OPTN

Public Comment Proposal

Ethical Analysis of Normothermic Regional Perfusion (NRP)

OPTN Ethics Committee

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Ethical Analysis of Normothermic Regional Perfusion (NRP)

Sponsoring Committee: *Ethics*
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Executive Summary

The mission and scope of the OPTN Ethics Committee (hereafter, the Committee) is to provide ethical analysis and guidance to the OPTN Board of Directors to support the sustainability of organ donation and transplantation in the United States and to maintain public trust. The Committee does this through the development of white papers, the goal of which is to offer a comprehensive ethical analysis regarding a complex issue, often one regarding a new or evolving practice. This ethical analysis will lay the groundwork for any future development of a policy related to the practice; it itself is not policy. As such, the feedback sought on a white paper is to ensure the analysis is complete, not to develop consensus on the practice being analyzed.

This white paper conducts an ethical analysis of the organ procurement practice of normothermic regional perfusion (NRP) in the United States. NRP is a technique for circulating blood through organs after declaration of circulatory death and includes blocking vessels to the brain to prevent cerebral perfusion. As a surgical technique there is some evidence that it may increase utilization and longevity of organs.[1] NRP has generated controversy, however, because it involves recirculation after circulatory declaration of death, and because of the need to demonstrate that no cerebral flow occurs during recirculation.[2,3]

This white paper is not a referendum on clinicians, centers, or OPOs that engage in the practice of NRP, nor does it preclude a future of ethically practicing NRP in the United States. The white paper focuses on fully exploring and mapping the relevant ethical considerations relevant to NRP and the ensuing implications for the OPTN and broader transplant community. This exploration was supported by the proactive engagement of members from the community (see Appendices A-C), with representation from the OPTN Patient Affairs, Heart, Liver, Lung, OPO, and Transplant Coordinators Committees on a workgroup designed to review the topic, as well as discussing the analysis with the chairs of the American Society of Transplant Surgeons (ASTS) Ethics Advisory Committee.

The Committee examined NRP according to the ethical principles of do no harm, respect for persons, and utility, and concludes:

- NRP has great potential for utility, but this alone is not sufficient to demonstrate that a procedure is ethical.

[1] 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.
[2] 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.
[3] 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.

- NRP raises concerns about compliance with the Dead Donor Rule, which requires 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.[4] The concern is that a person may legitimately meet criteria for determining death owing to permanent cessation of circulation at the time of death declaration, but that this criterion is subsequently violated when circulation is restored.
- NRP raises concerns about the potential for harm to the donor if cerebral flow occurs from the procedure. Additional evidence is needed to demonstrate that cerebral flow to brain is minimal.
- In the interest of public trust, respect for persons, and transparency, authorization 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.
- Uncontrolled scenarios for NRP, in which circulatory death occurs unexpectedly and not after the planned withdrawal of life support, raise very serious concerns for respect for persons and proceeding too quickly from therapeutic treatment to organ recovery.

[4] 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.

Purpose

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."[5] The purpose of this white paper is to conduct an ethical analysis of the organ procurement practice of NRP in the United States. The white paper focuses on fully exploring and mapping the relevant ethical considerations relevant to NRP to lay the groundwork for any future development of policy related to the practice. The Committee explores the ethical principles of respect for persons, non-maleficence (do no harm), and utility.

It is beyond the scope of this paper to speculate regarding potential future changes to the Uniform Declaration of Death Act (UDDA), and to opine on whether NRP complies with current law.[6] The Addendum to the white paper (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 standard DCD (donation after circulatory death), which have been considered extensively elsewhere.[7,8,9,10]

Background

What is NRP?

NRP is a machine perfusion technique used following the declaration of a donor's death and is aimed at improving organ quality by reducing cold ischemic time through recirculating oxygenated blood in the donor body before organ recovery and transplantation.[11] Abdominal 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.[12] Thoracoabdominal NRP (TA-NRP) involves perfusing the thoracic organs in addition to abdominal ones, and includes blood

[5] "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.
[6] 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. The Dead Donor Rule is also not legally binding but an underlying moral principle to organ transplantation.
[7] 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."
[8] "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.
[9] 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
[10] "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.
[11] 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.
[12] 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.

flow through the heart; both forms of NRP involve occlusion of arteries to the brain to prevent perfusion (blood flow), although this concern may be greater with TA-NRP.[13]

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

Table 1: 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 requires permanent cessation of circulation.[14] 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.[15]
Unlike other machine perfusion techniques, NRP is the only one that perfuses the organs while they are in the body.[16]
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.[17] In DCD, criteria for circulatory death are observed, so neurological testing is not needed as this person meets criteria for death determination. For NRP, neither of these occur.

Utilization of both types of NRP has expanded in recent years as the procedure shows significant promise to increase quality and quantity of transplantable organs, although lack of currently collected data on NRP limit the ability to confirm the extent of its use.[18] NRP has developed in the U.S. has without a formal, objective ethical evaluation being conducted by the OPTN or otherwise within the transplant community.[19] Currently, OPOs and transplant programs use a patchwork of varied approaches and decision making when it comes to NRP, which may represent inconsistencies within the transplant system.

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[13] 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.
[14] 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.
[15] 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
[16] "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/.
[17] 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.
[18] There is no currently collected OPTN data on NRP. There are no publications on Pub Med before 2014, and the number has gone steadily up, with 37 titles in 2022.
[19] Association of Organ Procurement Organizations (AOPO), American Society of Transplantation (AST), and the American Society of Transplant Surgeons (ASTS) all issued statements regarding NRP. AST acknowledged the need for "critical ethical analysis," while AOPO advocated for "consideration of important legal and ethical considerations" (AOPO). ASTS "strongly recommends that future guidelines for NRP protocols be developed, including ethical principles" and cites publications indicating that TA-NRP is "consistent with US ethical and legal standards." However, the organizations did not perform ethical analyses, although the statements do mention the importance of ethical considerations.

Need for Ethical Review and Development of Workgroup

As the use of NRP has expanded, concerns have been raised that its pursuit may violate ethical principles governing organ transplantation.[20] Concerns have been raised about NRP's consistency with the UDDA and the Dead Donor Rule, which provide part of the legal and operational framework allowing for organ transplantation in the United States.[21,22] Additional concerns related to nonmaleficence include unknown implications of circulation and potential blood flow to the brain.

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.[23] While still considering it necessary to have appropriate protocols, supporters of NRP do not consider that the Dead Donor Rule is violated or that donors are harmed because the procedure occurs after circulatory death has been declared.[24]

Given the varying perspectives within the community and the importance of maintaining public trust in transplantation, OPTN leadership identified that this was an area of importance and asked the Ethics Committee to consider undertaking it as a new project. The Committee agreed to perform an ethical analysis of NRP in February of 2022 and in July of that same year, convened a Workgroup to conduct a robust and balanced review of ethical implications.[25] The Workgroup was diverse in perspectives regarding NRP, and included expertise on ethics, donor family experience, organ procurement, U.S. law, and transplantation. Representatives from the Lung, Heart, Transplant Coordinators, OPO, and Patient Affairs Committees were included (Appendix C identifies the full list of Workgroup members).

The Workgroup sought out perspectives that would inform their ethical analysis by engaging presenters from programs participating in NRP procurement and also critics with relevant expertise in law or neurology (a list of presenters is an appendix to the white paper).[26,27,28,29] The 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.[30] The Workgroup reviewed protocols presented by U.S. transplant programs engaged in the practice, and sought out the perspectives of intensivists, neurological experts, anesthesiologists,

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[20] 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.
[21] Peled H, Mathews S, Rhodes D, et al. "Normothermic Regional..." Critical Care Med 2022;50(11):1644-1648, doi:10.1097/ccm.0000000000005632
[22] 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.
[23] 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.
[24] Ibid.
[25] OPTN Ethics Committee NRP Workgroup, *Meeting Summary,* July 14, 2022. Available at: https://optn.transplant.hrsa.gov/media/ilqdwkwc/20220714_ethics_nrp_meeting-summary_final.pdf
[26] OPTN Ethics Committee NRP Workgroup, *Meeting Summary,* August 4, 2022. Available at: https://optn.transplant.hrsa.gov/media/5jepcztx/20220804_nrp_meeting-summary_final.pdf
[27] OPTN Ethics Committee NRP Workgroup, *Meeting Summary,* August 11, 2022. Available at: https://optn.transplant.hrsa.gov/media/opzfcuim/20220811_ethics_nrp_meeting-summary_final.pdf
[28] OPTN Ethics Committee NRP Workgroup, *Meeting Summary,* September 8, 2022. Available at: https://optn.transplant.hrsa.gov/media/p2rn4fo5/20220908_ethics_nrp_meeting-summary_draft.pdf
[29] 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
[30] A full list of presenters and topics reviewed by the workgroup can be found in Appendix B.

researchers and clinical experts in determination of death.[31] An informal survey of the Workgroup indicated that throughout the course of Workgroup review, most respondents had changed their mind regarding if NRP can be appropriately and ethically pursued in the current environment.[32] This finding suggests that the deliberations of the group and the presentations it received influenced evolving perspectives of Workgroup members as they understood more about the practice of NRP and associated ethical implications.

While initially pursuing a January 2023 public comment cycle, given the changing perspectives of workgroup members and the depth and complexity of the topic, the Committee agreed that additional time was needed to adequately develop a white paper for public dissemination.[33] To proactively engage with important stakeholders, Committee leadership shared early drafts with OPTN Board leadership, incorporating relevant feedback, and discussed the analysis with the chairs of the American Society of Transplant Surgeons (ASTS) Ethics Advisory Committee. A member of the American Society of Transplantation (AST) Psychosocial and Ethics Community of Practice Executive Committee and ASTS Ethics Advisory Committee is currently on the OPTN Ethics Committee and participated in Workgroup discussions. This robust engagement and additional time has led to the development of the current white paper, created to be responsive to the timeliness of the topic, while thorough and abiding by the thoughtful and deliberative process followed by the Committee from the beginning. In March 2023, the full Committee first reviewed the white paper draft and began revising and editing the paper for clarity, consistency, and completeness.[34] After review by Workgroup and Committee members, the white paper was endorsed by the Committee via a vote in June 2023.[35]

Overview of White Paper

The Committee analyzes NRP through the ethical lenses of nonmaleficence or do no harm, respect for persons, and utility. The white paper considers the ethical analysis within the scope of the Ethics Committee and highlights the history of NRP in its historical perspective arising from DCD procurement. It also explores where the need for ethical review arose and details the deliberative process that led to the development of the white paper itself.

