, and European transplant clinicians.⁸⁵ Members updated a shared literature review with 60 relevant publications and participated in Workgroup subgroups to consider the particular implications of irreversibility, patient autonomy, and physician intent. The Workgroup met 15 times from July 2022 to March 2023, and members provided regular updates on progress and discussions to the Committee. An informal survey of the Workgroup indicated that throughout the course of Workgroup review, most respondents had changed their mind regarding whether NRP could be appropriately and ethically pursued in the current environment.⁸⁶ This finding suggests that the deliberations of the group and the presentations it received influenced

⁷⁹ Ibid.

⁸⁰ Ibid.

⁸¹ Parent, Brendan, et al. "Ethical and logistical concerns for establishing NRP-cDCD heart transplantation in the United States." *American Journal of Transplantation* 20, no. 6 (2020), 1508-1512. doi:10.1111/ajt.15772.

⁸² Summaries of the Committee's and Workgroup's deliberations are available here: <https://optn.transplant.hrsa.gov/about/committees/ethics-committee/>

⁸³ Ibid.

⁸⁴ A full list of presenters and topics reviewed by the workgroup can be found in Appendix B.

⁸⁵ Ibid.

⁸⁶ 84% of Workgroup members participated in the survey.

evolving perspectives of Workgroup members as they understood more about the practice of NRP and associated ethical implications. The discussions within the Workgroup directly led to the generation of initial drafts of the white paper, which were updated in iterative fashion based on feedback from the Workgroup and Committee. Further review by the Committee developed the paper, which was shared with the community and subsequently updated, reflecting adherence to a deliberative and thorough ethical analysis.

Ethical Implications of NRP

The analysis considers that adherence to the Dead Donor Rule and associated impact on non-maleficence, respect for persons, and utility are the most relevant and impactful principles to consider for NRP.

Do No Harm (nonmaleficence)

Although the Hippocratic precept of *primum non nocere* (“first, do no harm”) is often considered a fundamental principle of medical ethics, strict adherence to this rule would be incompatible with modern medical practice, since almost all medical interventions entail some risk of harm. Yet, the spirit of this principle can be retained by carefully considering whether the potential for benefits from an intervention outweighs the potential for harm. In the context of NRP, it is important to consider not only potential harms to the organ donor, but also harms that may come from a loss of public trust in the practice of organ procurement, particularly with regard to the Dead Donor Rule (DDR), an implicit but fundamental ethical foundation in the practice of organ transplantation. The paper considers potential harms here to the donor, while harm to others (including participating healthcare providers and to public trust) is included in a section below, “Utility.”

Argument that NRP does not violate the Dead Donor Rule (DDR) and does not harm the donor:

Proponents of NRP contend that NRP is a modification of standard DCD donation, which has been in use since 1992, and which is now a well-accepted approach to organ procurement.⁸⁷ In DCD donation in the US, death is declared (if it occurs) following a predetermined duration of pulselessness, provided that autoresuscitation has not occurred.⁸⁸ The 5-minute interval has been supported by evidence that autoresuscitation does not typically occur beyond this time interval, provided that there have been no prior attempts to resuscitate the patient.⁸⁹

Proponents further explain that NRP does not violate the DDR because the restoration of circulation is only regional (excluding the brain in TA-NRP, and excluding the brain and thoracic organs in A-NRP), and consider the fact that circulation is restored *in situ* rather than *ex vivo* to be ethically irrelevant.⁹⁰ The arteries that supply the brain are clamped or otherwise occluded, and arteries that lie distal to the

⁸⁷ DCD has grown in usage over time, and as of 2018, the percentage of DCD organs among deceased donor transplants was up to 50.9%, depending on the Donation Service Area (DSA). See: Scientific Registry of Transplant Recipients. *Annual Data Report*. OPTN/Scientific Registry of Transplant Recipients, 2018. https://srtr.transplant.hrsa.gov/annual_reports/2018/DOD.aspx.

⁸⁸ Manara, A.R., et al. "Donation after circulatory death." *British Journal of Anaesthesia* 108 (2012), i108-i121. doi:10.1093/bja/aer357.

⁸⁹ Lizza, John P. "Why DCD Donors Are Dead." *The Journal of Medicine and Philosophy: A Forum for Bioethics and Philosophy of Medicine* 45, no. 1 (2019), 42-60. doi:10.1093/jmp/jhz030.

⁹⁰ Wall, Anji E., et al. "Applying the ethical framework for donation after circulatory death to thoracic normothermic regional perfusion procedures." *American Journal of Transplantation* 22, no. 5 (2022), 1311-1315. doi:10.1111/ajt.16959.

occlusion are vented to atmospheric pressure to divert any potential collateral blood flow away from the brain in an effort to minimize the risk of cerebral reperfusion.⁹¹

On the question of whether re-establishing circulation invalidates the determination of death, Parent et al makes a parallel point on the legal issue: "The law is silent on whether subsequent acts can invalidate a declaration of death. Regardless, occluding cerebral circulation... does not cause death—the patient has already been pronounced dead by standard cDCD criteria."⁹² Moreover, proponents describe the importance of intention: "Resuscitation efforts require attempting to restart the heart for life-saving/prolonging purposes. In undertaking cDCD NRP, there is no intention or attempt to resuscitate because doing so would be medically ineffective... Perfusing the thoracic and abdominal organs after circulatory determination of death... does not alter the fact that... continued care would be medically ineffective and inconsistent with a meaningful existence."⁹³ Their presumption is that the intent to restart circulation merely for the purposes of regional reperfusion for donation does not constitute resuscitation. They note that the DDR is not violated in that the occlusion of the arteries ensure that the process of brain death continues unabated after circulatory death determination has been achieved.

On the question of potential harm to the donor, many argue that the donor is insensate because clamping the aortic arch vessels ensures a lack of cerebral blood flow that most closely mimics the level of blood flow to a brain in a standard DCD donor. As such, they perceive the conditions for NRP to be similar to those for DCD, where it is assumed that the donor is insensate and no harm is incurred by the procedure. This assumption could be confirmed by use of anesthetics on the donor, a practice which is not unique to NRP but raises questions beyond the purview of this paper to fully consider.⁹⁴ Do no harm and respect for persons do raise questions about whether anesthesia is appropriate.

Argument that NRP does violate the Dead Donor Rule (DDR) and may cause harm:

Yet, many raise concerns that the patient has been declared dead on the basis of the permanent cessation of circulation, with the full intent and understanding that regional circulation will be restored, invalidating the prior determination.⁹⁵ It is important to note that at that time of donation the patient may no longer meet criteria needed for declaration of circulatory death nor have they been demonstrated to meet the accepted criteria for the neurologic determination of death- which has not been assessed.⁹⁶

⁹¹ Ibid.

⁹² cDCD = controlled DCD. Quote from: Parent, Brendan, et al. "Ethical and logistical concerns..." *American Journal of Transplantation* 20, no. 6 (2020), 1508-1512. doi:10.1111/ajt.15772.

⁹³ Ibid. "cDCD" refers to controlled DCD scenarios in which life support is withdrawn in accordance with potential donor/family decisions.

⁹⁴ Cappucci, S. P., Smith, W. S., Schwartzstein, R., White, D. B., Mitchell, S. L., & Fehnel, C. R. (2022).

End-of-life care in the potential donor after circulatory death: A systematic review. *The Neurohospitalist*, 13(1), 61-68. <https://doi.org/10.1177/19418744221123194>

⁹⁵ Glazier, Alexandra K., and Alexander M. Capron. "Normothermic regional perfusion..." *American Journal of Transplantation* 22, no. 5 (2022), 1289-1290. doi:10.1111/ajt.17002.

⁹⁶ One could argue that determination of death in DCD (including DCD NRP) donation is premised on the condition that no attempt will be made to restore circulation after the onset of pulselessness. Intention notwithstanding, NRP arguably violates this condition, by using ECMO to restore circulation to the body's vital organs, except the brain. From this perspective, the problem is not so much that the determination of death has been reversed, but rather that it was arguably not valid in the first place, since a central requirement of DCD donation was violated. It is also true that others consider that the determination of death is not premised on the condition described above, and that nonmaleficence is maintained as long as the donor is insensate.

