

Briefing to the OPTN Board of Directors on **Ethical Analysis of Normothermic Regional Perfusion**

OPTN Ethics Committee

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Ethical Analysis of Normothermic Regional Perfusion

Sponsoring Committee: Ethics
Public Comment Period: July 26, 2023 – September 19, 2023
Board of Directors Meeting: December 4, 2023

Executive Summary

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 concerns regarding potential cerebral flow during recirculation.^{2,3}

The charge 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 is not a referendum on clinicians, centers, or organ procurement organizations (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.

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

- There are serious ethical concerns that NRP is not consistent with the Dead Donor Rule (DDR). There may be differences in degree to which the seriousness of these ethical concerns applies to abdominal NRP (A-NRP) versus thoracoabdominal NRP (TA-NRP).
- Nonmaleficence (do no harm) must not be violated in the pursuit of NRP, even if positive utility outcomes could result.
- Consistent and transparent protocols, including adequate informed decision making with

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>.

³American 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.

patients (pre-mortem) and of families approached about donation, are necessary pre-conditions for any ethical pursuit of NRP.

- Uncontrolled scenarios for any form of NRP should not be performed at this time because of added concern regarding nonmaleficence and respect for persons.

This white paper was issued for public comment from July 27, 2023 to September 19, 2023. The Committee reviewed the public comments and made changes to the white paper to incorporate feedback, discussed below.

Terms to Know

White paper: A white paper considers a complex issue and develops a position.

Ethics Committee's Scope: The Ethics Committee makes recommendations to OPTN Board of Directors for changing, creating, or eliminating policies if warranted by ethical concerns.

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

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

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

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

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

A more extensive glossary of relevant terms and acronyms is provided in Appendix A of the white paper.

Purpose

The 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.”⁴ 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, nonmaleficence (do no harm), and utility.

Though relevant to the overall discussion of NRP, it is beyond the scope of the Committee (and therefore, the paper) to speculate regarding potential future changes to the Uniform Declaration of

⁴ "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.

Death Act (UDDA), and to opine on whether NRP complies with current law.^{5,6} The Addendum to the white paper 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 through recirculating oxygenated blood in the donor body before organ recovery and transplantation.¹¹ Abdominal NRP (A-NRP) involves perfusing (providing blood flow to) the liver, kidney and pancreas and other tissue in the lower part of the body using thin tubes 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 flow through the heart; both forms of NRP involve occlusion of (blocking blood flow to) arteries to the brain.

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 standardized data on NRP limit the ability to confirm the extent of its use.¹³ NRP has developed in the U.S. without a formal, objective ethical evaluation being conducted, by the OPTN or otherwise, within the transplant

⁵ 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.

⁶ The Uniform Law Commission has suspended its deliberations on the UDDA as of 9/22/23, indicating that the UDDA may not be updated at all for the foreseeable future.

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.

¹³ There is no currently collected OPTN data on NRP, however, a field to collect whether a recovery was an NRP recovery or not was Board-approved in December 2022 and will be added to the OPTN Computer System upon implementation of the enhancement package. There are no publications on Pub Med before 2014, and the number has gone steadily up, with 381 titles in October 2023.

community.¹⁴ Currently, OPOs and transplant programs use a patchwork of varied approaches and decision making when it comes to NRP¹⁵, which may result in inconsistencies within the transplant system.

Need for Ethical Review

As the use of NRP has expanded, concerns have been raised that its pursuit may violate ethical principles governing organ transplantation.¹⁶ 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.^{17,18} Additional concerns related to nonmaleficence include unknown implications of circulation and potential blood flow to the brain. Although it is plausibly less likely that blood flow reaches the brain due to A-NRP, the Committee still finds questions regarding A-NRP's compliance with the DDR and respect for persons that warrant concern.¹⁹

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 convened a Workgroup to conduct a robust review of ethical implications.²⁰ The Workgroup represented diverse perspectives regarding NRP, and included expertise on ethics, donor family experience, organ procurement, U.S. law, and transplantation. The Workgroup also sought out perspectives that would inform their ethical analysis by engaging presenters from programs participating in NRP procurement (both within the U.S. and abroad) and critics with relevant expertise in law or neurology (a list of Workgroup members and presenters is provided in Appendix C). Overall, the paper did well in public comment and received broad general support for the purpose and goal of the white paper to provide an ethical analysis of NRP. While community opinions on the practice of NRP itself varied, many commenters thanked the Committee for taking on the issue and providing a comprehensive analysis. The following sections provide more details about overall sentiment from public comment, themes, and the Committee's response.

¹⁴ 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.

¹⁵ The Workgroup reviewed protocols presented by U.S. transplant programs engaged in the practice, and sought out the perspectives of intensivists, neurological experts, anesthesiologists, and researchers and clinical experts in determination of death. A full list of presenters and topics reviewed by the workgroup can be found in Appendix B.

¹⁶ 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.