Nonmaleficence

Ultimately the Committee identifies the OPTN should proceed with NRP, but cautiously, until questions of nonmaleficence are answered regarding compliance with the Dead Donor Rule. The Dead Donor Rule is defined as requiring that organ donors be dead at the time of procurement and that organ donation does not cause death.[36] The concern stems from the fact that an NRP donor may no longer meet criteria needed for declaration of circulatory death, while also not being shown to meet criteria for neurologic death. If reperfusion in the body would on its own make neurological criteria less likely to be met, then occluding vessels is a decisive act in preventing that from occurring. The Committee also finds that

[31] Ibid.
[32] 84% of Workgroup members participated in the survey.
[33] OPTN Ethics Committee, *Meeting Summary,* November 17, 2022. Available at: https://optn.transplant.hrsa.gov/media/m0ae3sia/20221117_ethics_meeting-summary_draft.pdf
[34] OPTN Ethics Committee, *Meeting Summary*, March 31, 2023. Available at: https://optn.transplant.hrsa.gov/media/dn0kn1x1/20230331_ethics-committee_meeting-summary_draft.pdf
[35] OPTN Ethics Committee, Meeting Summary, June 8, 2023. Available at: https://optn.transplant.hrsa.gov/media/0ihj242v/20230608_ethics_meeting_summary.pdf
[36] The formulation of the Dead Donor Rule used in this paper is based on what the OPTN Ethics Committee has used in the past in its review of Imminent Death Donation.

questions remain regarding potential for cerebral flow during perfusion of the NRP donor's body. There can be substantial anatomical variability in how the spinal cord receives circulation and whether ligation of aortic arch vessels is sufficient to eliminate perfusion of the entire brain and brainstem.[37] Physiologically, it is unknown how much collateral circulation results in perfusion of the posterior brain and brain stem.[38]

Utility

NRP shows great promise in terms of utility, by potentially increasing the number of organs transplanted per donor and improving graft function.[39,40] However, the Committee considers utility and justice (equity) must be balanced, as described in the "Ethical Principles in the Allocation of Human Organs" white paper.[41] The Committee finds that justification for any one principle is *necessary, but not sufficient*, for arriving at a conclusion about NRP.

Respect for Persons

The white paper explores the complex logistics of informed decision-making in the context of respect for persons, and discusses the challenges faced by organ procurement organizations (OPOs) and families, related to specific considerations of NRP. While NRP involves similar premortem interventions as DCD, there are crucial differences regarding recirculation and the potential restoration of any cerebral perfusion. The Committee considers that these may be meaningful distinctions for some populations and should therefore be disclosed. The Committee identifies that informed decision-making for NRP requires a reiteration of the purpose of the hands-off waiting period and a description of the steps involved in NRP. This includes information regarding occlusion of the cerebral vessels and an identification of the unknown issue of restoration of any cerebral perfusion. For TA-NRP, it also includes the restoration of heart function.

The Committee notes that uncontrolled NRP (organ retrieval after unexpected cardiac arrest) presents additional ethical concerns related to respect for persons and non-maleficence. Uncontrolled scenarios are rapid and potentially confusing in such a way that makes it difficult to have informed decision-making. The Workgroup participants and Committee members expressed unanimous support for this conclusion.

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[37] Griepp, Randall B., and Eva B. Griepp. "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.; Griepp, 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

[38] 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.

[39] 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.

[40] 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.

[41] 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/.

NOTA and Final Rule Analysis

The Committee submits this proposal for consideration under the authority of NOTA, which requires the OPTN to "adopt and use standards of quality for the acquisition … of donated organs, "[42] to "provide information to physicians and other health professionals regarding organ donation,"[43] and the OPTN Final Rule, which states that "an OPTN member procuring an organ shall assure that clinical examinations of potential organ donors are performed to determine any contraindications for donor acceptance."[44] This paper examines the practice of NRP as it is used during the process of organ procurement and if any requirements or standards should be set to ensure the ethics of its practice.

Conclusion

NRP presents an opportunity to increase the number of transplants and utilization of organs to help get patients with end-stage organ disease life-saving treatment. 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 Committee affirms the importance of maintaining the sacred trust and commitment of the transplant community to organ donors and donor families. The transplant community must therefore act in ways 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 in the white paper, that the Committee concludes that the OPTN should proceed, but proceed cautiously regarding the practice of NRP for organ procurement.

Considerations for the Community

The goal of a white paper is to offer a comprehensive ethical analysis regarding a complex issue, often one regarding a new or evolving practice. This ethical analysis will lay the groundwork for any future development of a policy related to the practice; it itself is not policy. As such, the feedback sought on this paper is to ensure the analysis is complete, not to develop a consensus on the practice of NRP.

The Committee encourages all interested individuals to comment on this white paper in its entirety, but specifically asks for feedback on the following:

- What information should be disclosed to potential donors and next of kin regarding NRP, and how should one approach disclosure?
- Are there any additional ethical considerations or evidence that should be taken into account in the analysis?

[42] 42 USC § 274 (b)(2)(E)
[43] 42 USC § 274 (b)(2)(H)
[44] 42 CFR 121.6(a).

White Paper

1 *Note: This white paper was developed by the OPTN Ethics Committee and reflects its consideration of the*
2 *ethical implications of NRP. The final version of this paper will be issued by the OPTN, contingent upon*
3 *OPTN Board of Directors review and approval.*

4 Executive Summary

5 Importantly, this white paper is not a referendum on clinicians, centers, or OPOs that engage in the
6 practice of NRP. It outlines conditions for ethical practice of donation in the United States, and
7 implications for NRP.[45] Of the many protocols and testimonials that the workgroup and Committee
8 reviewed, none undertook the pursuit of NRP lightly: all were thoughtful, well-intended, and followed
9 protocols that were well-developed. The Committee is aware that many viewpoints exist, and that the
10 analysis espoused here may not accord with the views of some, although all were taken into account in
11 the analysis. The mission and scope of the Committee is to support the transplant community and the
12 OPTN Board of Directors by providing ethical analysis and guidance at the systems-level to support the
13 sustainability of organ donation and transplantation in the United States and to maintain public trust.
14 The Committee recognizes the importance of increasing utility for candidates waiting for a transplant,
15 and notes the importance of maintaining public trust and adhering to longstanding ethical and legal
16 norms, which underpin support and sustainability of the entire transplant system.
17
18 Normothermic regional perfusion (NRP) is a technique for perfusion either of abdominal organs (A-NRP)
19 or thoracic and abdominal organs (TA-NRP) in a person's body after declaration of circulatory death, and
20 includes occlusion of vessels to prevent brain perfusion.[46] The OPTN Ethics Committee reviews the
21 ethical implications of NRP according to established ethical principles guiding donation and
22 transplantation, including: the principle of nonmaleficence (do no harm), respect for persons
23 (autonomy), and utility. The principle of nonmaleficence is important for maintaining public trust and
24 requires compliance with the Dead Donor Rule, which requires that patients must be dead at the time of
25 organ procurement (i.e. meet criteria for brain or circulatory death) and that organ donation does not
26 cause death.[47] This paper concludes that:

27 • NRP has great potential to improve utility for candidates with end-stage organ disease awaiting
28 organ transplantation, and as such should be strongly considered . Utility is necessary, but
29 insufficient to demonstrate that a practice is ethical.

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[45] The Committee appreciates presentations and participation of European transplant leaders who routinely conduct both A- and TA-NRP. While the Committee acknowledges that NRP is routinely conducted in some countries outside of the United States, and appreciates that there may come such a time where this may occur in the United States too, the Committee notes some important differences in basic premises underlying differences between donation practices between the United States and some European contexts 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.

[46] 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.

[47] 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.

30 - It is unclear whether NRP complies with the Dead Donor Rule. Circulation[48] is restored regionally in
31 the person after circulatory death has been declared, giving rise to questions that are morally
32 meaningful as to whether the person continues to meet criteria required for determination of
33 death—in this case permanent[49] cessation of circulation— at the time donation takes place. To
34 clarify, this concern implies that a person legitimately meets criteria for determining death owing to
35 permanent cessation of circulation at the time of death declaration, but that this criterion is violated
36 subsequently when circulation is restored (at the time of donation).
37 - NRP raises concerns about the potential for harm if the assumption that the donor is insensate is
38 incorrect following restoration of circulation following occlusion of the arteries.[50]
39 - This concern may be mitigated by studies demonstrating that blood flow to the brain during
40 regional perfusion is minimal (e.g. using transcranial Doppler, angiogram studies, or tissue
41 oxygenation measurement).
42 - It may also be mitigated by use of certain medications during NRP. However, use of such
43 medications may further undermine compliance with the Dead Donor Rule.
44 - In the interest of public trust, respect for persons, and transparency, informed decision making
45 should include disclosure of recirculation through the heart (TA-NRP) and the potential restoration
46 of any cerebral perfusion (TA-NRP and A-NRP), as well as considerations of meaningful differences
47 from other donation approaches.[51,52]
48 - This could be addressed by: clear requirements and guidelines for disclosure and
49 explanation of morally relevant components of NRP, standardization and oversight of the
50 authorization process.
51 - Uncontrolled scenarios for NRP raise very serious concerns for respect for persons and proceeding
52 too quickly from therapeutic treatment to organ recovery.[53]

[48] 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].

[49] 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.

[50] By "insensate" this paper means unable to feel pain.

[51] 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.

[52] "Transparency" in this context implies that unique elements of NRP are communicated in a plain-language way to individuals impacted by the donation process.