Although it is impractical for the team to pursue tests needed to confirm neurologic determination of death, without this, the patient donor does not meet either standard for circulatory or neurologic determination of death at the time of organ procurement. A reasonable person may ask: since the patient has been declared dead after the established duration of pulselessness, why is it necessary to ligate the aortic arch vessels? There is no single proffered answer to this question. Those in favor of NRP suggest that occluding the aortic arch vessels is something that occurs after death has been declared, which consequently has no ethical relevance, and as such ought simply to be characterized as an additional step of efficiency to bring about an already agreed upon outcome. Since, according to this logic, there is a tacit agreement by all parties that CPR will not be applied once the heart stops beating, DCD, including DCD-NRP, can, indeed, reliably be characterized as “permanent” even before occlusion is considered. In other words, occlusion merely makes explicit that which is already implicit. It is a prior act of omission, namely, the decision not to resuscitate, as opposed to any subsequent act of commission, because of which death follows. The decision to occlude is no more than one of economy and expedience, which ensures permanent cessation of circulation to the brain. It is not a decision to ensure that death takes place, as if there would otherwise have been any doubt.

Those who think NRP does run afoul of the “do no harm” principle ask: has any convincing evidence been put forth to demonstrate that brain death has occurred at the time circulatory death is declared? If not, it is arguably reasonable to assume that brain death criteria have not been met at the time circulatory death is declared. In situ reperfusion via ECMO without the additional step of occlusion serves, if anything, to move in a direction *away* from brain death. In light of this, any overt act preventing blood from getting to the brain is arguably its own determinative act of commission. In this case, one could reasonably conclude that the occlusion of these key vessels takes place in order to add an extra layer of assurance that dying is not thwarted, or that dying is sped up. As such, occlusion cannot rightly be characterized as merely a decision of “economy.”

It bears mentioning that in calling attention to these disparate explanations for why occlusion of the aortic arch vessels takes place in NRP, this analysis does not opine on which is more plausible. It does take the view, however, that the decision to occlude warrants scrutiny and better understanding. Moreover, how one understands the motive behind the decision to occlude will be revealing in the context of any rendered ethical analysis of NRP. Indeed, for the proponent of NRP, for whom the initial declaration of death based on circulatory criteria should be unquestionably trusted and therefore never second-guessed, intent is what governs the analysis and the perspective that the DDR is not violated.⁹⁷ That all parties have agreed that death is an inevitability, and that nothing should be done to undo this, takes precedence. While these intentions are undoubtedly sincere, they are a problematic defense against those who see NRP as a work-around to the DDR. Skeptics may argue that declaring the patient dead on the basis of the permanent loss of cardiorespiratory function is misleading, since that function is immediately restored, clearly showing that its loss was not permanent, nor irreversible.⁹⁸ Similarly, while proponents clearly do not intend to restore brain perfusion with ECMO, this is at least a theoretical possibility, and promises to terminate the procedure if this were to occur, can be alarming in the views of skeptics. Finally, proponents also allude to the near certainty that these patients will become brain dead, if they are not already, without acknowledging that brain death is a complex

⁹⁷ Parent, Brendan., et al. "Response to American College of Physician's statement on the ethics of transplant after normothermic regional perfusion." *American Journal of Transplantation* 22, no. 5 (2022), 1307-1310. doi:10.1111/ajt.16947.

⁹⁸ DeCamp, Matthew, Lois Snyder Sulmasy, and Joseph J. Fins. "POINT: Does Normothermic Regional Perfusion Violate the Ethical Principles Underlying Organ Procurement? Yes." *Chest* 162, no. 2 (2022), 288-290. doi:10.1016/j.chest.2022.03.012.

diagnosis that can only be made over a course of at least several hours.⁹⁹ From the perspective of one who has concerns about any taken human action which might impact the reliability upon which death criteria are invoked, more attention should be paid to compliance with the principle of “do no harm,” in which case right intent (like informed decision making), is a necessary, but not sufficient, element in the ethical analysis. Intent does not have overriding priority in the ethical analysis.

On the role of intention and justifying ligation through cautiousness, Glazier/Capron consider that “the legal standard for determining death is bare of intent: a patient is dead when circulation neither can nor will resume. That the patient is in a state where meaningful existence is not possible, that trying to induce spontaneous resumption of circulation would be futile, or even that the NRP protocol is consistent with the donor's wishes, are all irrelevant to whether the patient is deceased under US law, which turns on the person's physical condition not on anyone's intention.”¹⁰⁰

On the question of harm to the donor: potential for harm to the donor stems from being uncertain if occluding the arch vessels is sufficient to prevent blood flow to the brain and ensure that the donor is insensate. This should be tested for, and more studies to confirm that NRP donors are insensate are needed.¹⁰¹

Additional potential harms to public trust and dissenting healthcare providers are described under “utility” (page 20).

Respect for Persons

The ethical principle of respect for persons includes the belief that people with decision making ability should be allowed to make important, personal decisions for themselves, so long as those decisions do not impose harm to others. “This principle embraces the moral requirements of honesty and fidelity to commitments made, and respect for autonomy.”¹⁰² With NRP, the ethical principle of respect for persons suggests we have a duty to honor the potential donor’s first-person authorization for donation for ante-mortem interventions required for donation to occur.

Respect for persons requires honoring the potential donor’s and their family’s preferences for receiving information about NRP, as well as the intentions and wishes to become a donor, and to make the best possible use of this donation. Moreover, respect for persons acknowledges the importance of donor families in acting as surrogate or authorized decision-makers, acting in accordance with the preferences, values, and expectations of donor candidate patients. In this vein, some consider that NRP promotes autonomy.

⁹⁹ Wall, Anji E., et al. "Applying the ethical framework for donation after circulatory death to thoracic normothermic regional perfusion procedures." *American Journal of Transplantation* 22, no. 5 (2022), 1311-1315. doi:10.1111/ajt.16959.

¹⁰⁰ Glazier, Alexandra K., and Alexander M. Capron. "Normothermic regional perfusion..." *American Journal of Transplantation* 22, no. 5 (2022), 1289-1290. doi:10.1111/ajt.17002.

¹⁰¹ There is currently one available paper that found no cerebral blood flow in two human donors when ligation of arteries occurred during NRP. These data are promising, but the Committee considers more robust data are needed to confirm its implications. Reference: Frontera J., Lewis A., James L., Melmed, K., Parent, B., Raz, E., Hussain, S., Smith, D., Moazami, N., “Thoracoabdominal Normothermic Regional Perfusion in Donation after Circulatory Death Does Not Restore Brain Blood Flow.” *J Heart Lung Transplant*. 2023 May 19;S1053-2498(23)01862-4. doi: 10.1016/j.healun.2023.05.010. Online ahead of print.

¹⁰² OPTN Ethics Committee. *Ethical Principles...* OPTN, 2015. <https://optn.transplant.hrsa.gov/professionals/by-topic/ethical-considerations/ethical-principles-in-the-allocation-of-human-organs/>.

Striking this balance is difficult. The analysis acknowledges the considerable expertise OPOs bring to these conversations and strongly supports the work that they do in delicately tailoring conversations to meet the needs of particular donor families. This paper supports being sensitive and responsive to the individual information needs of particular families, and supports not presenting them with information they have asked not to be shared with them. As part of the shared decision-making process, the analysis encourages engaging with donor families to clarify their preferences for learning more about NRP.

However, concern for overwhelming families in itself doesn't override the responsibility to avoid situations in which families are later distressed to learn information they felt should have been presented to them initially and might have affected their donation decision. Given the paucity of data about public support for NRP, including among different groups and cultural or religious identities, and the unsettled legal implications, the analysis prioritizes the balance between these competing priorities accordingly.

Informed decision making is not equivalent to informed consent, and applies under authorization in the context of organ donation. This process of informed decision making may be similar to how families make decisions about timing of donation and restrictions around type of organs procured. Informed decision making implies that sufficient information about organ donation to make decisions as they pertain to core preferences and values will be provided. On the question of informed decision making, some opine that standards applicable to the authorization process for DCD donation are sufficient, because both TA- and A- NRP uses similar premortem interventions.^{103,104} Yet others, concerned with whether regional restoration of circulation negates the original determination of death, consider crucial differences must be disclosed to potential donors and families regarding recirculation and the potential restoration of any cerebral perfusion.¹⁰⁵ For some, these distinctions are meaningful in a way that may contradict their values and beliefs, and may alter their propensity to participate in NRP. Without sufficient public polling, outreach to communities of different faiths and cultures, etc., it is challenging to know how widely acceptable NRP is, and what elements must be included in informed decision making. Some critics of NRP argue that achieving informed consent or authorization to NRP is simply not possible if ligating arteries constitutes the cause of death, because an individual cannot give consent or authorization for something that causes their death. With these potential exceptions and limitations identified, the following section provides an overview of informed decision making for optimizing respect for persons in conversations with patients and their families who may be approached about organ donation and NRP specifically.