¹⁷ Peled H, Mathews S, Rhodes D, et al. "Normothermic Regional..." *Critical Care Med* 2022;50(11):1644-1648, doi:10.1097/ccm.0000000000005632

¹⁸ 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.

¹⁹ 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.

²⁰ 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

Following public comment, the Committee discussed the feedback, made associated modifications to the text, and voted to submit the modified white paper to the OPTN Board of Directors for approval.

Overall Sentiment from Public Comment

The proposal was released for public comment from July 27 through September 19, 2023. Respondents were able to participate through in-person/virtual regional meetings, committee meetings, and a form on the OPTN website. Feedback received from the OPTN Patient Affairs, Heart, Liver, Kidney, Lung, OPO, Pediatric, and Transplant Coordinators Committee, as well as from a variety of stakeholders, including transplant hospitals, OPOs, patients, and professional organizations indicated support for the paper. Seven professional organizations, five OPOs, and a number of transplant programs and individuals provided written public comments. The community was generally supportive of this white paper and its goal to provide an ethical analysis of NRP, though opinions on the practice of NRP itself varied. The proposal collected sentiment from 284 respondents, including 64 written comments. Sentiment is detailed below in **Figures 1-2**.

Figure 1 shows sentiment received from all respondents (regional meeting, online, and email) by their stated member type. All member types were represented. Sentiment is collected on public comment proposals and is measured on a 5-point Likert scale from strongly oppose to strongly support (1-5). These reports are helpful to spot high-level trends, but they are not meant as public opinion polls or to replace the substantive analysis below. There was overall support for the white paper, demonstrated by a sentiment score of 3.6. The general public showed opposition to the white paper, as demonstrated by a 2.0 sentiment score (note: comments from this group were likely to indicate opposition to the practice of NRP itself). There was also some opposition noted from OPOs, patients, stakeholder organizations, and transplant hospitals, however the concern was balanced in these groups by those who expressed support.

Figure 1: Sentiment by Member Type

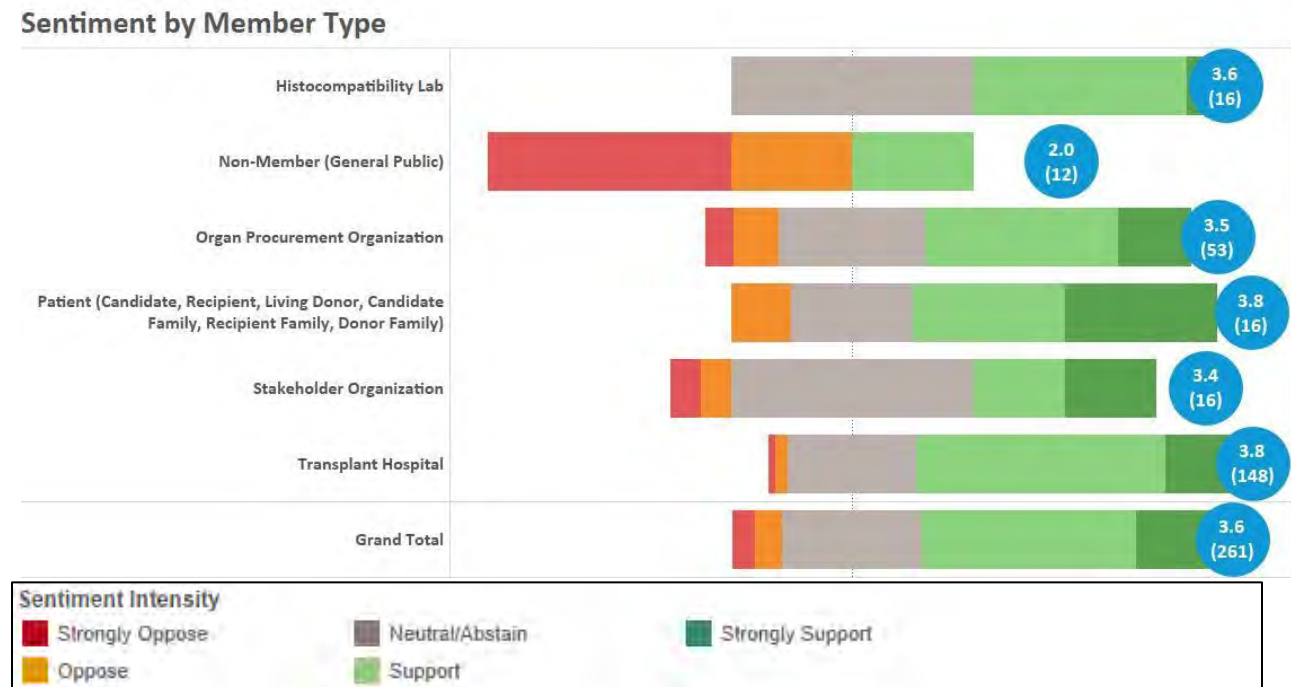
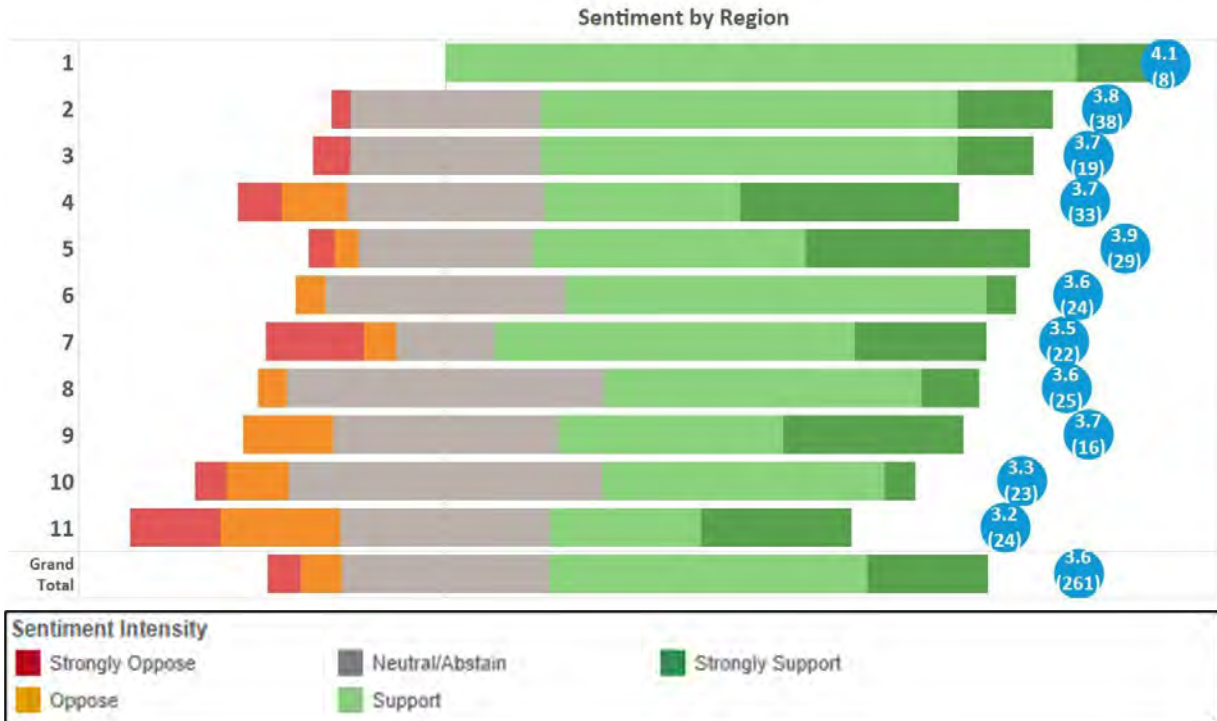