[53] 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

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

55 **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.[54] 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.[55]
Unlike other machine perfusion techniques, NRP is the only one that perfuses the organs *in situ*, while they are in the body.[56]
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.[57] In DCD, criteria for circulatory death are observed, so neurological testing is not needed as this person meets criteria for death determination. For NRP, neither of these occur.

56

57 *Scope of White Paper*

58 The OPTN Ethics Committee "aims to guide the policies and practices of the OPTN related to organ
59 donation, procurement, distribution, allocation and transplantation so they are consistent with ethical
60 principles."[58] White papers are developed for informational purposes and are intended to guide OPTN
61 operations. As such, it is beyond the scope of this paper to speculate regarding potential future changes
62 to the Uniform Determination of Death Act (UDDA), and to opine on whether NRP complies with current
63 law.[59] The Addendum (page 25) provides background on the UDDA and its relevance for the NRP
64 discussion. **This paper's scope does not include reviewing the ethical foundations of DCD, which have**

[54] 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.

[55] 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

[56] "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/.

[57] 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.

[58] "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.

[59] 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. The Dead Donor Rule is also not legally binding but an underlying moral principle to organ transplantation.

65 **been considered extensively elsewhere.**[60,61,62,63] The focus of this white paper is to fully explore and
66 map the relevant ethical principles applied to NRP and the ensuing implications for the OPTN and
67 broader transplant community.

68 Introduction

69 There has been an increasing interest in machine perfusion techniques to improve organ quality and
70 utilization, and multiple machines that perfuse organs *ex vivo* (outside the body) have received FDA
71 approval within the last five years.[64,65] **NRP is unique in perfusing organs *in situ* (in the body), which**
72 **involves ligating the major blood vessels to the brain prior to restoration of circulatory blood flow; in**
73 **contrast, other machine perfusion techniques are *ex vivo* (outside the body).** While NRP has expanded
74 significantly in the United States since 2020, no formal ethical analysis or guidance has been issued by
75 the OPTN regarding the implications for *in situ* organ perfusion.[66] Many other countries that have
76 pursued NRP or have decided against it have provided additional guidance and consideration of its
77 ethical implications.[67,68,69] Transplant centers and OPOs have developed a patchwork of approaches and
78 decisions related to NRP in the U.S., creating fragmentation and inconsistency in protocols for treatment
79 of potential organ donors. Many questions remain at this time about the science of NRP as it relates to
80 potential blood flow to the brain, particularly in a retrograde fashion through collateral flow to the
81 spinal cord.[70] While some studies reflect rapid progress in identifying the potential for cerebral flow to

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[60] 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."

[61] "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.

[62] 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

[63] "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.

[64] "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-metrar-system-p200035.

[65] "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.

[66] 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.

[67] 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.

[68] 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.

[69] 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.

[70] Bernat, James., et al. "Understanding the Brain-based Determination of Death When Organ Recovery is Performed with DCDD

82 be minimal during NRP when vessels are occluded,[71,72] and although the Committee acknowledges that
83 the potential for harm may be low, more research is needed to confirm that the perfusion of the brain
84 or brainstem during NRP does not occur.
85
86 Appendix A (page 30) provides an overview of all relevant terms and acronyms that are defined in this
87 paper; it may be referenced throughout where technical terms are used. Finally, an overview of
88 presenters and topics discussed by the Workgroup is included in Appendix B (page 32).
89

90 Overview of Ethical Findings

91 Ethical principles guiding transplantation provide a system of checks and balances.[73] This is spelled out
92 in the Final Rule according to which utility, justice, and respect for persons are "the major ethical
93 principles to be balanced to achieve an equitable outcome in the allocation of organs for
94 transplantation."[74] Another important cornerstone of organ transplantation is public trust, since no
95 transplant would occur without the endorsement of society and the generosity of individual donors and
96 their families.
97
98 The **Dead Donor Rule** states that donors must meet criteria for death at the time of donation, to ensure
99 that persons donating organs do not die by or for donation.[75] The Dead Donor Rule is a fundamental
100 tenet of trust in the organ donation system. Adherence to this is critical despite the paradoxical need to
101 reduce ischemic time and optimize perfusion to improve transplant outcomes. NRP raises questions
102 about whether the act of ligating the arteries or using an occluding balloon prior to perfusion with the
103 knowledge and intent of restarting regional circulation constitutes a violation of the Dead Donor Rule, as
104 well as a violation of the UDDA, by rendering the initial death by circulatory criteria invalid (as circulation
105 was restarted successfully), and without a determination of death by brain death criteria.[76]
106
107 To provide assurance, the question should be asked: Does regional postmortem circulatory restoration
108 imply that the criteria for meeting death, legitimately established at the time death was declared, is
109 overturned following that restoration?[77] Has adequate brain monitoring been conducted to examine

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In Situ Normothermic Regional Perfusion." Transplantation ():10.1097/TP.0000000000004642, May 12, 2023. | *DOI:* 10.1097/TP.0000000000004642

[71] 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.

[72] 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.

[73] 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/.

[74] "Final Rule." OPTN: Organ Procurement and Transplantation Network - OPTN. https://optn.transplant.hrsa.gov/about/final-rule/.

[75] 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.

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

[77]This 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.

110 brain function in circumstances where the carotid and vertebral arteries cannot be perfused? Would
111 such function be restored, or even somewhat improved, if these arteries were not occluded?[78] Evidence
112 demonstrating lack of blood flow to the brain would be instructive to address concerns about harm, but
113 may not address the larger question about whether the act of occluding the arteries itself violates the
114 Dead Donor Rule. While there are differing ethical opinions regarding the implications of NRP and the
115 Dead Donor Rule, assurance that the Dead Donor Rule has not been violated must be met to be
116 consistent with current ethical practice.
117
118 NRP has further implications on the requirement of **non-maleficence**, or do no harm. Non-maleficence
119 requires demonstrating that the performance of NRP occurs when a donor is insensate and that this
120 state is maintained, which may be demonstrated by definitive lack of neurological activity. Evidence for
121 non-maleficence could include transcranial Dopplers, angiograms, or tissue oxygenation measurement
122 demonstrating lack of blood flow to the brain when vessels are occluded with NRP. Experts from related
123 fields, such as neurology, should be consulted to determine the strength and quality of the evidence.
124
125 Another important ethical consideration is whether and how NRP upholds **respect for persons**
126 (autonomy). This entails demonstrating a proactive and transparent process of informed decision-
127 making. The principle of autonomy refers to one's capacity to self-determine and have a say over what
128 happens to oneself.[79] Autonomy implies "respect for persons" insofar as it signals decision-making that
129 preserves the dignity of the decision-maker.[80] In order for NRP to adhere to the principle of autonomy,
130 clearer guidelines and standards are needed to ensure that patients and families approached about
131 organ donation understand and can opt to, or not to, proceed with NRP.[81] The paper also acknowledges
132 the potential benefit to respect for persons that NRP could allow in manifesting autonomy by facilitating
133 the desire to donate.
134
135 Lastly, the principle of **utility** is a highly relevant consideration to any ethical analysis of NRP. The
136 principle of utility takes into account all possible goods and harms that can be envisioned, considering
137 the quantity and probability of the various outcomes. Current evidence suggests that the *in situ* manner
138 in which NRP organs are acquired yields optimal results for the recipient by maximizing the number of
139 organs procured, as well as the quality and longevity of these organs.[82] The alternative methods of *ex*
140 *vivo* machine perfusion also have positive impacts on organ utilization while avoiding the central
141 controversy of perfusing organs and creating blood flow in the body of someone who was declared dead
142 by circulatory criteria, but the utility benefits for hearts may be lessened by increased post-transplant

[78] 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

[79] 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/.

[80] Ibid.; Beauchamp, Tom L., and James F. Childress. *Principles of Biomedical Ethics*. New York: Oxford University Press, USA, 2009. ICh.

[81] That 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.

[82] Jochmans, 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.

143 graft failure.[83] In its deliberations, the Committee considered the available attestations on the part of
144 transplant professionals working in, and intimately familiar with NRP.[84] It is of central importance to the
145 Committee to consider potential recipients whose lives stand to be improved for the better as a result of
146 NRP, and this mattered a great deal in the overall ethical analysis.
147
148 As previously mentioned, all of the ethical principles considered are important to consider in tandem, to
149 which end the Committee has taken the approach that fulfilling the expectations for normative
150 justification for any one principle is *necessary, but not sufficient*, for arriving at a conclusion about NRP.
151

152 Background

153 *NRP Procedure[85]*

154 Currently, there are two major classifications of NRP, abdominal (A-NRP) and thoraco-abdominal NRP
155 (TA-NRP). A-NRP involves perfusing the liver, kidney and pancreas and other tissue In the lower part of
156 the body using cannulas inserted below the diaphragm, either into the iliac artery and vein or into the
157 abdominal aorta.[86] TA-NRP involves perfusing the thoracic organs in addition to abdominal ones, and
158 also implies blood flow through the heart; both forms of NRP involve occlusion of arteries to the brain to
159 prevent perfusion to the brain, although it is less likely that blood flow reach the brain due to A-NRP
160 perfusing organs further from the brain and not perfusing the heart.[87]
161
162 The development of NRP in the U.S. emerged as a patchwork, with each center/OPO adopting different
163 approaches, some with rigorous ethical oversight through institutional review boards (IRBs) and formal
164 ethics consultations, others with more informal oversight. No objective, formal ethical evaluations have
165 occurred, similar to prior reports issued by the Institute of Medicine with DCD donation.[88] It is important
166 to note that any actions taken prior to and including declaration of death are those taken solely by the
167 non-OPO, critical care team. Details of how NRP is performed vary but typically reflect utilization of
168 standard DCD protocols. The ethically salient elements are as follows:[89]

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[83] Langmuur, 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.
[84] Summaries of the Committee's deliberations are available here: https://optn.transplant.hrsa.gov/about/committees/ethics-committee/
[85] A note that portions of this section are highly technical and a reminder that all relevant terms are defined in Appendix A, page 30.
[86]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.
[87] 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.
[88] 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.
[89] 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.