Informed Decision Making

This paper acknowledges the challenges faced by OPOs in approaching potential donors and donor families, and the difficulty in explaining the components needed for informed decision making (for procedures pre- and post-mortem) and balancing the need for adequately informing potential donor patients and families with the understanding that many families, grief-stricken, do not wish to hear

¹⁰³ While there is a difference between informed consent and authorization in this context, without greater information, these differences may be meaningless to members of the general public. This analysis errs on the side of transparency to support maintaining public trust, which is the bedrock of any successful organ donation system.

¹⁰⁴ Parent, Brendan, et al. "Ethical and logistical concerns..." *American Journal of Transplantation* 20, no. 6 (2020), 1508-1512. doi:10.1111/ajt.15772.

¹⁰⁵ American College of Physicians. Ethics, Determination of Death, and Organ Transplantation in Normothermic Regional Perfusion (NRP) with Controlled Donation after Circulatory Determination of Death (cDCD): American College of Physicians Statement of Concern. American College of Physicians, 2021.

details of these procedures. To uphold commitments to autonomy, and to maintain public trust in the organ donation and transplant system, it is critical to be transparent about methods used to facilitate organ donation and facilitate an informed decision-making process with the donor and/or surrogate decision maker. Transplant professionals should avoid evasive and paternalistic attitudes toward bereaved family members that preclude sharing of information and instead focus on an informed decision making process with clear goals for upholding transparency, respect for the rights and interests of the donor and/or their surrogate decision maker, and good stewardship of gifted organs.^{106,107} This is especially true for NRP, as feelings regarding this specific procedure may differ from other more established forms of organ procurement. More research is needed to better articulate these.

The basis for informed decision making for NRP, rests on the foundational principles of authorization for DCD, which include, among other things:

1. Informed decision making for ante-mortem procedures and authorization for post-mortem procedures must be obtained. The potential donor's clinical care team and OPO staff obtaining this permission should be "capable of disclosing information accurately, interacting compassionately with grieving families, and answering all relevant questions... optimal requestors will be those persons who are able to be transparent and are best able to relay information to families in a comprehensive, compassionate, and even-handed manner."¹⁰⁸
2. Ideally, the trained requestor for potential donation is a member of the OPO staff with specific training and education to support conversations about NRP with donor family members and hospital staff.¹⁰⁹
3. "If patients have provided first-person consent for organ donation, those obtaining consent from surrogates for ante-mortem procedures ... should consider using language that frames the conversation around a default assumption of donation."¹¹⁰ If the donor family declines ante-mortem interventions that may be necessary for NRP, options for proceeding with standard DCD should be discussed.
4. Authorization from potential donor or surrogate decision maker must be obtained for ante-mortem interventions to maximize transplantable organs as part of the consent for donation.¹¹¹

¹⁰⁶ Bauchner, H. "What have we learnt from the Alder Hey affair?" *BMJ* 322, no. 7282 (2001), 309-310. doi:10.1136/bmj.322.7282.309.; American Society of Transplantation. "Guidelines Regarding Communication to Donor Families in Cases Where Normothermic Regional Perfusion (NRP) is Planned." AST. Last modified August 12, 2022. www.myast.org/sites/default/files/DTO%20COP_NRP%20Guidance_final%20%281%29.pdf.

¹⁰⁷ Gries, Cynthia J., et al. "An Official American Thoracic Society/International Society for Heart and Lung Transplantation/Society of Critical Care Medicine/Association of Organ and Procurement Organizations/United Network of Organ Sharing Statement: Ethical and Policy Considerations in Organ Donation after Circulatory Determination of Death." *American Journal of Respiratory and Critical Care Medicine* 188, no. 1 (2013), 103-109. doi:10.1164/rccm.201304-0714st.

¹⁰⁸ Gries, Cynthia J., et al. "An Official ... Statement: Ethical and Policy Considerations in Organ Donation after Circulatory Determination of Death." *American Journal of Respiratory and Critical Care Medicine* 188, no. 1 (2013), 103-109. doi:10.1164/rccm.201304-0714st.

¹⁰⁹ Parent, Brendan, et al. "Ethical and logistical concerns for establishing NRP-cDCD heart transplantation in the United States." *American Journal of Transplantation* 20, no. 6 (2020), 1508-1512. doi:10.1111/ajt.15772.

¹¹⁰ Gries, Cynthia J., et al. "An Official ... Statement: Ethical and Policy Considerations in Organ Donation after Circulatory Determination of Death." *American Journal of Respiratory and Critical Care Medicine* 188, no. 1 (2013), 103-109. doi:10.1164/rccm.201304-0714st.

¹¹¹ American Society of Anesthesiologists. *Statement on Controlled Organ Donation After Circulatory Death*. American Society of Anesthesiologists, 2022. <https://www.asahq.org/standards-and-guidelines/statement-on-controlled-organ-donation-after-circulatory-death>.

These include heparin administration, bronchoscopy, liver biopsy, placement of cannulae, prep and drape of the donor, and transport to a separate location or operating room for recovery as applicable.¹¹²

5. The requestor must include an explanation of the hands-off period after circulatory cessation.

In addition to the elements of informed decision making included for a DCD recovery as described above, NRP raises questions about the need to disclose additional information about the recovery procedure. Recommendations for NRP include a reiteration of the purpose and function of the hands-off waiting period, as well as a description of the steps of the procurement procedure.¹¹³ For TA-NRP, this includes the ligation of vessels to prevent cerebral circulation and the reperfusion of targeted organs before they are removed from the body. Disclosure for TA-NRP should also include a statement that heart function may be restored to provide blood flow to organs.¹¹⁴ Both TA- and A- NRP should include informed decision-making discussions that identify the potential restoration of any cerebral perfusion.

Experienced requestors understand that the needs and preferences of donor family members and surrogate decision makers may be different based on the unique circumstances of each case. The informed decision-making process for organ donation has the obligation to refrain from burdening the donor family during their time of suffering any more than is absolutely necessary. Information must be clear and easy to understand to meet legal standards including whether the proposed protocol is understood and whether justification for failure to disclose risk is acceptable.¹¹⁵ Considering strongly held beliefs in the transplant community regarding the ethical, moral, and legal ramifications of NRP, it is especially critical that the potential donor family be educated about the unique procedures associated with NRP.

Although OPOs must abide with consideration for not burdening donor families with unnecessary or unwanted details, the ethical principle of respect for persons supports giving the surrogate decision maker the option to opt out of detailed information about the recovery procedure, while requiring that some key pieces of information are always explained. In the case of NRP, this likely includes describing clearly that although the donor is declared dead by circulatory death criteria, circulation will be restored regionally (A-NRP) and this may include the heart (TA-NRP), at a time the patient donor has not been assessed to meet the criteria for brain death. It may be especially important in the case of NRP to provide comprehensive support to donor families following the donation event, such that if questions or concerns about the recovery method arise after the fact, donor families have access to information and support. The analysis acknowledges that in rare circumstances the potential donor's surrogate may decline, after serious efforts are undertaken, to hear the information that will ensure Informed decision making is provided. Such "noninformed decision making" should be fully documented and should not

¹¹² Gries, Cynthia J., et al. "An Official ... Statement: Ethical and Policy Considerations in Organ Donation after Circulatory Determination of Death." *American Journal of Respiratory and Critical Care Medicine* 188, no. 1 (2013), 103-109. doi:10.1164/rccm.201304-0714st.

¹¹³ Entwistle, John W., et al. "Normothermic regional perfusion: Ethical issues in thoracic organ donation." *The Journal of Thoracic and Cardiovascular Surgery* 164, no. 1 (May 2022), 147-154. doi:10.1016/j.jtcvs.2022.01.018.

¹¹⁴ American Society of Transplantation. "Guidelines Regarding Communication to Donor Families in Cases Where Normothermic Regional Perfusion (NRP) is Planned." AST. Last modified August 12, 2022. www.myast.org/sites/default/files/DTO%20COP_NRP%20Guidance_final%20%281%29.pdf.

¹¹⁵ Showalter, Stuart J. *The Law of Healthcare Administration*, 9th ed. Chicago: Health Administration Press, 2020. NCh. p. 411

preclude proceeding with the NRP protocol.¹¹⁶ Requestor training should specifically include these elements.

This paper strongly recommends that local hospitals' ethics committees review NRP practices to promote and support transparency within the surrounding community. A clear process for anonymous reporting of complaints or concerns by staff should be developed. In rare occasions potential donors may be moved to another hospital or to an OPO recovery center, if the donor care unit is within a licensed hospital. It is especially important in such instances that informed decision making, including review of the NRP procedure, occurs prior to any transfer of a potential donor. Another consideration relevant to transfers is assurance of local ethics committee review, which may be more challenging for smaller hospitals.