Figure 2 shows sentiment received at regional meetings. Again, overall sentiment was supportive, as indicated by a total sentiment score of 3.6. Regions 1 and 2 showed the most support, while Regions 10 and 11 expressed more concern. The “Public Comment Themes” section below provides an overview of the most frequent comments, questions, and concerns received during the public comment period.

Figure 2: Sentiment from Regional Meetings



Public Comment Themes and Considerations

Feedback from the community varied by region and by stakeholder type, and perspectives differed within these categories as well. The community was asked to provide input on what information should be disclosed to donors and next of kin regarding NRP and the approach to these conversations, and many commenters provided valuable insight on this topic. Another theme that was consistent throughout public comment discussions was the distinction between TA- and A- NRP. All themes and the Committee's responses are reviewed below, organized to closely mirror the structure of the paper.

Feedback on Purpose, Position, and Balance of Principles Analyzed in the White Paper

Many commenters provided feedback on the purpose and position of the white paper, as well as the balance of the principles considered in the analysis.

Purpose and Position

A majority of comments received from all stakeholders were supportive of the goal of the paper to provide an ethical analysis of NRP. In particular, many commenters noted that the analysis was well-balanced, timely, neutral, and comprehensive. While positions on NRP itself varied, commenters were highly supportive of the OPTN Ethics Committee reviewing NRP. While a few comments indicated concern that the paper was taking a certain position or providing policy recommendations, most comments indicated that the white paper is an important step for developing a societal understanding of NRP. Some commenters felt as though certain groups, such as clergy and minority communities, should have been more engaged as stakeholders.