169 **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. The only difference is that the informed decision making process should include language specific to NRP.
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) is done with the authorization of the 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 an independent physician based on determination of death by circulatory criteria.[90]

170 At this point in the process of NRP organ procurement, TA-NRP and A-NRP procedures diverge. The
171 Committee notes the relevant elements below:[91]

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[90] 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.

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

172 **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**,[92] 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.**[93]

173

174 *Historical Perspective*[94]

175 To appreciate the current ethical discussions regarding NRP, it is helpful to understand the context from
176 which it arose. In 1993, the University of Pittsburgh developed a protocol that provided a path to obtain
177 organs from individuals deemed dead by cessation of circulation or donors after circulatory death (DCD)

---

[92] 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.

[93] 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

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

178 to address a growing need for transplantation.[95] The growth of DCD donors, and its subsequent
179 acceptance by the medical community and society, was promoted in two Institute of Medicine reports
180 that outlined the ethical and medical issues of non-heart beating donors.[96,97] One report identified that
181 the demand for organ transplantation had increased by 212% in the prior decade and that organs from
182 DCD donors could increase organ transplantation by 25%.[98] Important contributions outlined the
183 practice of separating the organ procurement teams from physicians charged with the management of
184 the terminally ill patients and their death declaration.[99] They also defined the 5 minute "standoff"
185 period from death declaration to procurement, that would minimize the chances of spontaneous re-
186 animation.[100] Early experience with DCD liver and kidney transplants demonstrated that these
187 transplants were safe and had a significant survival benefit compared to remaining on the waitlist.[101]
188

189 The ethical underpinning of DCD transplantation relies on the fact that it adheres to the Dead Donor
190 Rule, in that the donation itself was not the cause of death, and that it was consistent with the UDDA
191 definition that the donor had irreversible cessation of circulatory and respiratory function, interpreted in
192 this case as "permanent" cessation of circulatory function**.**[102] An essential corollary is the implicit
193 understanding that no attempts would be made to resuscitate the donor and as such, the lack of
194 circulation to the brain also causes irreversible cessation of all functions of the brain, including the
195 brainstem.[103,104]
196

197 The first challenge to the irreversibility clause of the UDDA came from the use of DCD hearts in three
198 pediatric heart transplant recipients.[105] If circulatory cessation is irreversible, then how is restarting
199 cardiac function in the recipient permissible?[106] Although ethical debates continue regarding the DCD
200 heart transplantation, its expansion has been allowed by the notion that despite challenging the
201 irreversibility of asystole, higher brain functions in the donor are not impacted and are consistent with

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[95]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

[96]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

[97]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.

[98]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

[99]Ibid.

[100] Ibid.

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

[102] See footnote 5.

[103] 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

[104] 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."

[105] 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.

[106] 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.

202 the UDDA definition of brain death.[107] Terminology was therefore modified to reflect the currently
203 accepted terminology "Donation after Circulatory Death" instead of "Donation after Cardiac Death." [108]
204 Indisputable in this debate was the agreement that attempts at reversing asystole in the donor, even
205 after death declaration, were not consistent with the process of withdrawing support in a terminally ill
206 patient.[109]
207
208 The use of ECMO in a DCD donor was protocolized in the U.S. by the University of Michigan and was
209 originally performed for intra-abdominal organs only.[110] The use of an intra-aortic occlusion balloon
210 above the diaphragm eliminated cardiopulmonary resuscitation and thus, the NRP procedure was
211 deemed "regional" and reportedly consistent with the principle that there were no attempts to
212 resuscitate a donor following the death declaration. During TA-NRP, the aortic arch vessels are ligated to
213 address concerns that ECMO or cardio-pulmonary bypass may result in cerebral circulation.[111] Some
214 protocols in Europe use a venting procedure to expose arch vessels to atmospheric pressure to further
215 reduce the chances of collateral cerebral perfusion.[112] TA-NRP protocols in Spain uses Bispectral index
216 (BIS) monitoring to confirm lack of frontal lobe brain activity following the initiation of ECMO.[113]
217
218 NRP poses significant questions, and its use has not had an *a priori* consensus in terms of its legality,
219 ethical foundation, or societal acceptance. This is critical, as its further expansion may lead to improved
220 survival for many patients waiting for transplant. However, a lack of transparency and failure to address
221 gaps in knowledge have the potential to impact societal credibility in the overall transplant system.
222 Spontaneous reversal of asystole has been observed in TA-NRP when cardio-pulmonary bypass was
223 used, which then directly questions the defined event of death declaration prior to the standoff
224 period.[114] From a physiological perspective, it is also unknown to what extent collateral circulation
225 results in perfusion of the posterior brain and brain stem.[115] Anatomically, there is substantial variability
226 in how the spinal cord receives circulation and our current knowledge challenges the assertion that
227 ligation of aortic arch vessels is sufficient to eliminate perfusion of the entire brain and brainstem, as
228 required by the UDDA.[116]

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[107] 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.
[108] "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.
[109] 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.
[110]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.
[111] Dalsgaard, Frederik F., et al. "Clamping of the Aortic Arch Vessels..." *Transplantation* 106, no. 9 (2022), 1763-1769. doi:10.1097/tp.0000000000004047.
[112] 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.
[113] 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.
[114] 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.
[115] 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.
[116] Griepp, Randall B., and Eva B. Griepp. "Spinal Cord Perfusion and Protection During Descending Thoracic and

229 The ethical integrity of DCD donation is highly dependent on the societal acceptance that terminally ill
230 individuals may have cardiopulmonary support withdrawn and following the act of dying, they could
231 donate organs to help others. Implicit in the act of dying is that the individual is not experiencing harm
232 from the organ procurement as they are declared dead by accepted definitions. Unknown in NRP is if
233 the issues regarding brain/brainstem circulation have been scientifically investigated, if organ
234 resuscitation practices conducted in NRP result in inadvertent harm, and if there are in fact potential
235 violations of the Dead Donor Rule.[117]
236

237 *Need for Ethical Review*

238 As the use of NRP has expanded, so have concerns that its pursuit may violate ethical principles
239 governing organ transplantation and legal boundaries.[118] The UDDA, which provides part of the legal
240 framework for organ transplantation in the United States, defines death as "***An individual who has***
241 ***sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible***
242 ***cessation of all functions of the entire brain, including the brain stem***."[119] A 2021 statement by the
243 American College of Physicians (ACP) expressed concern that NRP does not comply with the UDDA
244 because it entails recirculation of blood in the body after death is declared, violating irreversibility, and
245 potentially the Dead Donor Rule.[120] Additional concerns related to nonmaleficence include unknown
246 implications of circulation and potential blood flow to the brain.
247
248 Those in favor of NRP consider that the procedure does not violate irreversibility because the circulation
249 is localized, or "regional." Under this view, the UDDA may need to be clarified to expand the
250 interpretation of irreversibility understood as permanence to allow for regional recirculation.[121]
251 However, proponents argue that no ethical norm is violated and this may be merely a legal
252 clarification.[122] Proponents of NRP consider respect for persons (patient autonomy in choosing to
253 donate) and utility (increased use of organs and improved outcomes for recipients) as strong ethical
254 reasons to pursue NRP.[123] While still considering it necessary to have appropriate protocols and
255 informed decision making, supporters of NRP do not consider that the Dead Donor Rule is violated or
256 that harm is being done to donors because the procedure occurs after circulatory death has been
257 declared.[124] Given the varying perspectives within the community and the importance of maintaining
258 public trust, the Committee convened an NRP Workgroup of experts with diverse and diverging opinions
259 and backgrounds to conduct a robust and balanced review of ethical implications as described in the
260 "Deliberative Process section," below.

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.; Griepp, 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

[117] 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.

[118] 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

[119] National Conference of Commissioners on Uniform State Laws. *Uniform Determination of Death Act*. 1980.

[120] 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.

[121] 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.

[122] Ibid.

[123] Ibid.

[124] 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.

261 *Deliberative Process*

262 In circumstances where no *a priori* agreement exists on the hierarchy of principles or values governing
263 ethical decision-making exist, people turn to a procedural justice approach. This type of approach (in
264 contrast to distributive justice approaches) stems from the following: if diverse stakeholders are
265 engaged and the process is transparent, and if stakeholders can agree at the outset on the terms for a
266 fair deliberative process, then the outcome arising from the deliberation must be seen and accepted as
267 fair.[125]
268
269 For such a new technology as NRP, with its complexity and potential for controversy, the Committee
270 considered it imperative to create a deliberative process for review that was thorough and inclusive of
271 all relevant perspectives. To that end, the Committee brought together a diverse workgroup with
272 expertise on NRP, organ donation, ethics, donor family experience, organ procurement, and
273 transplantation to assess the ethical justification for NRP. The Workgroup included supporters and
274 skeptics of NRP, as well as representatives from all key transplant communities, and diverse medical
275 specialties.[126]
276
277 Committee leadership sought out and obtained membership on the Workgroup that was diverse in
278 perspective and experience. Guest presentations included proponents and critics of NRP. The
279 Committee started its deliberation with presentations from both European surgical teams engaged in
280 the practice of NRP and the American College of Physicians (ACP), which had recently issued a position
281 statement critical of NRP.[127] The Workgroup reviewed protocols presented by U.S. transplant programs
282 engaged in the practice, and sought out the perspectives of intensivists, neurological experts,
283 anesthesiologists, researchers and clinical experts in determination of death, and European transplant
284 clinicians.[128] Members updated a shared literature review with 60 relevant publications and participated
285 in Workgroup subgroups to consider the particular implications of irreversibility, patient autonomy, and
286 physician intent. The Workgroup met 15 times from July 2022 to March 2023, and members provided
287 regular updates on progress and discussions to the Committee. An informal survey of the Workgroup
288 indicated that throughout the course of Workgroup review, most respondents had changed their mind
289 regarding whether NRP could be appropriately and ethically pursued in the current environment.[129] This
290 finding suggests that the deliberations of the group and the presentations it received influenced
291 evolving perspectives of Workgroup members as they understood more about the practice of NRP and
292 associated ethical implications. The discussions within the Workgroup directly led to the generation of
293 initial drafts of the white paper, which were updated in iterative fashion based on feedback from the
294 Workgroup and Committee. Further review by the Committee ultimately developed the current paper,
295 which reflects adherence to a deliberative and thorough ethical analysis.
296

297 Ethical Implications of NRP

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

[125] Summaries of the Committee's and Workgroup's deliberations are available here:
https://optn.transplant.hrsa.gov/about/committees/ethics-committee/
[126] Ibid.
[127] A full list of presenters and topics reviewed by the workgroup can be found in Appendix B.
[128] Ibid.
[129] 84% of Workgroup members participated in the survey.