Uncontrolled NRP

Uncontrolled scenarios are those in which circulatory death occurs unexpectedly, not after the planned withdrawal of life support.¹¹⁷ While the process of organ recovery following the decision for donation is largely the same in uncontrolled NRP as in controlled NRP (hands-off period, occlusion of vessels, and so on), uncontrolled NRP presents additional ethical concerns related to respect for persons and non-maleficence.¹¹⁸

The transition between living patient and organ donor in uncontrolled NRP is rapid and potentially confusing for both potential donor families and clinical teams. This raises concerns about compressed timing and difficulty of informed consent discussions with potential donor families. Putting potential donor families in a situation where they do not fully understand the implications of what they are consenting to is extremely risky.

The potential for teams to make decisions that do not fully honor respect for persons or potentially cause harm is greater given the rapidity and urgency of uncontrolled settings. Trust in clinical teams and in donation processes are a cornerstone to the organ transplantation system. There is a greater potential for harm or concern for autonomy where there is a lack of procedures and protocols to ensure safety and maintain trust. The transplant community owes itself and the general public assurance that no harm will occur and respect for persons is maintained. The potential for harm is greater in uncontrolled scenarios, and additional caution should be reflected accordingly.

Utility

Utility is a foundational principle that guides the United States' transplant system. Applied to organ donation and allocation, utility "specifies that allocation should maximize the expected net amount of overall good (that is, good adjusted for accompanying harms), thereby incorporating the principle of beneficence (do good) and the principle of non-maleficence (do no harm)."¹¹⁹

¹¹⁶ Sade, Robert M. "A Noninformed Patient Consents to Cardiac Surgery." *The Annals of Thoracic Surgery* 108, no. 6 (2019), 1605-1606. doi:10.1016/j.athoracsur.2019.06.009.

¹¹⁷ Dunne, Kathryn., Doherty, Pamela. "Donation after circulatory death." *Continuing Education in Anaesthesia Critical Care & Pain*, Volume 11, Issue 3, June 2011, Pages 82-86, <https://doi.org/10.1093/bjaceaccp/mkr003>

¹¹⁸ Wu, Diana A., and Gabriel C. Oniscu. "Piloting Uncontrolled DCD Organ Donation in the UK; Overview, Lessons and Future Steps." *Current Transplantation Reports* 9, no. 4 (2022), 250-256. doi:10.1007/s40472-022-00374-1.

¹¹⁹ OPTN Ethics Committee. *Ethical Principles...* OPTN, 2015. <https://optn.transplant.hrsa.gov/professionals/by-topic/ethical-considerations/ethical-principles-in-the-allocation-of-human-organs/>.

Potential Increases to Utility

NRP is a promising development in the field of organ transplantation, since it has the potential to substantially improve both the number and the quality of organs that are available for transplantation, and in particular for the heart, which may be difficult to effectively procure by standard DCD donation.¹²⁰ The number of organs would likely be increased by enabling the transplantable organs to be resuscitated in situ, such that otherwise unusable organs could become transplantable. Similarly, in situ resuscitation has the potential to increase the function and the quality of the organs before they are removed for transplantation, which should improve graft function and survival in the long run.¹²¹

Preliminary data are promising, but contingent on further evidence. Initial studies show there is an overall increase in the average number of organs transplanted per donor with NRP compared to controlled DCD (cDCD) (3.3 versus 2.6).¹²² Specifically, TA-NRP is positively associated with hearts being recovered and available for transplant, and has been successfully performed with triple organ transplants and pediatric heart transplants.^{123,124,125,126,127} A study showed NRP may improve utilization of livers that had been previously declined.¹²⁸

Some data show potential for improved outcomes and graft survival. For livers procured through NRP, decreased rates of early allograft dysfunction, 30-day graft loss, ischemic cholangiopathy, and anastomotic strictures were found compared to cDCD livers; A-NRP shows positive results in preventing

¹²⁰ Miñambres, Eduardo, Mario Royo-Villanova, and Beatriz Domínguez-Gil. "Normothermic Regional Perfusion Provides a Great Opportunity to Maximize Organ Procurement in Donation After the Circulatory Determination of Death." *Critical Care Medicine* 50, no. 11 (2022), 1649-1653. doi:10.1097/ccm.0000000000005645.

¹²¹ Ibid.

¹²² Oniscu, Gabriel C., et al. "Improved Organ Utilization and Better Transplant Outcomes With In Situ Normothermic Regional Perfusion in Controlled Donation After Circulatory Death." *Transplantation* 107, no. 2 (2023), 438-448. doi:10.1097/tp.0000000000004280.

¹²³ Messer, Simon., et al. "Outcome after heart transplantation from donation after circulatory-determined death donors." *Journal of Heart and Lung Transplant* 36, no. 12 (October 2017), 1311-1318. doi: 10.1016/j.healun.2017.10.021.

¹²⁴ Kwon, J. H., Usry, B., Hashmi, Z. A., Bhandari, K., Carnicelli, A. P., Tedford, R. J., Welch, B. A., Shorbaji, K., & Kilic, A. (2023). Donor utilization in heart transplant with donation after circulatory death in the United States. *American Journal of Transplantation*. <https://doi.org/10.1016/j.ajt.2023.07.019>

¹²⁵ Kagawa, H., Goodwin, M., Stehlik, J., Campsen, J., Baker, T., & Selzman, C. (2023). A case report of triple organ transplantation from a donor after circulatory death using thoraco-abdominal Normothermic regional perfusion. <https://doi.org/10.2139/ssrn.4464191>

¹²⁶ Beckerman, Z., Overbey, D., Bryner, B. S., Schroder, J. N., Andersen, N. D., Carboni, M. P., Casalinova, S., & Turek, J. W. (2023). Infant heart transplant following donation after circulatory death using normothermic regional perfusion and distant transport, first reported case in North America. *JTCVS Techniques*, 20, 156-157. <https://doi.org/10.1016/j.xjtc.2023.04.001>

¹²⁷ Biniwale, R., Lahar, S., Balasubramanya, S., Caraccio, C., Ngang, B., Barone, H., Stimpson, E., Dela Cruz, K., Alejos, J. C., Williams, R., Halnon, N., Reardon, L., Si, M., Shemin, R., Ardehali, A., & Van Arsdell, G. (2023). Pediatric heart transplantation from donation after circulatory death using normothermic regional perfusion and cold storage from a distant donor: First US experience. *JTCVS Techniques*, 20, 158-161. <https://doi.org/10.1016/j.xjtc.2023.05.010>

¹²⁸ Schurink, I. J., De Goeij, F. H., Habets, L. J., Van de Leemkolk, F. E., Van Dun, C. A., Oniscu, G. C., Alwayn, I. P., Polak, W. G., Huurman, V. A., & De Jonge, J. (2022). Salvage of declined extended-criteria DCD livers using in situ Normothermic regional perfusion. *Annals of Surgery*, 276(4), e223-e230. <https://doi.org/10.1097/sla.0000000000005611>

ischemic type biliary lesions.^{129,130,131} Compared with static cold storage, NRP shows improved outcomes for liver transplants.¹³² Research has also shown decreased delayed graft function (DGF), decreased 1-year graft loss, and improved 12-month kidney function for NRP kidneys compared to cDCD kidneys.¹³³ NRP kidneys are also associated with lower DGF compared to cold perfusion techniques.¹³⁴ One area that the transplant community should monitor closely is the impact on lung utilization. There are some data suggesting positive outcomes for lungs and heart-lungs procured with NRP.^{135,136,137} However, there is concern about lower utilization of lungs when NRP is the procurement method.¹³⁸ While initial data suggest that heart, liver, and kidney utilization are positively impacted by NRP, further research should clarify how lungs are impacted.