Because public comment was supportive of the purpose and position of the paper, the Committee did not make any changes to this aspect. The Committee reviewed the comments submitted on this topic and affirmed that while community opinions on the practice of NRP itself were expected to vary, it was very promising to see that the feedback was supportive of the Committee considering the issue and providing an ethical analysis. Committee members noted that the paper specifically points out that it does not provide policy recommendations and is not a referendum on those currently practicing NRP. Outreach efforts included communication to encourage clergy groups, minority groups, and donor families to provide feedback on the paper as well, several of whom participated in the public comment process. The Committee actively considered a wide spectrum of stakeholders throughout the development of the white paper and appreciate the public offering opportunities to expand outreach and inclusion further. In discussion of the purpose and position of the paper, members reviewed the Committee's charge and scope and affirmed that the paper is in alignment.

Balance of Principles Analyzed

Many comments received across stakeholder types indicated that the Committee appropriately considered and weighed the ethical principles considered in the analysis. However, some commenters noted concern that the principles were not adequately balanced. In particular, they indicated concern that utility was too heavily weighted, concerns that the potential violation of the DDR was not given

enough weight, and a request to give the donor’s intentions for donating their organs as a “last gift” more weight were noted.

The Committee discussed feedback received on this theme and acknowledged some disagreement was expected for a controversial topic, but that most commenters felt as though the Committee struck the correct balance of ethical principles. In reviewing the public comments submitted on this topic, the Committee worked to ensure the perspectives on each principle were balanced and reflected the diversity of opinion in the community, while preserving the implications that follow from the analysis. From this discussion of public comment feedback, the Committee made the following changes:

- Further distinguished between TA-NRP and A- NRP,
- Added context to, and modified, the respect for persons section for clarity and consistency, and
- Updated the utility section to include recently published literature,

These changes are described in more detail in the following sections.

TA-NRP versus A-NRP

The paper explains the procedural differences between TA-NRP and A-NRP. Multiple (a total of thirteen) comments received from a variety of stakeholder types recommended further elaborating on the ethical and procedural differences between the two, citing additional ethical concerns related to recirculation, added political risk, and greater negative utility impact on lung procurement in TA-NRP as compared to A-NRP. Comments also noted differences in adoption of TA- and A-NRP both in the US and globally, as well as the potential to create confusion among the public if the paper does not clearly differentiate between the two types.

The Committee responded to this feedback after extensive discussion by further differentiating between TA- and A-NRP in several key portions of the paper, including the executive summary, background, and the conclusion. The Committee considers that the difference between TA- and A-NRP is a difference in degree, not in kind, and ultimately, the concerns for do no harm and compliance with the DDR still apply to A-NRP. However, the Committee explains the distinction between the two in occlusion processes and purpose and acknowledges that the potential for harm may be more significant with TA-NRP.

The paper was modified in response to public comment to:

- Clarify the discussion of occlusion of arteries in both forms of NRP,
- State more clearly the distinction between TA-NRP and A-NRP, and
- Explain in greater detail why considerations about restoration of circulation are still present for both forms.

The executive summary and the conclusion were also updated to reflect the revised discussion in the body of the paper.

Do No Harm (Non-Maleficence)

The paper considers potential harms to the organ donor and harms that may come from a loss of public trust in the practice of organ procurement, particularly with regard to the Dead Donor Rule (DDR), in the

do no harm section. Robust feedback was received on this section of the ethical analysis, and feedback was mixed regarding adherence to the DDR, its relevance, and ligation of cerebral vessels.

Many commenters pointed out the importance of the DDR as a cornerstone to ethical transplantation. On the other hand, some commenters debated the ongoing relevance of the DDR and suggested that NRP may be an opportunity to reconsider it. A comment also indicated concern that the ethical acceptability of NRP cannot be addressed properly without a larger, public forum where the broader community is made aware that the transplant community is contemplating a shift away from adherence to the DDR. Feedback also indicated that risks associated with adoption of NRP related to the DDR and other topics under respect for persons can be mitigated with careful standards and protocols. Some comments discussed the possibility of giving NRP donors anesthesia during procurement would lessen non-maleficence concerns.

Several commenters indicated that NRP is not a violation of the DDR, citing the artificial re-establishment of circulation after declaration of natural death, the intent of the donor/next of kin to donate organs, and the intent of the NRP procedure itself. However, several comments received indicated that NRP violates the DDR and/or fails to respect the initial declaration of death. These commenters noted concern that NRP procurement may cause brain death, the possibility of pain or harm to the donor, and the importance of adhering to the DDR for moral and legal reasons.

Feedback on the purpose and ethical considerations regarding occlusion or ligation of (blocking blood flow to) cerebral vessels was varied. Some comments indicated the opinion that ligation of cerebral vessels is a safeguard against the possibility of re-emergence of cerebral function and guarantees that the donor does not suffer. Commenters with this view explained that there is a difference between brain function and perfusion and between a heartbeat and circulatory function, as well as the impossibility of reversing death once a legal declaration has been made. Recommendations to further explain the existing literature on brain blood flow and brain activity were noted.

Yet, many comments across stakeholder types noted concern for the act of ligation of cerebral vessels. Commenters with this view pointed out that ligation of the vessels causes death and/or does not occur when a donor is legally dead, is not precautionary but instead necessary for preventing the return of brain function, hastens death, and has not been adequately studied and/or ethically debated.