301 *Do No Harm (nonmaleficence)*

302 Although the Hippocratic precept of *primum non nocere* ("first, do no harm") is often considered a
303 fundamental principle of medical ethics, strict adherence to this rule would be incompatible with
304 modern medical practice, since almost all medical interventions entail some risk of harm. Yet, the spirit
305 of this principle can be retained by carefully considering whether the potential for benefits from an
306 intervention outweigh the potential for harm. In the context of NRP, it is important to consider not only
307 potential harms to the organ donor, but also harms that may come from a loss of public trust in the
308 practice of organ procurement, particularly with regard to the Dead Donor Rule (DDR), an implicit but
309 fundamental ethical foundation in the practice of organ transplantation. The paper considers potential
310 harms here to the donor, while harm to others (including participating healthcare providers and to
311 public trust) is included in a section below, "Utility."
312
313 **Argument that NRP does not violate the Dead Donor Rule (DDR) and does not harm the**
314 **donor:**
315
316 Proponents of NRP contend that NRP is a modification of standard DCD donation, which has been in use
317 since 1992, and which is now a well-accepted approach to organ procurement.[130] In DCD donation in the
318 US, death is declared (if it occurs) following a predetermined duration of pulselessness, provided that
319 autoresuscitation has not occurred.[131] The 5-minute interval has been supported by evidence that
320 autoresuscitation does not typically occur beyond this time interval, provided that there have been no
321 prior attempts to resuscitate the patient.[132]
322
323 Proponents further explain that NRP does not violate the DDR because the restoration of circulation is
324 only regional (excluding the brain in TA-NRP, and excluding the brain and thoracic organs in A-NRP), and
325 consider the fact that circulation is restored *in situ* rather than *ex vivo* to be ethically irrelevant.[133] The
326 arteries that supply the brain are clamped or otherwise occluded, and arteries that lie distal to the
327 occlusion are vented to atmospheric pressure to divert any potential collateral blood flow away from
328 the brain in an effort to minimize the risk of cerebral reperfusion.[134]
329
330 On the question of whether re-establishing circulation invalidates the determination of death, Parent et
331 al makes a parallel point on the legal issue: "The law is silent on whether subsequent acts can invalidate
332 a declaration of death. Regardless, occluding cerebral circulation… does not cause death—the patient
333 has already been pronounced dead by standard cDCD criteria."[135] Moreover, proponents describe the
334 importance of intention: "Resuscitation efforts require attempting to restart the heart for life-saving/
335 prolonging purposes. In undertaking cDCD NRP, there is no intention or attempt to resuscitate because
336 doing so would be medically ineffective… Perfusing the thoracic and abdominal organs after circulatory

[130] 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.

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

[132] 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.

[133]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.

[134] Ibid.

[135] 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.

337 determination of death… does not alter the fact that… continued care would be medically ineffective
338 and inconsistent with a meaningful existence."[136] Their presumption is that the intent to restart
339 circulation merely for the purposes of regional reperfusion for donation does not constitute
340 resuscitation. They note that the DDR is not violated in that the occlusion of the arteries ensure that the
341 process of brain death continues unabated after circulatory death determination has been achieved.
342
343 On the question of potential harm to the donor, many argue that the donor is insensate because
344 clamping the aortic arch vessels ensures a lack of cerebral blood flow that most closely mimics the level
345 of blood flow to a brain in a standard DCD donor. As such, they perceive the conditions for NRP to be
346 similar to those for DCD, where it is assumed that the donor is insensate and no harm is incurred by the
347 procedure.
348
349 **Argument that NRP does violate the Dead Donor Rule (DDR) and may cause harm:**

350 Yet, many raise concerns that the patient has been declared dead on the basis of the permanent
351 cessation of circulation, with the full intent and understanding that regional circulation will be restored,
352 invalidating the prior determination.[137] It is important to note that at that time of donation the patient
353 may no longer meet criteria needed for declaration of circulatory death nor have they been
354 demonstrated to meet the accepted criteria for the neurologic determination of death- which has not
355 been assessed. Although it is impractical for the team to pursue tests needed to confirm neurologic
356 determination of death, without this, the patient donor does not meet either standard for circulatory or
357 neurologic determination of death at the time of organ procurement.
358
359 A reasonable person may ask: since the patient has been declared dead after the established duration of
360 pulselessness, why is it necessary to ligate the aortic arch vessels?
361 There is no single proffered answer to this question. Those in favor of NRP suggest that occluding the
362 aortic arch vessels is something that occurs after death has been declared, which consequently has no
363 ethical relevance, and as such ought simply to be characterized as an additional step of efficiency to
364 bring about an already agreed upon outcome. Since, according to this logic, there is a tacit agreement by
365 all parties that CPR will not be applied once the heart stops beating, DCD, including DCD-NRP, can,
366 indeed, reliably be characterized as "permanent" even before occlusion is considered. In other words,
367 occlusion merely makes explicit that which is already implicit. It is a prior act of omission, namely, the
368 decision not to resuscitate, as opposed to any subsequent act of commission, because of which death
369 follows. The decision to occlude is no more than one of economy and expedience, which ensures
370 permanent cessation of circulation to the brain. It is not a decision to ensure that death takes place, as if
371 there would otherwise have been any doubt.

372 Those who think NRP does run afoul of the "do no harm" principle ask: has any convincing evidence
373 been put forth to demonstrate that brain death has occurred at the time circulatory death is declared? If
374 not, it is arguably reasonable to assume that brain death criteria have not been met at the time
375 circulatory death is declared. Furthermore, if in situ reperfusion via ECMO without the additional step of
376 occlusion would serve, if anything, to move in a direction away from brain death, then any overt act
377 preventing blood from getting to the brain ought not merely to be characterized as an non-decisive act
378 of commission following the determinative act of omission, but rather as a determinative act of

[136] Ibid. "cDCD" refers to controlled DCD scenarios in which life support is withdrawn in accordance with potential donor/family decisions.
[137] 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.

379 commission itself. In this case, the occlusion of these key vessels takes place in order to add an extra
380 layer of assurance that dying is not thwarted. As such, occlusion cannot rightly be characterized as a
381 decision of "economy."

382 It bears mentioning that in calling attention to these disparate explanations for why occlusion of the
383 aortic arch vessels takes place in NRP, the Committee does not opine on which is more plausible. The
384 Committee does take the view, however, that the decision to occlude warrants scrutiny and better
385 understanding. Moreover, the Committee maintains that how one understands the motive behind the
386 decision to occlude will be revealing in the context of any rendered ethical analysis of NRP. Indeed, for
387 the proponent of NRP, for whom the initial declaration of death based on circulatory criteria should be
388 unquestionably trusted and therefore never second-guessed, intent is what governs the analysis and the
389 perspective that the DDR is not violated.[138] That all parties have agreed that death is an inevitability, and
390 that nothing should be done to undo this, takes precedence. While these intentions are undoubtedly
391 sincere, they are a problematic defense against those who see NRP as a work-around to the DDR.
392 Skeptics may argue that declaring the patient dead on the basis of the permanent loss of
393 cardiorespiratory function is misleading, since that function is immediately restored, clearly showing
394 that its loss was not permanent, nor irreversible.[139] Similarly, while proponents clearly do not intend to
395 restore brain perfusion with ECMO, this is at least a theoretical possibility, and promises to terminate
396 the procedure if this were to occur, can be alarming in the views of skeptics. Finally, proponents also
397 allude to the near certainty that these patients will become brain dead, if they are not already, without
398 acknowledging that brain death is a complex diagnosis that can only be made over a course of at least
399 several hours.[140] From the perspective of one who has concerns about any taken human action which
400 might impact the reliability upon which death criteria are invoked, more attention should be paid to
401 compliance with the principle of "do no harm," in which case right intent (like informed decision
402 making), is a necessary, but not sufficient, element in the ethical analysis. Intent does not have
403 overriding priority in the ethical analysis.
404
405 On the role of intention and justifying ligation through cautiousness, Glazier/Capron consider that "the
406 legal standard for determining death is bare of intent: a patient is dead when circulation neither can nor
407 will resume. That the patient is in a state where meaningful existence is not possible, that trying to
408 induce spontaneous resumption of circulation would be futile, or even that the NRP protocol is
409 consistent with the donor's wishes, are all irrelevant to whether the patient is deceased under US law,
410 which turns on the person's physical condition not on anyone's intention."[141]
411
412 On the question of harm to the donor: potential for harm to the donor stems from being uncertain if
413 occluding the arch vessels is sufficient to prevent blood flow to the brain and ensure that the donor is
414 insensate. **This should be tested for, and more studies to confirm that NRP donors are insensate are**
415 **needed.[142]**

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[138] 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.
[139] 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.
[140] 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.
[141] 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.
[142] 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

416 Additional potential harms to public trust and dissenting healthcare providers are described under
417 "utility" (page 20).
418