NRP may also increase utility for donor families, who may receive comfort from the knowledge that their loved one was able to save a greater number of lives with fewer complications. As previously noted, data on public attitudes toward NRP are limited. However, it is known that families experience psychosocial distress when their loved one is a DCD donor whose death does not occur in time to allow the donation of organs.¹³⁹ Other studies suggest that the public is open to expanding donor protocols

¹²⁹ Watson, Christopher J., et al. "In situ normothermic perfusion of livers in controlled circulatory death donation may prevent ischemic cholangiopathy and improve graft survival." *American Journal of Transplantation* 19, no. 6 (2019), 1745-1758. doi:10.1111/ajt.15241

¹³⁰ Durán, M., Calleja, R., Hann, A., Clarke, G., Ciria, R., Nutu, A., Sanabria-Mateos, R., Ayllón, M. D., López-Cillero, P., Mergental, H., Briceño, J., & Perera, M. T. (2023). Machine perfusion and the prevention of ischemic type biliary lesions following liver transplant: What is the evidence? *World Journal of Gastroenterology*, 29(20), 3066-3083. <https://doi.org/10.3748/wjg.v29.i20.3066>

¹³¹ Schurink, I. J., De Goeij, F. H., Habets, L. J., Van de Leemkolk, F. E., Van Dun, C. A., Oniscu, G. C., Alwayn, I. P., Polak, W. G., Huurman, V. A., & De Jonge, J. (2022). Salvage of declined extended-criteria DCD livers using in situ Normothermic regional perfusion. *Annals of Surgery*, 276(4), e223-e230. <https://doi.org/10.1097/sla.0000000000005611>

¹³² Liang, A., Cheng, W., Cao, P., Cai, S., Zhang, L., Zhong, K., & Nie, Y. (2023). Effects of machine perfusion strategies on different donor types in liver transplantation: A systematic review and meta-analysis. *International Journal of Surgery*. <https://doi.org/10.1097/js9.0000000000000661>

¹³³ Padilla, Maria. "Improved short-term outcomes of kidney transplants in controlled donation after the circulatory determination of death with the use of normothermic regional perfusion." *American Journal of Transplantation* 21, no. 11 (May 2021), 2618-3628. <https://doi.org/10.1111/ajt.16622>.

¹³⁴ Ghoneima, A. S., Sousa Da Silva, R. X., Gosteli, M. A., Barlow, A. D., & Kron, P. (2023). Outcomes of kidney perfusion techniques in transplantation from deceased donors: A systematic review and meta-analysis. *Journal of Clinical Medicine*, 12(12), 3871. <https://doi.org/10.3390/jcm12123871>

¹³⁵ Gomes, B., Ribeiro, R., Alvarez, J., Ribeiro, R., Honjeu, A., Gazzalle, A., Bissoondath, V., Yu, F., Adamson, M., Meineri, M., Rao, V., Badiwala, M., Keshavjee, S., & Cypel, M. (2020). Normothermic regional perfusion (NRP) during heart DCD recovery: Is lung quality impacted? A pre-clinical study. *The Journal of Heart and Lung Transplantation*, 39(4), S353-S354. <https://doi.org/10.1016/j.healun.2020.01.415>

¹³⁶ Tanaka, S., Campo-Canaverall de la Cruz, J., & Crowley Carrasco, S. (2020). Effect on the donor lungs of using abdominal normothermic regional perfusion in controlled donation after circulatory death. *European Journal of Cardio-Thoracic Surgery*, 59(2), 359-366. <https://doi.org/10.1093/ejcts/ezaa398>

¹³⁷ Spencer, P. J., Saddoughi, S. A., Choi, K., Dickinson, T. A., Richman, A., Reynolds, F. A., & Villavicencio, M. A. (2023). Heart-lung transplantation from donation after circulatory death using mobile Normothermic regional perfusion. *ASAIO Journal*. <https://doi.org/10.1097/mat.0000000000002029>

¹³⁸ Francois, S., Popa, S., Shaver, C., Mallea, J., Hartwig, M., Patel, Y., Tucker, W., Zofkie, B., Shelton, R., Benjamin, J., Brown, A., & Bacchetta, M. (2023). (1234) comparison of lung utilization from nrp-dcd vs non-nrp Dcd using Evlp. *The Journal of Heart and Lung Transplantation*, 42(4), S527. <https://doi.org/10.1016/j.healun.2023.02.1444>

¹³⁹ Taylor, Lauren J., et al. "Harms of unsuccessful donation after circulatory death: An exploratory study." *American Journal of Transplantation* 18, no. 2 (2018), 402-409. doi:10.1111/ajt.14464.

(imminent death donation) in a way that maximizes the chance that a donor will be able successfully donate.¹⁴⁰

Potential to decrease utility

Although NRP may benefit utility by saving more lives, decreasing post-transplant morbidity, and providing comfort to donor families, there is also a potential for it to adversely impact donor families and public trust.

If a potential donor or donor family does not fully understand NRP and subsequently had concerns about the process, they could experience psychosocial distress. The potential to exacerbate psychological distress, regret, grief, and loss of trust among donor families presents a weighty consideration, and one that must be considered and addressed before proceeding with NRP. Practices to ensure that sufficient information is given, received, and understood must be in place to reduce potential harm to donor families.

Potential Harm to Public Trust

Loss or decline in public trust in organ transplantation may be a direct harm of NRP. This harm may be amplified given the current societal challenges regarding misinformation of scientific and health information.¹⁴¹ While loss of trust in the organ donation process is a harm in itself, it may also have a secondary effect of decreasing the number of people willing to consent to deceased or living donation. Additionally, given the lack of consensus among leading legal scholars about the legality of NRP, the potential for lawsuits associated with potential DDR and UDDA violations could further magnify the public relations challenge of sustaining public support for the mission of organ procurement and transplantation.¹⁴² These lawsuits may not only undermine public support, but they may also strain the transplant system and community in response.

Moral distress among transplant clinicians

The ethical and legal concerns described above have raised concerns among clinicians and other health care providers, including some clinicians at centers that perform NRP, that can be characterized as moral distress: the perception that a clinician must engage in an action as part of their clinical role that they believe to be morally wrong.¹⁴³ In the absence of greater clarity from the UDDA, and without better

¹⁴⁰ Washburn, Laura., et al. "Survey of public attitudes towards imminent death donation in the United States." *American Journal of Transplantation* 21, no. 1 (2021), 114-122. doi:10.1111/ajt.16175.; Zimmermann, Christopher J., et al. "Family and transplant professionals' views of organ recovery before circulatory death for imminently dying patients: A qualitative study using semistructured interviews and focus groups." *American Journal of Transplantation* 19, no. 8 (2019), 2232-2240. doi:10.1111/ajt.15310.

¹⁴¹ West., J., Bergstrom, C., "Misinformation in and about science." *Proc Natl Acad Sci U S A*. 2021 Apr 13; 118(15): e1912444117. Published online 2021 Apr 9. doi: 10.1073/pnas.1912444117. Swire-Thompson, B., Lazer, D., "Public Health and Online Misinformation: Challenges and Recommendations." *Annu Rev Public Health*. 2020 Apr 2;41:433-451. doi: 10.1146/annurev-publhealth-040119-094127. Epub 2019 Dec 24.

¹⁴² Glazier, Alexandra K., and Alexander M. Capron. "Normothermic regional perfusion..." *American Journal of Transplantation* 22, no. 5 (2022), 1289-1290. doi:10.1111/ajt.17002.; Adams, Bradley L., et al. "cDCDD-NRP is consistent with US legal standards for determining death." *American Journal of Transplantation* 22, no. 10 (2022), 2302-2305. doi:10.1111/ajt.17083.

¹⁴³ Le Dorze, Matthieu., et al. "'A Delicate balance'—Perceptions and Experiences of ICU Physicians and Nurses Regarding

understanding the scope and extent of potential harms particularly to the potential donors (pre-mortem) and of donor families, either by virtue of the NRP procedure itself, or merely by not sufficiently informing the potential donor patient and family of the ethically salient distinctions imposed by NRP, these clinicians may suffer moral injury. A number of clinicians have reached out to members of the NRP Workgroup and Ethics Committee to express their concerns about NRP.¹⁴⁴ These concerns were often related privately, and there are not public data on clinician attitudes on NRP particularly within the United States. It is also important to acknowledge, in the interest of being able to help patients in need and respect donors, some clinicians and other health care providers expressed during public comment that they may feel moral distress at not being able to perform NRP and avoid non-utilization of an organ.

Conclusions

NRP presents a promising and exciting technology that has potential to increase the number of transplantable organs and the quality of these organs. Undoubtedly, this is a worthy and important goal. As with all new technologies, consideration for how the technology can be implemented ethically is critical to its widespread adoption and acceptance by the public.

The OPTN shares the enthusiasm of the transplant community in developing and implementing solutions to improve the transplant system and reduce wait times and deaths for patients awaiting organ transplantation. This analysis also affirms the sacred trust and commitment of the transplant community to organ donors and donor families. Finally, the paper underscores that the transplant community is entrusted to preserve and foster public trust and support in organ donation through ensuring donation procedures that are ethical and transparent.

It is with these commitments and understandings, and based on the analysis described herein, that this paper concludes that:

- There are serious ethical concerns that NRP is not consistent with the Dead Donor Rule. There may be differences in the degree to which these ethical concerns apply to A-NRP versus TA-NRP.
- Nonmaleficence must not be violated in the pursuit of NRP, even if positive utility outcomes could result.
- Consistent and transparent protocols, including adequate informed decision making with patients (pre-mortem) and of families approached about donation, are necessary pre-conditions for any ethical pursuit of NRP.
- Uncontrolled scenarios for any form of NRP should not be performed at this time because of added concern regarding nonmaleficence and respect for person

Controlled Donation After Circulatory Death. A Qualitative Study." *Transplant International* 35 (2022). doi:10.3389/ti.2022.10648.