In considering the divergence of perspectives within the community on the question of the DDR and NRP, the Committee ultimately affirmed its position that there are still outstanding, meaningful questions whether NRP complies with the DDR. Questions as to the importance of the DDR within the transplant community, or modifications to it, are beyond the scope of this paper. As previously noted, the Committee did distinguish that TA-NRP may raise more concern with the DDR than A-NRP in response to public comment. The Committee maintains that A-NRP still raises questions about potential for blood flow to the brain through the spinal cord (even if the potential is less than for TA-NRP) and involves recirculation in the donor after circulatory death is declared. In response to the suggestion to further explain the existing literature on brain blood flow, the Committee ensured that the paper references and appropriately explains the existing literature on brain activity and blood flow.

The Committee made the following modifications to the text in response to the public comment feedback described above:

- A brief discussion of the use of anesthesia during procurement was added
- A footnote was updated to discuss the conditions for neurological and circulatory death and their role for NRP
- Clarification was added to the discussion of the act of ligation and its connection to do no harm

Respect for Persons

The ethical principle of respect for persons includes the belief that people with decision making ability should be allowed to make important, personal decisions for themselves, so long as those decisions do not impose harm to others. This section of the paper discusses this in relation to NRP, focusing on honoring the potential donor's first-person authorization for donation, respecting the donor family's preferences for receiving information about NRP, and the landscape of authorization and disclosure for NRP, including informed decision making. In public comment, the community was asked to provide feedback on what information should be disclosed to donors and next of kin regarding NRP and how disclosure should be approached. Many commenters across stakeholder types provided feedback, suggestions, and context in response.

Feedback indicated that best practices surrounding authorization and disclosure in donation in general would be a good future topic for the Committee to consider. Many comments suggested broader community education and engagement on NRP, especially with clergy, minority communities, and those with lower health literacy.

Feedback was mixed on how NRP supports or undermines autonomy in transplant related to donors, recipients, OPOs, and transplant hospitals. There was concern that the analysis in the white paper does not adequately consider the Uniform Anatomical Gift Act, registration as an organ donor, and NRP as methods to support autonomy by improving the chances of successful organ transplantation. On the other hand, there was also concern that NRP targets a vulnerable patient and harms them despite the intention to respect their autonomy and that the donor family community is being left out of the discussion.

Commenters noted that neither recipients nor clinicians should be required to accept NRP organs or to perform NRP, and that donors and donor families should be offered procurement without NRP. Comments also suggested examining how recipients are informed and involved with the NRP process, noting that potential recipients or their families may feel there is a moral difference between NRP organs and non-NRP organs.

In consideration of potential modifications, the Committee confirmed the need to acknowledge the challenges OPOs face in informing donor families to the degree to which each particular family desires. The Committee made the following changes post-public comment:

- Language was added to provide additional context to the ultimate recommendations that information on NRP-specific elements of donation should be disclosed, with the understanding that some families may decline to hear these details.

Feedback on approach to authorization conversations

Many comments were received across stakeholder types indicating that the NRP conversation with donor families should:

- Consider their grief, trauma, and exhaustion
- Reassure the family that everything was done to save their loved one
- Be consistent and guided by a trained OPO professional
- Seek to achieve the goal of transparency while allowing families to guide the conversations
- Consider that families of pediatric donors typically undergo a much longer decision and pre-recovery process and not interfere with this

There was broad general support for qualitative research into what donor families find important and morally relevant and development of verbiage and dialogue to provide families to ensure consistent messaging. Broad support for including a variety of perspectives in this research and development was also indicated. However, feedback from OPO stakeholders was mixed on whether conversations should be standardized and/or mandated.

One OPO opined on the paper's treatment of the authorization and disclosure process, suggesting that it may not adhere to current best practices. Other comments discussed use of the terms "informed decision making," "informed consent," and "authorization," and suggested revisions for clarity and/or accuracy.

The Committee made the following changes to this section as a result of the public comment feedback discussed above:

- Clarified terms and ensured that consistent terminology is used throughout
- Explanatory language was added to further clarify the term "informed decision making"
- Discussion regarding timing of these conversations was modified and reviewed in response to OPO feedback
- Details of the section were reviewed for consistency regarding the allocation of roles in the approach to disclosure.

Feedback on content of authorization conversations

There was mixed feedback on the level of detail appropriate in disclosure for NRP. Some advocated for including details as critically important; however, others cautioned against including too many details during a devastating time of grief. Several OPO stakeholders noted that typically, details of other procurement processes are not shared with donor families unless they ask (though OPO professionals should always be prepared to answer specific questions should a family ask). Commenters noted that while high level information about declaration of death and use of a machine to circulate blood after death seemed reasonable, graphic language is not appropriate or morally relevant.