419 *Respect for Persons*

420 The ethical principle of respect for persons refers to the belief that people should be allowed to make
421 decisions for themselves, so long as those decisions do not impose harm to others. "This principle
422 embraces the moral requirements of honesty and fidelity to commitments made, and respect for
423 autonomy."[143] With NRP, the ethical principle of respect for persons suggests we have a duty to honor
424 the potential donor's first-person authorization for donation for antemortem interventions required for
425 donation to occur.
426
427 Respect for persons requires honoring the potential donor patient's intentions and wishes to become a
428 donor, and to make the best possible use of this donation. Moreover, respect for persons acknowledges
429 the importance of donor candidate families in acting as surrogate or authorized decision-makers, acting
430 in accordance with the preferences, values, and expectations of donor candidate patients. In this vein,
431 some consider that NRP promotes autonomy.
432
433 On the question of informed decision making, some opine that standards applicable to the authorization
434 process for DCD donation are sufficient, because both TA- and A- NRP uses similar premortem
435 interventions.[144] Yet others, concerned with whether regional restoration of circulation negates the
436 original determination of death, consider crucial differences must be disclosed to potential donors and
437 families regarding recirculation and the potential restoration of any cerebral perfusion.[145] For some,
438 these distinctions are meaningful in a way that may contradict their values and beliefs, and may alter
439 their propensity to participate in NRP. Without sufficient public polling, outreach to communities of
440 different faiths and cultures, etc., it is challenging to know how widely acceptable NRP is, and what
441 elements must be included in informed decision making. Some critics of NRP argue that achieving
442 informed consent or authorization to NRP are simply not possible if ligating arteries constitutes the
443 cause of death, because an individual cannot give consent or authorization for something that causes
444 their death. With these potential exceptions and limitations identified, the following section provides
445 an overview of informed decision making for optimizing respect for persons in conversations with
446 patients and their families who may be approached about organ donation and NRP specifically.
447

448 Informed Decision Making

449 The Committee acknowledges the challenges faced by OPOs in approaching donor candidates and
450 potential donor families, and the difficulty in explaining the components needed for informed decision
451 making (for procedures pre- and post-mortem) and balancing the need for adequately informing
452 potential donor patients and families with the understanding that many families, grief-stricken, do not

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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.

[143] 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/.

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

[145] 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.

453 wish to hear details of these procedures. To uphold commitments to autonomy, and to maintain public
454 trust in the organ donation and transplant system, it is critical to be transparent about methods used to
455 facilitate organ donation and facilitate an informed decision making process with the donor and/or
456 surrogate decision maker. Transplant professionals should avoid evasive and paternalistic attitudes
457 toward bereaved family members that preclude sharing of information and instead focus on an
458 informed decision making process with clear goals for upholding transparency, respect for the rights and
459 interests of the donor and/or their surrogate decision maker, and good stewardship of gifted
460 organs.[146,147] This is especially true for NRP, as feelings regarding this specific procedure may differ from
461 other more established forms of organ procurement. More research is needed to better articulate
462 these.
463
464 The basis for informed decision making for NRP, rests on the foundational principles of authorization for
465 DCD:

466 1. The withdrawal of life sustaining treatment (WLST) conversation must occur before any
467 discussion of donation. This conversation should occur only with the potential donor's clinical
468 care team, *not* OPO staff. The donation conversation, whenever possible, should not occur until
469 after an informed decision has been made to withdraw life sustaining treatment. The
470 Committee acknowledges that this effort is impacted when families spontaneously raise
471 questions about the opportunity to donate organs before or in tandem with the WLST
472 conversation.[148]
473 2. Informed decision making for ante-mortem procedures and authorization for post-mortem
474 procedures must be obtained by the potential patient donor's clinical care team, "Capable of
475 disclosing information accurately, interacting compassionately with grieving families, and
476 answering all relevant questions… optimal requestors will be those persons who are able to be
477 transparent and are best able to relay information to families in a comprehensive,
478 compassionate, and even-handed manner."[149]
479 3. Ideally, the trained requestor for potential donation is a member of the OPO staff with specific
480 training and education to support conversations about NRP with donor family members and
481 hospital staff.[150]

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[146] 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.

[147] 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.

[148] Holm, Are M., et al. "ISHLT position paper on thoracic organ transplantation in controlled donation after circulatory determination of death (cDCD)." *The Journal of Heart and Lung Transplantation* 41, no. 6 (2022), 671-677. doi:10.1016/j.healun.2022.03.005.

[149] 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.

[150] 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.

482 4. "If patients have provided first-person consent for organ donation, those obtaining consent
483 from surrogates for ante mortem procedures … should consider using language that frames the
484 conversation around a default assumption of donation."[151]
485 5. Authorization from potential patient donor or surrogate decision maker must be obtained for
486 ante-mortem interventions to maximize transplantable organs as part of the consent for
487 donation.[152] These include heparin administration, bronchoscopy, liver biopsy, placement of
488 cannulae, prep and drape of the donor, and transport to a separate location or operating room
489 for recovery as applicable.[153]
490 6. The requestor must include an explanation of the hands-off period after circulatory cessation.
491
492 In addition to the elements of informed decision making included for a DCD recovery as described
493 above, NRP raises questions about the need to disclose additional information about the recovery
494 procedure. Recommendations for NRP include a reiteration of the purpose and function of the hands-
495 off waiting period, as well as a description of the steps of the procurement procedure.[154] For TA-NRP,
496 this includes the ligation of vessels to prevent cerebral circulation and the reperfusion of targeted
497 organs before they are removed from the body. Disclosure for TA-NRP should also include a statement
498 that heart function may be restored to provide blood flow to organs.[155] The Committee also considers
499 that both TA- and A- NRP should include in informed decision making discussions the identification of
500 the potential restoration of any cerebral perfusion.
501
502 Experienced requestors understand that the needs and preferences of donor family members and
503 surrogate decision makers may be different based on the unique circumstances of each case. The
504 informed decision making process for organ donation has the obligation to refrain from burdening the
505 donor family during their time of suffering any more than is absolutely necessary. Information must be
506 clear and easy to understand to meet legal standards including whether the proposed protocol is
507 understood and whether justification for failure to disclose risk is acceptable.[156] Considering strongly
508 held beliefs in the transplant community regarding the ethical, moral, and legal ramifications of NRP, it is
509 especially critical that the potential donor family be educated about the unique procedures associated
510 with NRP.
511
512 Although OPOs must abide with consideration for not burdening potential donor families with
513 unnecessary or unwanted details, the ethical principle of respect for persons supports giving the
514 surrogate decision maker the option to opt out of detailed information about the recovery procedure,
515 while requiring that some key pieces of information are always explained. In the case of NRP, this likely

[151] 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.
[152] 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.
[153] 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.
[154] 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.
[155] 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.
[156] Showalter, Stuart J. *The Law of Healthcare Administration*, 9th ed. Chicago: Health Administration Press, 2020. NCh. p. 411

516 includes describing clearly that although the donor is declared dead by circulatory death criteria,
517 circulation will be restored regionally (A-NRP) and this may include the heart (TA-NRP), at a time the
518 patient donor has not been assessed to meet the criteria for brain death. It may be especially important
519 in the case of NRP to provide comprehensive support to donor families following the donation event,
520 such that if questions or concerns about the recovery method arise after the fact, donor families have
521 access to information and support. The Committee accepts that in rare circumstances the potential
522 donor's surrogate may decline, after serious efforts are undertaken, to hear the information that will
523 ensure informed decision making is provided. Such "noninformed decision making" should be fully
524 documented and should not preclude proceeding with the NRP protocol.[157] Requestor training should
525 specifically include these elements.
526
527 The Committee strongly recommends that local hospitals' ethics committees review NRP practices to
528 promote support and transparency within the surrounding community. A clear process for anonymous
529 reporting of complaints or concerns by staff should be developed. The Committee recognizes that in
530 rare occasions potential donors may be moved to another hospital or to an OPO recovery center. It is
531 especially important in such instances that informed decision making, including review of the NRP
532 procedure, occurs prior to any transfer of a potential donor. Another consideration relevant to transfers
533 is assurance of local ethics committee review, which may be more challenging for smaller hospitals.
534

535 ## Uncontrolled NRP

536 Uncontrolled scenarios are those in which circulatory death occurs unexpectedly, not after the planned
537 withdrawal of life support.[158] While the process of organ recovery following the decision for donation is
538 largely the same in uncontrolled NRP as in controlled NRP (hands-off period, occlusion of vessels, and so
539 on), uncontrolled NRP presents additional ethical concerns related to respect for persons and non-
540 maleficence.[159]
541
542 The transition between living patient and organ donor in uncontrolled NRP is rapid and potentially
543 confusing for both potential donor families and clinical teams. This raises concerns about compressed
544 timing and difficulty of informed consent discussions with potential donor families. Putting potential
545 donor families in a situation where they do not fully understand the implications of what they are
546 consenting to is extremely risky.
547 An additional complication to uncontrolled NRP stems from the use of ECMO. If a clinical team has
548 decided against using ECMO to prolong life (due to low chance of recovery or quality of life judgement),
549 but then ECMO is used to resume circulation after the hands-off period, this presents significant concern
550 regarding respect for persons. Uncontrolled NRP is additionally challenged by the need to balance
551 clinical decisions with factors relevant to organ preservation and informed consent, all of which need to
552 be conducted in a setting of high acuity.
553
554 The potential for teams to make decisions that do not fully honor respect for persons or potentially
555 cause harm is greater given the rapidity and urgency of uncontrolled settings. Trust in clinical teams and
556 in donation processes are a cornerstone to the organ transplantation system. There is a greater

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[157] 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.
[158] 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
[159] 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.