¹⁴⁴ Summaries of the Committee's deliberations are available here: <https://optn.transplant.hrsa.gov/about/committees/ethics-committee/>

Addendum

Addendum: The Uniform Determination of Death Act and NRP

This white paper concerns the ethics of NRP and does not purport to provide an opinion on the legality of NRP in any U.S. state, a topic outside the committee's charge. At the same time, given that the Uniform Determination of Death Act (UDDA) is currently being considered for revision,¹⁴⁵ it is important to at least briefly discuss the implications of the current text of the UDDA and its possible revisions for NRP.

What is the UDDA?

The UDDA is a uniform act promulgated by the Uniform Law Commission (ULC). The UCL, also known as the National Conference of Commissioners on Uniform State Laws, established in 1892, is made up of a non-partisan group of experts that formulates model legislation in many areas of the law from various fields of law.¹⁴⁶ The process also pushes the individual states towards uniformity, a goal that is particularly important in areas like the determination of death because "[a]n individual should not be simultaneously dead and alive pursuant to the laws of two different states. It should not be possible to 'statutorily resurrect' a person from state A merely by applying law of state B."¹⁴⁷ The other uniform law that is most relevant to organ donation is the Uniform Anatomical Gift Act.¹⁴⁸

The UDDA specifically traces its origin to 1978, when Congress enacted legislation creating the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, which had as part of its charge study "the matter of defining death, including the advisability of developing a uniform definition of death."¹⁴⁹ It produced a report and draft legislation (in consultation with American Medical Association (AMA) and American Bar Association (ABA)) and recommended that all states adopt it.

The UDDA provides that: "An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead. A determination of death must be made in accordance with accepted medical standards."¹⁵⁰

Many states have adopted the UDDA, albeit some with modification. "As of 2016, the UDDA had been adopted by 38 states, either word for word or with similar wording. Another nine states had adopted the UDDA, but with an express qualification that the neurological criteria for death could be

¹⁴⁵ The Drafting Committee to Revise the Uniform Determination of Death Act, a Committee of the Uniform Law Commission, was previously meeting to determine if revisions to the UDDA were appropriate.

¹⁴⁶ "About Us - Uniform Law Commission." Uniform Law Commission. <https://www.uniformlaws.org/aboutulc/overview>.

¹⁴⁷ Ariane Lewis, Richard J. Bonnie, Thaddeus Pope, Leon G. Epstein, David M. & Greer, Matthew P. Kirschen, Michael Rubin, James A. Russell, Determination of Death by Neurologic Criteria in the United States: The Case for Revising the Uniform Determination of Death Act, 47 J.L. Med. & Ethics 9, 11. 2019.

¹⁴⁸ National Conference of Commissioners on Uniform State Laws. *Anatomical Gift Act*. 2006.

¹⁴⁹ President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, 42 USC, 1981.

¹⁵⁰ National Conference of Commissioners on Uniform State Laws. *Uniform Determination of Death Act*. 1980.

used only where an individual's respiratory and circulatory functions were maintained by artificial means."¹⁵¹

What Implications Does the UDDA have for NRP?

The meaning of the term “irreversible” in the UDDA has long been contested and at least some of the debate as to whether NRP is in tension with the UDDA turns on how the term is understood.

Alexandra Glazier and Alex Capron read the wording so as to make at least some forms of NRP incompatible with the UDDA. As they write: “For years the term ‘irreversible’ (cannot be changed) has been interpreted as ‘permanent’ (will not change). Accordingly, an individual is dead under US law when circulation has ceased and will not return through either autoresuscitation or medical intervention.”¹⁵² They then respond to an argument that this proves too much because the same might be said of DCD by arguing that with NRP “after death is declared, circulation resumes with artificial support” and that this “contradicts the legal requirement that death depends on circulation having permanently ceased.”¹⁵³

By contrast, Les James et al. argue that irreversibility as defined by the Uniform Determination of Death Act specifically relates to the function of the organ within the person: “After an organ has lost the ability to function within the organism, electrical and metabolic activity at the level of individual cells or even groups of cells may continue for a period of time.”¹⁵⁴ During NRP, the organs’ inability to function within the organism was confirmed with the determination of death. The [views of their opponents] mistakenly applies a rigid and impractical conception of irreversibility to NRP, without recognizing that the same conception would undermine most determinations of death. If we support determinations of death in accordance with accepted medical standards, then we should accept that NRP respects nonmaleficence, because it causes no harm to individuals.¹⁵⁵

Matthew DeCamp, Joseph J. Fins, and Lois Synder Sulmasy in turn criticize these authors for insisting that the:

“pronouncement of death, biologic reality notwithstanding, is what makes someone dead and that this declaration is sufficient to permit organ procurement. They misunderstand and misapply basic ethical principles and US law.

. . . James et al suggest NRP is no different than standard donation after circulatory determination of death (DCD). Their text proves our point by describing, yet not acknowledging, the morally salient differences between standard DCD and NRP. Instead of using cold perfusate before explantation, NRP restarts the circulation of warm blood that stopped moments before. Recognizing the alarming fact that this will restart brain circulation, active steps are taken to ensure brain death, improperly shifting lanes from circulatory death to brain death. But brain

¹⁵¹ Klein, Daniel. Uniform Determination of Death Act. American Law Reports, 7th Edition, Art. 5, 2020.

¹⁵² Glazier, Alexandra K., and Alexander M. Capron. "Normothermic regional perfusion..." *American Journal of Transplantation* 22, no. 5 (2022), 1289-1290. doi:10.1111/ajt.17002.

¹⁵³ Ibid.

¹⁵⁴ James, Les, Brendan Parent, Nader Moazami, and Deane E. Smith. "Rebuttal From Dr James et al." *Chest* 162, no. 2 (2022), 293-294. doi:10.1016/j.chest.2022.03.013.

¹⁵⁵ Ibid.

death could not possibly be declared based on the timeframe and existing requirements for doing so.”¹⁵⁶

They further argue that: “The technical details of NRP can obfuscate the straightforward point that a person is not dead based solely on a declaration. Consider a counterexample: In standard DCD, after a 5-min “hands-off period,” death is declared. But what if, just before explantation, autoresuscitation occurs, and the heart restarts (a known phenomenon)?¹⁵⁷ Would explantation proceed? It should not. Was this patient dead, then raised from the dead? No. What happened proved the prior declaration wrong. The patient was not dead. Restarting circulation invalidated the prior declaration of death. Likewise in NRP.”¹⁵⁸

A major part of the debate concerns the relevance of the intention of the transplant team in performing NRP. One argument is that even when NRP restores circulation, the transplant team is not attempting to resuscitate because that would be medically ineffective and its sole goal is to preserve the organs, such that this does not reverse the loss of function (or otherwise put the loss of function remains permanent). The same is true of the individual who has authorized organ donation, they intend any restoration of circulation solely for the purpose of maintaining the viability of the organs not for resuscitation and this should not disturb the conclusion that function has been irreversibly (or permanently) lost.

Glazier and Capron respond by drawing a distinction between the ethical significance of intention versus its legal significance (or lack thereof) under the UDDA.¹⁵⁹ They argue that:

“Although intentions may be important when evaluating the ethical acceptability of physicians’ actions, the legal standard for determining death is bare of intent: a patient is dead when circulation neither can nor will resume. That the patient is in a state where meaningful existence is not possible, that trying to induce spontaneous resumption of circulation would be futile, or even that the NRP protocol is consistent with the donor’s wishes, are all irrelevant to whether the patient is deceased under US law, which turns on the person’s physical condition not on anyone’s intention.”¹⁶⁰

A further complication in assessing what the UDDA means for NRP is the circulation of blood flow to the brain. Glazier and Capron argue that if an NRP protocol calls for the occluding of the carotids, the transplant team:

“may indeed intend to improve organ viability but it is also true that preventing oxygen from reaching the brain removes the risk that in some DCDD patients the restoration of blood flow to the brain could prompt at least temporary resumption of functions that are inconsistent with either or both the neurological or the circulatory respiratory standard for determining death. An ambitious district attorney might convincingly argue that physicians following the NRP

¹⁵⁶ DeCamp, Matthew, Lois Snyder Sulmasy, and Joseph J. Fins. "POINT: Does Normothermic Regional Perfusion Violate the Ethical Principles Underlying Organ Procurement? Yes." *Chest* 162, no. 2 (2022), 288-290. doi:10.1016/j.chest.2022.03.012.