Commenters were divided on the need to disclose ligation of cerebral vessels. Other comments suggested that disclosure should include that standard criteria for assessing brain death will not be used, should provide details of NRP and the potential to recirculate blood after death in the spirit of transparency, and include information about the timeline of NRP (especially for families of pediatric donors). Several commenters indicated that it would be important to include that families can opt-out of NRP if desired; however, other feedback suggested that the burden of deciding whether NRP is appropriate should not be placed on grieving families. On whether the existing DCD authorization and disclosure process is also sufficient for NRP, the feedback was also mixed. The Committee's conclusion that uncontrolled NRP cannot be ethically supported at this time was supported by public comment.

The Committee discussed the public comments received on the content of disclosure and authorization conversations and made several changes to the section:

- Further explained the roles within the disclosure and authorization process,
- Clarified the basis for informed decision making for NRP
- The substance of recommendations (to disclose unique aspects of NRP to donor families) was maintained, but language was added emphasizing the uniqueness of each conversation with donor families and to emphasize the importance of these individual conversations in ascertaining the level of information each family may wish to have.

Utility

Many comments discussed possible utility benefits of using NRP and the risks that come with it. Many commenters discussed the improved outcomes, increased utilization, ability to reduce waitlist time, increased control during recovery, and lowered costs with NRP usage. Some commenters pointed out that there may be potential harm from not engaging in NRP and that there are clinicians who believe that NRP is morally obligatory. However, many commenters also discussed the risks that expanding NRP may pose to utility, including concern for negative impact on procurement of kidneys and lungs, concern that the community is overlooking viable ex-vivo alternatives, and the potential negative impact on public trust and donation rates.

The Committee discussed this feedback and elected to leave this narrative mostly intact, as members felt that the mixed public comment feedback indicated that the paper's treatment of the utility considerations of NRP on both sides was accurate and balanced. The Committee made the following changes in response to public comment:

- A paragraph was added to further explain utility considerations relating to lung procurement.
- Footnotes and references to current literature were updated throughout to reflect additional literature published on the topic since the paper was issued for public comment.
- A sentence discussing potential moral distress on the part of clinicians who feel NRP is morally obligated to prevent non-utilization was added.

Conclusions of the White Paper

While most commenters appreciated the goal of the white paper, feedback was mixed regarding the conclusion to proceed, but proceed cautiously regarding NRP. Several commenters expressed agreement with the recommendation, citing the positive utility impacts. However, other commenters noted concern, explaining the need for additional data, limited public understanding, lack of standardized protocols, and unanswered ethical and legal questions. Some commenters felt as though the framing of the conclusion did not follow clearly from the analysis, explaining that the analysis details problematic, unresolved ethical concerns, yet the conclusion recommends proceeding with NRP. Clarification on what was meant by "proceed cautiously" was recommended.

The Committee discussed feedback over the course of two meetings and opted to modify the conclusions of the paper in response. Members highlighted the need for the Committee to be consistent in its analysis, true to the Committee's charge, clear to the public, and expressed that it is the role of the

Committee to describe the ethical considerations involved in NRP, then leave it up to society and the Board of Directors to ultimately decide how to move forward.

The Committee elected to make the following changes to the conclusion in response to public comment:

- Remove “proceed, but proceed cautiously.” The text now reads: “the paper concludes that” and then lists the ethical considerations for how the technology may be implemented ethically.
- The bullet point describing concerns about NRP and its consistency with DDR was clarified, and a sentence was added to explain that there may be differences in degree to which the seriousness of the ethical concerns applies to A-NRP versus TA-NRP.

Clarifications and Perceived Inaccuracies

Several comments pointed out minor grammatical and consistency concerns. Some commenters also asked for specific clarification not otherwise alluded to in the themes covered above and pointed out certain perceived inaccuracies.

The Committee reviewed feedback in this category and made the following modifications to the text in response to public comment:

- Corrected grammatical errors and ensured consistency and flow
- Added terms to the glossary
- Clarified terms and processes
- The discussion of ECMO as it relates to uncontrolled NRP was removed as the Committee ultimately found it to be inaccurate according to practice.

For example, a public comment received indicated that the description of the process of moving potential donors to OPO recovery centers was inaccurate, and this section was updated accordingly.

Comments on the Addendum: The Uniform Declaration of Death Act (UDDA) and NRP

The Addendum to the paper briefly addresses the implications of the current text of the UDDA and its possible revisions relevant to NRP. Several comments were received on topics covered in the addendum or that have to do with the UDDA that are otherwise outside the scope of the Committee and the NRP white paper, such as

- the difference between “permanence” and “irreversibility,”
- suggested and/or possible revisions to the UDDA,
- the need for a unified brain-based concept of death, and
- legal frameworks in the United States as well as broader legal frameworks related to NRP abroad.