557 potential for harm or concern for autonomy where there is a lack of procedures and protocols to ensure
558 safety and maintain trust. The transplant community owes itself and the general public assurance that
559 no harm will occur and respect for persons is maintained. The potential for harm is greater in
560 uncontrolled scenarios, and additional caution should be reflected accordingly.
561

562 ### *Utility*

563 Utility is a foundational principle that guides the United States' transplant system. Applied to organ
564 donation and allocation, utility "specifies that allocation should maximize the expected net amount of
565 overall good (that is, good adjusted for accompanying harms), thereby incorporating the principle of
566 beneficence (do good) and the principle of non-maleficence (do no harm)."[160]
567

568 #### Potential Increases to Utility

569 NRP is a promising development in the field of organ transplantation, since it has the potential to
570 substantially improve both the number and the quality of organs that are available for transplantation,
571 and in particular for the heart, which may be difficult to effectively procured by standard DCD
572 donation.[161] The number of organs would likely be increased by enabling the transplantable organs to be
573 resuscitated in situ, such that otherwise unusable organs could become transplantable. Similarly, in situ
574 resuscitation has the potential to increase the function and the quality of the organs before they are
575 removed for transplantation, which should improve graft function and survival in the long run.[162]
576

577 There is an overall increase in the average number of organs transplanted per donor with NRP compared
578 to controlled DCD (cDCD) (3.3 versus 2.6).[163] Specifically, for heart: Increased number of hearts available
579 for transplant (applies to TA-NRP only); for liver, decreased rates of early allograft dysfunction, 30-day
580 graft loss, ischemic cholangiopathy, and anastomotic strictures compared to cDCD livers; and for kidney:
581 Decreased DGF and 1-year graft loss, improved 12-month kidney function compared to cDCD kidneys.[164]
582

583 NRP may also increase utility for donor families, who may receive comfort from the knowledge that
584 their loved one was able to save a greater number of lives with fewer complications. As previously
585 noted, data on public attitudes toward NRP are limited. However, it is known that families experience
586 psychosocial distress when their loved one is a DCD donor whose death does not occur in time to allow
587 the donation of organs.[165] Other studies suggest that the public is open to expanding donor protocols

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[160] 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/.

[161] 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.

[162] Ibid.

[163] 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.

[164] 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.; 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.; 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.

[165] 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.

588 (imminent death donation) in a way that maximizes the chance that a donor will be able successfully
589 donate.[166]
590
591 ## Potential to decrease utility

592 Although NRP may benefit utility by saving more lives, decreasing post-transplant morbidity, and
593 providing comfort to donor families, there is also a potential for it to adversely impact donor families
594 and public trust.
595
596 If a potential donor or donor family does not fully understand NRP and subsequently had concerns
597 about the process, they could experience psychosocial distress. The potential to exacerbate
598 psychological distress, regret, grief, and loss of trust among donor families presents a weighty
599 consideration, and one that must be considered and addressed before proceeding with NRP. Practices
600 to ensure that sufficient information is given, received, and understood must be in place to reduce
601 potential harm to donor families.
602
603 Potential Harm to Public Trust
604 Loss or decline in public trust in organ transplantation may be a direct harm of NRP. This harm may be
605 amplified given the current societal challenges regarding misinformation of scientific and health
606 information.[167] While loss of trust in the organ donation process is a harm in itself, it may also have a
607 secondary effect of decreasing the number of people willing to consent to deceased or living donation.
608 Additionally, given the lack of consensus among leading legal scholars about the legality of NRP, the
609 potential for lawsuits associated with potential DDR and UDDA violations could further magnify the
610 public relations challenge of sustaining public support for the mission of organ procurement and
611 transplantation.[168] These lawsuits may not only undermine public support, but they may also strain the
612 transplant system and community in response.
613
614 Moral distress among transplant clinicians
615 The ethical and legal concerns described above have raised concerns among clinicians and other health
616 care providers, including some clinicians at centers that perform NRP, that can be characterized as moral
617 distress: the perception that a clinician must engage in an action as part of their clinical role that they
618 believe to be morally wrong.[169] In the absence of greater clarity from the UDDA, and without better
619 understanding the scope and extent of potential harms particularly to the potential patient donors (pre-
620 mortem) and of donor families, either by virtue of the NRP procedure itself, or merely by not sufficiently

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[166] 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.

[167] 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.

[168] 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.

[169] Le Dorze, Matthieu., et al. "'A Delicate balance'—Perceptions and Experiences of ICU Physicians and Nurses Regarding Controlled Donation After Circulatory Death. A Qualitative Study." *Transplant International* 35 (2022). doi:10.3389/ti.2022.10648.

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.[170] These concerns were often related privately and there are not public data on clinician attitudes on NRP particularly within the United States.

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.

This Committee 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 Committee also affirms the sacred trust and commitment of the transplant community to organ donors and donor families. Finally, the Committee 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 the Committee concludes that the OPTN should proceed, but proceed cautiously regarding the practice of NRP for organ procurement. The following ethical considerations require consideration and resolution:

- Assurance that NRP adheres to the Dead Donor Rule.
- Nonmaleficence must not be violated in the pursuit of NRP, even if positive utility outcomes could result.
- Standardized 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.
- The Committee agreed that the uncontrolled scenarios for any form of NRP should not be performed at this time because of added concern regarding nonmaleficence and respect for persons.

[170] Summaries of the Committee's deliberations are available here: https://optn.transplant.hrsa.gov/about/committees/ethics-committee/

Addendum

<u>Addendum: The Uniform Determination of Death Act and NRP</u>

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[171], 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 in various fields of law.[172] The process also pushes the individual states towards uniformity, a goal that 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."[173] The other uniform law that is most relevant to organ donation is the Uniform Anatomical Gift Act.[174]

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."[175] 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."[176]

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

[171] The Drafting Committee to Revise the Uniform Determination of Death Act, a Committee of the Uniform Law Commission, is meeting to determine if revisions to the UDDA are appropriate.
[172] "About Us - Uniform Law Commission." Uniform Law Commission. https://www.uniformlaws.org/aboutulc/overview.
[173] 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.
[174] National Conference of Commissioners on Uniform State Laws. *Anatomical Gift Act.* 2006.
[175] President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, 42 USC, 1981.
[176] National Conference of Commissioners on Uniform State Laws. *Uniform Determination of Death Act*. 1980.

could be used only where an individual's respiratory and circulatory functions were maintained by artificial means."[177]

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."[178] 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."[179]

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."[180] 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.[181]

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

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[177] Klein, Daniel. Uniform Determination of Death Act. American Law Reports, 7th Edition, Art. 5, 2020.
[178] 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.
[179] Ibid.
[180] 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.
[181] Ibid.

730 death could not possibly be declared based on the timeframe and existing requirements for
731 doing so.”[182]
732
733 They further argue that: “The technical details of NRP can obfuscate the straightforward point
734 that a person is not dead based solely on a declaration. Consider a counterexample: In standard
735 DCD, after a 5-min “hands-off period,” death is declared. But what if, just before explantation,
736 autoresuscitation occurs, and the heart restarts (a known phenomenon)?[183] Would explantation
737 proceed? It should not. Was this patient dead, then raised from the dead? No. What happened
738 proved the prior declaration wrong. The patient was not dead. Restarting circulation invalidated
739 the prior declaration of death. Likewise in NRP.”[184]
740
741 A major part of the debate concerns the relevance of the intention of the transplant team in
742 performing NRP. One argument is that even when NRP restores circulation, the transplant team
743 is not attempting to resuscitate because that would be medically ineffective and its sole goal is
744 to preserve the organs, such that this does not reverse the loss of function (or otherwise put the
745 loss of function remains permanent). The same is true of the individual who has authorized
746 organ donation, they intend any restoration of circulation solely for the purpose of maintaining
747 the viability of the organs not for resuscitation and this should not disturb the conclusion that
748 function has been irreversibly (or permanently) lost.
749
750 Glazier and Capron respond by drawing a distinction between the ethical significance of
751 intention versus its legal significance (or lack thereof) under the UDDA.[185] They argue that:
752
753 “Although intentions may be important when evaluating the ethical acceptability of physicians’
754 actions, the legal standard for determining death is bare of intent: a patient is dead when
755 circulation neither can nor will resume. That the patient is in a state where meaningful existence
756 is not possible, that trying to induce spontaneous resumption of circulation would be futile, or
757 even that the NRP protocol is consistent with the donor's wishes, are all irrelevant to whether
758 the patient is deceased under US law, which turns on the person's physical condition not on
759 anyone's intention.”[186]
760
761 A further complication in assessing what the UDDA means for NRP is the circulation of blood
762 flow to the brain. Glazier and Capron argue that if an NRP protocol calls for the occluding of the
763 carotids, the transplant team:
764
765 “may indeed intend to improve organ viability but it is also true that preventing oxygen from
766 reaching the brain removes the risk that in some DCDD patients the restoration of blood flow to
767 the brain could prompt at least temporary resumption of functions that are inconsistent with
768 either or both the neurological or the circulatory respiratory standard for determining death. An
769 ambitious district attorney might convincingly argue that physicians following the NRP protocol

[182] 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.
[183] 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.
[184] Ibid.
[185] 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.
[186] Ibid.

770 also intended to render irreversible any brain functions that had not permanently ceased, thus
771 ensuring the patient's death."[187]
772
773 As Harry Peled et al. put it "Although it is true that the intent of NRP is to produce permanent
774 cessation of brain circulation, if brain blood flow does occur, the permanence requirement was
775 never met, and therefore, the declaration of death was not valid."[188]
776
777 Rendering matters more complicated, not all NRP protocols are the same as to the risk of blood
778 recirculation. As Basmaji et al note that there are two types of NRP:
779
780 "abdominal NRP (A-NRP) and thoracoabdominal NRP (TA-NRP). A-NRP supports the liver, kidney,
781 and pancreas, whereas TA-NRP supports the heart, lungs, and abdominal organs. In A-NRP,
782 cannulas are inserted either into the iliac artery and vein or into the abdominal aorta and
783 inferior vena cava, whereas the thoracic aorta is occluded at the level of the diaphragm. In TA-
784 NRP, the cannulas are placed in the right atrium and the iliac artery or abdominal aorta (6). A
785 critical anatomic difference exists between these two NRP modalities: A-NRP excludes blood
786 flow into the thoracic aorta but TA-NRP does not."[189]
787
788 They are not the same when it comes to the risk of brain reperfusion:
789
790 "Unlike TA-NRP, A-NRP excludes the thoracic aorta from the extracorporeal circuit, preventing
791 collateral flow via the internal thoracic, intercostal, and thoracic spinal arteries. Surgical
792 techniques, such as selective cannulation of the aorta and inferior vena cava as well as manual
793 transection of the lumbar collaterals, eliminate the possibility of collateral flow via the inferior
794 epigastric and lumbar arteries, respectively. Although neither technique "definitively" rules out
795 the possibility of brain reperfusion, A-NRP is the safer modality in this respect."[190]
796
797 Thus for those for whom the possibility of brain reperfusion is relevant to whether the UDDA's
798 criteria for declaring death have been met, the details of the NRP protocol might matter.
799
800 *UDDA Revisions*
801
802 The ULC is currently considering potential revisions to the UDDA, upon which this paper will not
803 speculate.[191]

[187] Ibid.
[188] Peled H, Mathews S, Rhodes D, et al. "Normothermic Regional..." Critical Care Med 2022;50(11):1644-1648, doi:10.1097/ccm.0000000000005632
[189] 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.
[190] Ibid.
[191] The Drafting Committee to Revise the Uniform Determination of Death Act, a Committee of the Uniform Law Commission, is currently meeting to determine if revisions to the UDDA are appropriate.