¹⁵⁷ Hannig, Kjartan E., Rasmus W. Hauritz, and Erik L. Grove. "Autoresuscitation: A Case and Discussion of the Lazarus Phenomenon." *Case Reports in Medicine* 2015 (2015), 1-5. doi:10.1155/2015/724174.

¹⁵⁸ Ibid.

¹⁵⁹ Glazier, Alexandra K., and Alexander M. Capron. "Normothermic regional perfusion..." *American Journal of Transplantation* 22, no. 5 (2022), 1289-1290. doi:10.1111/ajt.17002.

¹⁶⁰ Ibid.

protocol also intended to render irreversible any brain functions that had not permanently ceased, thus ensuring the patient's death."¹⁶¹

As Harry Peled et al. put it "Although it is true that the intent of NRP is to produce permanent cessation of brain circulation, if brain blood flow does occur, the permanence requirement was never met, and therefore, the declaration of death was not valid."¹⁶²

Rendering matters more complicated, not all NRP protocols are the same as to the risk of blood recirculation. As Basmaji et al note that there are two types of NRP:

"abdominal NRP (A-NRP) and thoracoabdominal NRP (TA-NRP). A-NRP supports the liver, kidney, and pancreas, whereas TA-NRP supports the heart, lungs, and abdominal organs. In A-NRP, cannulas are inserted either into the iliac artery and vein or into the abdominal aorta and inferior vena cava, whereas the thoracic aorta is occluded at the level of the diaphragm. In TA-NRP, the cannulas are placed in the right atrium and the iliac artery or abdominal aorta (6). A critical anatomic difference exists between these two NRP modalities: A-NRP excludes blood flow into the thoracic aorta but TA-NRP does not."¹⁶³

They are not the same when it comes to the risk of brain reperfusion:

"Unlike TA-NRP, A-NRP excludes the thoracic aorta from the extracorporeal circuit, preventing collateral flow via the internal thoracic, intercostal, and thoracic spinal arteries. Surgical techniques, such as selective cannulation of the aorta and inferior vena cava as well as manual transection of the lumbar collaterals, eliminate the possibility of collateral flow via the inferior epigastric and lumbar arteries, respectively. Although neither technique "definitively" rules out the possibility of brain reperfusion, A-NRP is the safer modality in this respect."¹⁶⁴

Thus for those for whom the possibility of brain reperfusion is relevant to whether the UDDA's criteria for declaring death have been met, the details of the NRP protocol might matter.

UDDA Revisions

The ULC was considering potential revisions to the UDDA; those discussions have ceased as of September 2023. This paper will not speculate upon any potential future revisions.¹⁶⁵

¹⁶¹ Ibid.

¹⁶² Peled H, Mathews S, Rhodes D, et al. "Normothermic Regional..." *Critical Care Med* 2022;50(11):1644-1648, doi:10.1097/ccm.0000000000005632

¹⁶³ Basmaji, John, et al. "Paving the Road for the Adoption of Normothermic Regional Perfusion in Canada." *Critical Care Explorations* 3, no. 11 (2021), e0553. doi:10.1097/cce.0000000000000553.

¹⁶⁴ Ibid.

¹⁶⁵ The Drafting Committee to Revise the Uniform Determination of Death Act, a Committee of the Uniform Law Commission, was previously meeting to determine if revisions to the UDDA were appropriate.

Appendix A: Relevant Terms and Acronyms

Ethical Terms – Definitions

A priori: knowledge from theoretical deduction, as opposed to from observation or experience

Authorization: The act of giving someone permission to do something on your behalf. Organ donation abides by the Uniform Anatomical Gift Act (UAGA) which permits donation through authorization processes.

Dead donor rule: Organ donors must not be killed by and for organ donation. Not in law directly but embedded within the context of how organ transplantation could be ethically pursued.

Distributive justice: Requires fairness in the distribution of scarce resources so that patients of similar need have an equal opportunity to benefit from transplantation

Informed consent: While donor's decision to donate is governed by UAGA and gift law, informed consent is relevant to donor family members understanding and agreeing to specifics of DCD; similar protocols apply to most NRP programs in obtaining informed consent procedure.

Irreversible: Not able to be undone or altered. Noted in UDDA definition of death; its implications for NRP is whether NRP violates irreversibility by the recirculation of blood.

Non-informed consent: A rare situation where the potential donor's surrogate may decline, after serious efforts are undertaken, to hear the information that will ensure informed consent is provided.

Nonmaleficence: Do no harm. One concern related to NRP is whether the donor could be harmed by the procedure.

Permanent: Lasting or intended to last or remain unchanged indefinitely. Relevance: some have interpreted "irreversible" to be "permanent", which is relevant to determining circulatory death.

Procedural justice: Upholds a commitment to treating like cases similarly, transparently, and predictably

Respect for persons: Respect for autonomy holds that actions or practices tend to be right insofar as they respect independent (without coercion or interference) choices made by individuals, as long as the choices do not impose harm to others. Relevance: upholding autonomy in honoring donor decision to register to become an organ donor.

Utility: The maximization of net benefit to the community (taking into account both the amount of benefit and harm and the probability of such benefit and harm). Utility is often discussed with NRP in the context of improving organ quality and increasing the number of organs procured.

White paper: an authoritative report or guide that informs readers about a complex issue and presents the issuing body's philosophy on the matter. White papers do not change OPTN policy in and of themselves.

Medical Terms - Definitions

Abdominal Aorta: the major artery supplying the vital organs in the human body

Allograft dysfunction: Transplanted organs that are not functioning optimally and may be caused by several donor or recipient-derived mechanisms

Anastomotic strictures: Narrowing of an anastomosis.

Anesthetic: a substance that reduces sensitivity to pain

Angiogram: a medical imaging method that uses X-ray to visualize arteries or veins

Asystole: cessation of all electrical and mechanical activity of the heart

Atrial cannula: a cannula inserted into an artery

Autoresuscitation: a rare phenomenon where there is a delayed unassisted return of spontaneous circulation after medical teams stop CPR or other life support means

Bispectral index (BIS) monitoring: a type of electroencephalogram (EEG) monitoring that assesses brain activity

Brachiocephalic arteries: the arteries that branch off of the aorta and go into the upper chest and brain

Brain death: death based on the absence of all neurologic function to the brain and brainstem

Bronchoscopy: a procedure where an instrument is inserted into the airway through the nose or trachea to allow medical teams to look inside the lungs

Bypass: refers to cardiopulmonary bypass, a procedure that pumps blood into a machine outside the body (heart-lung machine) and allows it to be oxygenated before returning it to the body. This procedure is commonly used in heart and lung surgery

Cannulation: The process of entering a blood vessel with a fabricated instrument to gain access to the blood vessel.

Cardiopulmonary arrest: cessation of heart and lung function (colloquially known as cardiac arrest)

Collateral blood flow: Describes a collateral network of blood vessels that may provide blood flow to an area of the body where the main blood flow is blocked.

Coronary arteries: Main blood flow vessels to the heart.

Critical care team: a group of specially trained medical personnel (including doctors, nurses, and technicians) who care for patients in critical condition, usually in the intensive or critical care unit of a hospital

Distal: further away from

End of life comfort measures: measures taken as part of a patient care plan focused on symptom management and pain relief, and can include anesthetics and social, emotional, and spiritual support measures

Ex vivo: outside the body

Graft loss: when a transplanted organ no longer functions. Definitions vary by organ, but can include graft removal, re-transplant, death, or return to dialysis (for kidney).

Heparin: a medication that inhibits blood clotting, sometimes given to potential donors before declaration of death to reduce the potential that blood clots will present problems in the recovery and transplant process

Imminent death donation: recovery of a living donor organ immediately prior to an impending and planned withdrawal of ventilator support expected to result in the patient's death

Inferior vena cava: the blood vessel that transports deoxygenated blood back from the lower part of the body to the heart for re-oxygenation

Intensivist: a board-certified physician who provides special care for critically ill patients. Also known as a critical care physician, the intensivist has advanced training and experience in treating this complex type of patient.

Intra-abdominal organs: the spleen, stomach, liver, large and small intestine, gallbladder, appendix, pancreas, adrenal glands, and kidneys

Intubation: a procedure where a tube is inserted to maintain a patient's airway and to allow ventilation

Insensate: unable to feel pain

In situ: Latin that could be translated "on site" or "locally." Used in reference to perfusion that is within the body.

Ischemia: inadequate or no blood flow to a body part. In organ transplant, the time where an organ is not connected to a blood supply is referred to ischemic time, and can be warm ischemia (inside the deceased donor's body before recovery or removed from the donor's body but not yet iced) or cold ischemia (on ice).