The Committee reviewed comments received on topics covered in the addendum and decided to keep the text of the addendum largely as originally written, noting that that while the legality of NRP is outside of the Committee’s scope and charge, it is important to discuss the implications of the current

text of the UDDA and its possible revisions for NRP. The Committee added the following in response to public comment:

- A sentence to note that as of September 2023, the Uniform Law Commission has suspended its deliberations on the UDDA, indicating that the UDDA may not be updated at all for the foreseeable future.

Compliance Analysis

NOTA and OPTN Final Rule

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,”²¹ to “provide information to physicians and other health professionals regarding organ donation,”²² 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.”²³ 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.

OPTN Strategic Plan

The white paper is in alignment with the following aspect of the OPTN Strategic Plan:

Increase the number of transplants:

This project analyzes the ethical implications of NRP, including the potential impact on utility. NRP may increase the number and quality of deceased donor organs which could positively impact utilization. However, the concerns regarding NRP could negatively impact public engagement with donation which could decrease the number of transplants. The paper explores these considerations.

Conclusion

The OPTN Ethics Committee’s white paper, *Ethical Analysis of Normothermic Regional Perfusion*, outlines the conditions for ethical practice of donation in the United States and implications for NRP. The paper considers a wide variety of perspectives and viewpoints and is in accordance with the Committee’s mission and scope. The analysis recognizes both the importance of increasing utility for candidates waiting for a transplant, and notes the importance of maintaining public trust and adhering to longstanding ethical and legal norms, that underpin support and sustainability of the entire transplant system. The Committee analyzes NRP through the lenses of do no harm, respect for persons, and utility.

The Committee modified the white paper in response to public comment in several key respects, as detailed above:

- The conclusion was modified for clarity and consistency with the analysis.
- The distinction between TA- and A- NRP was expanded upon and more clearly stated throughout the paper.

²¹ 42 USC § 274 (b)(2)(E)

²² 42 USC § 274 (b)(2)(H)

²³ 42 CFR 121.6(a).

- The do no harm section was updated for clarity and completeness.
- The respect for persons section was revised to ensure consistency in roles and practice, add additional language regarding authorization and disclosure, include clarification of terminology, and ensure accuracy.
- The utility section was updated to include recent publications and to describe the potential utility impact on lungs procured using NRP.
- The paper was updated to ensure flow, consistency, correct grammar, and readability.
- The addendum was modified to note that the Uniform Law Commission has suspended deliberations on the UDDA.

The Committee largely kept the essence of the ethical analysis intact following broad community support for the goals of and approach to the paper throughout public comment, in affirmation of the importance of providing a comprehensive ethical analysis of NRP. The Committee ultimately concludes that:

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

White Paper

Proposed new language is underlined (example) and language that is proposed for removal is struck through (~~example~~). Heading numbers, table and figure captions, and cross-references affected by the numbering of these policies will be updated as necessary.

Ethical Analysis of Normothermic Regional Perfusion

Executive Summary

This white paper outlines conditions for ethical practice of donation in the United States, and implications for normothermic regional perfusion (NRP).²⁴ Many viewpoints exist on NRP, and while the analysis espoused here may not accord with the views of some, all were taken into account in the analysis. The purpose of this paper is to provide the transplant community and the OPTN Board of Directors with ethical analysis and guidance at the systems-level to support the sustainability of organ donation and transplantation in the United States and to maintain public trust. This analysis recognizes both the importance of increasing utility for candidates waiting for a transplant, and the importance of maintaining public trust and adhering to longstanding ethical and legal norms that underpin support and sustainability of the entire transplant system.

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

NRP is a technique for perfusion either of abdominal organs (A-NRP) or thoracic and abdominal organs (TA-NRP) in a person's body after declaration of circulatory death, and includes occlusion of vessels to prevent brain perfusion.²⁵ This paper reviews the ethical implications of NRP according to established ethical principles guiding donation and transplantation, including: the principle of nonmaleficence (do no harm), respect for persons (which includes respect for autonomy), and utility. The principle of nonmaleficence is important for maintaining public trust and requires compliance with the Dead Donor Rule, which requires that patients must be dead at the time of organ procurement (i.e. meet criteria for brain or circulatory death) and that organ donation does not cause death.²⁶ This paper concludes that:

²⁴ The analysis benefited from presentations and participation of European transplant leaders who routinely conduct both A- and TA-NRP. There are important differences in basic premises underlying differences between donation practices between the United States and some European contexts, which include: support for interventions related to donation, adherence to the Dead Donor Rule, determinations of death criteria, differences in policies regarding provision of analgesics as part of organ donation practices, and differences in public attitudes and expectations regarding donation practices.

²⁵ 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.

²⁶ 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.