804 # Appendix A: Relevant Terms and Acronyms

805

806 *Ethical Terms – Definitions*

807 **A priori:** knowledge from theoretical deduction, as opposed to from observation or experience
808 **Dead donor rule:** Organ donors must not be killed by and for organ donation. Not in law directly but
809 embedded within the context of how organ transplantation could be ethically pursued.
810 **Distributive justice:** Requires fairness in the distribution of scarce resources so that patients of similar
811 need have an equal opportunity to benefit from transplantation
812 **Informed consent:** While donor's decision to donate is governed by UAGA and gift law, informed
813 consent is relevant to donor family members understanding and agreeing to specifics of DCD; similar
814 protocols apply to most NRP programs in obtaining informed consent procedure.
815 **Irreversible:** Not able to be undone or altered. Noted in UDDA definition of death; its implications for
816 NRP is whether NRP violates irreversibility by the recirculation of blood.
817 **Non-informed consent:** A rare situation where the potential donor's surrogate may decline, after
818 serious efforts are undertaken, to hear the information that will ensure informed consent is provided.
819 **Nonmaleficence:** Do no harm. One concern related to NRP is whether the donor could be harmed by the
820 procedure.
821 **Permanent:** Lasting or intended to last or remain unchanged indefinitely. Relevance: some have
822 interpreted "irreversible" to be "permanent", which is relevant to determining circulatory death.
823 **Procedural justice:** Upholds a commitment to treating like cases similarly, transparently, and predictably
824 **Respect for persons:** Respect for autonomy holds that actions or practices tend to be right insofar as
825 they respect independent (without coercion or interference) choices made by individuals, as long as the
826 choices do not impose harm to others. Relevance: upholding autonomy in honoring donor decision to
827 register to become an organ donor.
828 **Utility:** The maximization of net benefit to the community (taking into account both the amount of
829 benefit and harm and the probability of such benefit and harm). Utility is often discussed with NRP in
830 the context of improving organ quality and increasing the number of organs procured.
831 **White paper:** an authoritative report or guide that informs readers about a complex issue and presents
832 the issuing body's philosophy on the matter. White papers do not change OPTN policy in and of
833 themselves.
834

835 *Medical Terms - Definitions*

836 **Abdominal Aorta:** the major artery supplying the vital organs in the human body
837 **Allograft dysfunction:** Transplanted organs that are not functioning optimally and may be caused by
838 several donor or recipient-derived mechanisms
839 **Anastomotic strictures:** Narrowing of an anastomosis.
840 **Anesthetic:** a substance that reduces sensitivity to pain
841 **Angiogram:** a medical imaging method that uses X-ray to visualize arteries or veins **Asystole:** cessation
842 of all electrical and mechanical activity of the heart
843 **Atrial cannula:** a cannula inserted into an artery
844 **Autoresuscitation:** a rare phenomenon where there is a delayed unassisted return of spontaneous
845 circulation after medical teams stop CPR or other life support means
846 **Bispectral index (BIS) monitoring:** a type of electroencephalogram (EEG) monitoring that assesses brain
847 activity
848 **Brachiocephalic arteries:** the arteries that branch off of the aorta and go into the upper chest and brain

849 **Brain death:** death based on the absence of all neurologic function to the brain and brainstem
850 **Bronchoscopy:** a procedure where an instrument is inserted into the airway through the nose or trachea
851 to allow medical teams to look inside the lungs
852 **Bypass:** refers to cardiopulmonary bypass, a procedure that pumps blood into a machine outside the
853 body (heart-lung machine) and allows it to be oxygenated before returning it to the body. This
854 procedure is commonly used in heart and lung surgery
855 **Cannulation:** The process of entering a blood vessel with a fabricated instrument to gain access to the
856 blood vessel.
857 **Cardiopulmonary arrest:** cessation of heart and lung function (colloquially known as cardiac arrest)
858 **Collateral blood flow:** Describes a collateral network of blood vessels that may provide blood flow to an
859 area of the body where the main blood flow is blocked.
860 **Coronary arteries:** Main blood flow vessels to the heart.
861 **Critical care team:** a group of specially trained medical personnel (including doctors, nurses, and
862 technicians) who care for patients in critical condition, usually in the intensive or critical care unit of a
863 hospital
864 **Distal:** further away from
865 **End of life comfort measures:** measures taken as part of a patient care plan focused on symptom
866 management and pain relief, and can include anesthetics and social, emotional, and spiritual support
867 measures
868 **Ex vivo:** outside the body
869 **Graft loss:** when a transplanted organ no longer functions. Definitions vary by organ, but can include
870 graft removal, re-transplant, death, or return to dialysis (for kidney).
871 **Heparin:** a medication that inhibits blood clotting, sometimes given to potential donors before
872 declaration of death to reduce the potential that blood clots will present problems in the recovery and
873 transplant process
874 **Imminent death donation:** recovery of a living donor organ immediately prior to an impending and
875 planned withdrawal of ventilator support expected to result in the patient's death
876 **Inferior vena cava:** the blood vessel that transports deoxygenated blood back from the lower part of the
877 body to the heart for re-oxygenation
878 **Intensivist:** a board-certified physician who provides special care for critically ill patients. Also known as
879 a critical care physician, the intensivist has advanced training and experience in treating this complex
880 type of patient.
881 **Intra-abdominal organs:** the spleen, stomach, liver, large and small intestine, gallbladder, appendix,
882 pancreas, adrenal glands, and kidneys
883 **Intubation:** a procedure where a tube is inserted to maintain a patient's airway and to allow ventilation
884 **Insensate**: unable to feel pain
885 **In situ:** Latin that could be translated "on site" or "locally." Used in reference to perfusion that is within
886 the body.
887 **Ischemia:** inadequate or no blood flow to a body part. In organ transplant, the time where an organ is
888 not connected to a blood supply is referred to ischemic time, and can be warm ischemia (inside the
889 deceased donor's body before recovery or removed from the donor's body but not yet iced) or cold
890 ischemia (on ice).
891 **Ischemic cholangiopathy:** a complication from liver transplant, where there is damage to one or more of
892 the body's bile ducts attributed to inadequate blood flow
893 **Laparotomy:** a medical procedure that cuts into the abdominal cavity, used in NRP to gain access to
894 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

Spontaneous reanimation: see autoresuscitation

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:

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.

940 **FDA:** The United States Food and Drug Administration. A federal agency of the Department of Health
941 and Human Services that ensures safety, efficacy, and security of human drugs, medical procedures and
942 techniques, and foods.
943 **IRB:** Institutional Review Board. Per the FDA definition, an IRB is a group that has been formally
944 designated to review and monitor biomedical research involving human subjects, including ensuring
945 human rights and welfare of the subjects and compliance with ethical principles.
946 **NRP:** Normothermic Regional Perfusion – the process by which organs are locally perfused in the body
947 after circulatory death is declared.
948 OPO:
949 **TA-NRP:** Thoracic-abdominal Normothermic regional perfusion. In the context of the ethical
950 implications, concern was especially focused around the implications of perfusing the heart after death
951 is declared.
952 **UAGA**: Uniform Anatomical Gift Act – the law that dictates the ability of individuals to choose to become
953 an organ donor and gift their organs.
954 **UDDA**: Uniform Declaration of Death Act – defines legal death as "An individual who has sustained
955 either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all
956 functions of the entire brain, including the brain stem"
957 **ULC**: Uniform Law Commission – the group that is reviewing the UDDA and considering potential
958 changes to it.
959 **VA-ECMO**: venoarterial extra corporeal membrane oxygenation. Machine technology used in both TA-
960 and A- NRP for perfusion.
961 **WLST**: withdraw life-sustaining therapy. Context: cDCD is pursued after getting consent for withdrawal
962 of life-sustaining therapy.

963 # Appendix B: Review of Presentations to Workgroup

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

965 **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[192]
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[193]
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[194]
University Hospitals Leuven	Arne Neyrinck, MD, PhD	Anesthesiologist perspective on TA-NRP developments in Europe.[195]
University of Cambridge	Christopher JE Watson, MD	Provided an update on the efforts and efforts of NRP in the UK.[196]
Geisel School of Medicine - Dartmouth	James Bernat, MD	Dr. Bernat shared his expertise as a neurologist, specifically focusing on declaration of brain death[197]
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[198]
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.[199]

966

[192] OPTN Ethics Committee NRP Workgroup, *Meeting Summary,* August 4, 2022.
[193] OPTN Ethics Committee NRP Workgroup, *Meeting Summary,* August 11, 2022.
[194] OPTN Ethics Committee NRP Workgroup, *Meeting Summary,* September 8, 2022.
[195] OPTN Ethics Committee. *Meeting Summary*, March 22, 2022
[196] OPTN Ethics Committee NRP Workgroup, *Meeting Summary,* September 8, 2022.
[197] OPTN Ethics Committee NRP Workgroup, *Meeting Summary,* September 22, 2022.
[198] OPTN Ethics Committee NRP Workgroup, *Meeting Summary,* December 8, 2022.
[199] OPTN Ethics Committee. *Meeting Summary*, March 22, 2022

967 ## Appendix C: Workgroup Members

968 The Workgroup contributed greatly to this analysis through their participation and engagement. They
969 are listed below:
970 **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	Ethics