Ischemic cholangiopathy: a complication from liver transplant, where there is damage to one or more of the body's bile ducts attributed to inadequate blood flow

Laparotomy: a medical procedure that cuts into the abdominal cavity, used in NRP to gain access to abdominal organs

Life support: can refer to a variety of medical interventions aimed at keeping someone alive while their normal body processes are not functioning properly, including cardiopulmonary resuscitation (CPR), defibrillation, and ECMO

Ligation: a medical procedure that involves completely occluding a blood vessel or tubular structure by the act of a ligature

Liver biopsy: when a piece of the liver is removed for examination

Machine perfusion (ex vivo): refers to a process of keeping donated organs viable through circulation of blood or perfusate outside the body with a machine

Neuronal hypoxemia: when not enough oxygen is reaching the neurons of the brain

Occlusion: a blockage of a blood vessel or passageway in the body, can be complete or partial.

Perfusion: The act of providing flow of fluid, blood, or other substances into a blood vessel and/or organ.

Postmortem: after death

Resuscitation: refers to the act of restoring someone from unconsciousness or the act of re-invigorating something that is dying

Standoff period: a period of time between circulatory arrest and final declaration of death, to ensure that there is no spontaneous irreversibility. In the US, standoff periods typically range from 2-10 minutes, with 5 minutes being a common hospital procedure.

Sternotomy: a medical procedure that opens up the chest via a transection of the breastbone (sternum)

Tissue oxygenation measurement: measures the average oxygen saturation of hemoglobin in the red blood cells, which carry oxygenated blood to the body's tissues.

Transcranial doppler: a type of ultrasound that measures blood flow through the blood vessels in the brain

Uncontrolled NRP: use of NRP after unexpected cardiac arrest, in contrast to the typical use of NRP following controlled withdraw of life sustaining therapy

Acronyms

ACP: American College of Physicians. The ACP issued a statement in 2021 expressing concern about the ethical and legal ramifications of NRP due to potential violation of the dead donor rule and irreversibility.

A-NRP: Abdominal NRP

DBD: Donation after Brain Death. Most organ donors are DBD donors but an increasing proportion are DCD.

DCD: Donation after Circulatory Death. Circulatory death is determined after waiting a set time period following withdrawal of life support (cDCD or controlled DCD) or waiting a certain amount of time for circulatory functions to cease (uDCD or uncontrolled DCD). Note: all organ transplant teams are separate from the medical teams determining death). While DCD has historically accounted for a smaller proportion of organ transplants, that percentage is growing steadily as outcomes and techniques have improved.

DGF: delayed graft function. A common complication of transplant where the transplant does not function right away.

ECMO: extracorporeal membrane oxygenation. A medical technique that oxygenates blood outside the body using tubing to pump blood through a lung machine. In NRP, ECMO is used to keep the heart beating and oxygenated after donor death and before transplant.

FDA: The United States Food and Drug Administration. A federal agency of the Department of Health and Human Services that ensures safety, efficacy, and security of human drugs, medical procedures and techniques, and foods.

IRB: Institutional Review Board. Per the FDA definition, an IRB is a group that has been formally designated to review and monitor biomedical research involving human subjects, including ensuring human rights and welfare of the subjects and compliance with ethical principles.

NRP: Normothermic Regional Perfusion – the process by which organs are locally perfused in the body after circulatory death is declared.

OPO:

TA-NRP: Thoracic-abdominal Normothermic regional perfusion. In the context of the ethical implications, concern was especially focused around the implications of perfusing the heart after death is declared.

UAGA: Uniform Anatomical Gift Act – the law that dictates the ability of individuals to choose to become an organ donor and gift their organs.

UDDA: Uniform Declaration of Death Act – defines legal death as “An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem”

ULC: Uniform Law Commission – the group that is reviewing the UDDA and considering potential changes to it.

VA-ECMO: venoarterial extra corporeal membrane oxygenation. Machine technology used in both TA- and A- NRP for perfusion.

WLST: withdraw life-sustaining therapy. Context: cDCD is pursued after getting consent for withdrawal of life-sustaining therapy.

Appendix B: Review of Presentations to Workgroup

The Workgroup heard presentations from the following experts and stakeholders on NRP.

Presentations to Workgroup:

| Organization Name | Presenter Names | Presentation details/ethical perspective: |
|---|--|--|
| University of Minnesota | Cindy Martin, MD Andrew Shaffer, MD Jennifer Needle, MD, MPH Joel WU, JD, MPH, MA | Presentation detailed the University's process and experience ethically reviewing and implementing NRP, including how their Ethics Committee concluded that cardiac function was irreversible and that clamping neck vessels did not precipitate death because death already had occurred ¹⁶⁶ |
| New England Donor Services | Alex Glazier, JD, MPH | Presentation focused on aligning law, ethics, and practice in declaring death and donation protocols, and that ethical principles may be considered once all legal thresholds are met ¹⁶⁷ |
| European Society of Organ Transplant (ESOT) | Amelia Hessheimer, MD | Presentation focused on importance of public trust, honoring donor family wishes, the potential for monitoring cerebral activity, defining death, and sharing models of growth ¹⁶⁸ |
| University Hospitals Leuven | Arne Neyrinck, MD, PhD | Anesthesiologist perspective on TA-NRP developments in Europe. ¹⁶⁹ |
| University of Cambridge | Christopher JE Watson, MD | Provided an update on the efforts and efforts of NRP in the UK. ¹⁷⁰ |
| Geisel School of Medicine - Dartmouth | James Bernat, MD | Dr. Bernat shared his expertise as a neurologist, specifically focusing on declaration of brain death ¹⁷¹ |
| St. Jude Heritage Fullerton | Harry Peled, MD | Dr. Peled shared the perspective of an intensivist (a physician who provides specialized care for critically ill patients) in relation to NRP ¹⁷² |
| American College of Physicians (ACP) | Matthew DeCamp, MD | Dr. DeCamp shared concerns raised by the ACP about the implications of ligating arteries to the brain post circulatory death declaration in NRP donors. ¹⁷³ |

¹⁶⁶ OPTN Ethics Committee NRP Workgroup, *Meeting Summary*, August 4, 2022.

¹⁶⁷ OPTN Ethics Committee NRP Workgroup, *Meeting Summary*, August 11, 2022.

¹⁶⁸ OPTN Ethics Committee NRP Workgroup, *Meeting Summary*, September 8, 2022.

¹⁶⁹ OPTN Ethics Committee. *Meeting Summary*, March 22, 2022

¹⁷⁰ OPTN Ethics Committee NRP Workgroup, *Meeting Summary*, September 8, 2022.

¹⁷¹ OPTN Ethics Committee NRP Workgroup, *Meeting Summary*, September 22, 2022.

¹⁷² OPTN Ethics Committee NRP Workgroup, *Meeting Summary*, December 8, 2022.

¹⁷³ OPTN Ethics Committee. *Meeting Summary*, March 22, 2022

Appendix C: Workgroup Members

The Workgroup contributed greatly to this analysis through their participation and engagement. They are listed below:

Workgroup Members

| Name | Membership on Other Committees | Area(s) of Specialty |
|---------------------------------|--|-------------------------------------|
| Keren Ladin, PhD | OPTN Ethics Committee (Chair) | Ethics |
| Andrew Flescher, PhD | OPTN Ethics Committee (Vice Chair) | Ethics |
| Glenn Cohen, JD | OPTN Ethics Committee | Health Law and Policy |
| Bob Truog, MD | OPTN Ethics Committee | Ethics |
| Amy Friedman, MD | OPTN Ethics Committee | OPO Operations, Ethics |
| Sena Wilson-Sheehan, MA | OPTN Ethics Committee | Transplant Administration, Ethics |
| Nader Moazami, MD | OPTN Heart Transplantation Committee | Clinical |
| Sophoclis Alexopoulos, MD | OPTN Liver Transplantation Committee | Clinical |
| Erin Halpin | OPTN Organ Procurement Organizations (OPO) Committee | OPO Operations |
| Julie Spear | OPTN Patient Affairs Committee | Patient Perspective |
| Johnathan Fisher, MD | N/A | Clinical |
| Sanjay Kulkarni, MD, MHCM, FACS | OPTN Ethics Committee | Clinical, Ethics |
| Kevin Myer, MSHA | N/A | OPO Operations |
| Matthew Hartwig, MD | OPTN Lung Transplantation Committee (Chair) | Clinical |
| Rosa Guajardo, RN | OPTN Transplant Coordinators Committee | Transplant Administration, Clinical |
| Lainie Ross, MD, PhD | N/A | Ethics |
| Carrie Thiessen, MD, PhD | OPTN Ethics Committee, AST Psychosocial and Ethics Community of Practice | Clinical, Ethics |