- 28 ● NRP has great potential to improve utility for candidates with end-stage organ disease awaiting
 29 organ transplantation, and as such should be strongly considered. Utility is necessary, but
 30 insufficient to demonstrate that a practice is ethical.
- 31 ● It is unclear whether NRP complies with the Dead Donor Rule. Circulation²⁷ is restored regionally in
 32 the person after circulatory death has been declared, giving rise to questions that are meaningful as
 33 to whether the person continues to meet criteria required for determination of death—in this case
 34 permanent²⁸ cessation of circulation— at the time donation takes place. To clarify, this concern
 35 implies that a person legitimately meets criteria for determining death owing to permanent
 36 cessation of circulation at the time of death declaration, but that this criterion is violated
 37 subsequently when circulation is restored (at the time of donation).
- 38 ○ There may be important differences in the degree to which the seriousness of these
 39 ethical concerns apply to A-NRP versus TA-NRP.
- 40 ● NRP raises concerns about the potential for harm if the assumption that the donor is insensate is
 41 incorrect following restoration of circulation following occlusion of the arteries.²⁹
- 42 ○ Concern that the donor may still be sensate may be mitigated by studies demonstrating that
 43 blood flow to the brain during regional perfusion is minimal (e.g. using transcranial Doppler,
 44 angiogram studies, or tissue oxygenation measurement).
- 45 ○ It may also be mitigated by the use of certain medications during NRP. However, use of such
 46 medications may further undermine compliance with the Dead Donor Rule.
- 47 ● In the interest of public trust, respect for persons, and transparency, informed decision making for
 48 NRP should include disclosure of recirculation through the heart (TA-NRP) and the potential
 49 restoration of any cerebral perfusion (TA-NRP and A-NRP), as well as considerations of meaningful
 50 differences from other donation approaches.^{30,31}
- 51 ○ Clear requirements and guidelines for disclosure, explanation of morally relevant
 52 components of NRP, and consistency within the authorization process are necessary
 53 components of informed decision making.
- 54 ○ The paper emphasizes the importance of encouraging engagement with donor families to
 55 ensure the level of information shared reflects their individual preferences.

²⁷ 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].

²⁸ 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>.

²⁹ By “insensate” this paper means unable to feel pain.

³⁰ 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.

³¹ “Transparency” in this context implies that unique elements of NRP are communicated in a plain-language way to individuals impacted by the donation process.

- 56 • Uncontrolled scenarios for NRP raise additional serious concerns for respect for persons and
 57 proceeding too quickly from therapeutic treatment to organ recovery.³²
 58 The table below provides a brief overview of the relevant uniqueness of NRP in relation to other forms
 59 of organ transplantation.

Uniqueness of NRP

NRP entails restoring blood flow through a portion of a person’s body after that person has been declared dead by loss of circulatory function, which by definition requires permanent cessation of circulation.³³ 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.³⁴

Unlike other machine perfusion techniques, NRP is the only one that perfuses the organs *in situ*, i.e. while they are in the body.³⁵

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.³⁶ In DCD, criteria for circulatory death are maintained, so neurological testing is not needed as this person already meets criteria for death determination. For NRP, neurological criteria are not demonstrated to have been met, while at the same time, criteria for circulatory death may not be demonstrated to be maintained following the process of reperfusion.

- 61
- 62 **Scope of White Paper**
- 63 The OPTN Ethics Committee “aims to guide the policies and practices of the OPTN related to organ
 64 donation, procurement, distribution, allocation and transplantation so they are consistent with ethical
 65 principles.”³⁷ White papers are developed for informational purposes and are intended to guide OPTN
 66 operations. As such, it is beyond the scope of this paper to speculate regarding potential future changes
 67 to the Uniform Determination of Death Act (UDDA), and to opine on whether NRP complies with current

³² 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>

³³ 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>.

³⁴ 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

³⁵ “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/>.

³⁶ 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.

³⁷ “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.

68 law.^{38,39} The Addendum (page 25) provides background on the UDDA and its relevance for the NRP
 69 discussion. **This paper's scope does not include reviewing the ethical foundations of DCD, which have**
 70 **been considered extensively elsewhere.**^{40,41,42,43,44} The focus of this white paper is to fully explore and
 71 map the relevant ethical principles applied to NRP and the ensuing implications for the OPTN and
 72 broader transplant community.

74 Introduction

75 There has been an increasing interest in machine perfusion techniques to improve organ quality and
 76 utilization, and multiple machines that perfuse organs *ex vivo* (outside the body) have received FDA
 77 approval within the last five years.^{45,46} NRP is unique in perfusing organs *in situ* (in the body), which
 78 involves ligating the major blood vessels to the brain prior to restoration of circulatory blood flow; in
 79 contrast, other machine perfusion techniques are *ex vivo* (outside the body). While NRP has expanded
 80 significantly in the United States since 2020, no formal ethical analysis or guidance has been issued by
 81 the OPTN regarding the implications for *in situ* organ perfusion.⁴⁷ Many other countries that have
 82 pursued NRP or have decided against it have provided additional guidance and consideration of its

³⁸ It is important to note that the UDDA is not itself legally binding. Each state may consider the UDDA in enacting its laws, which are legally binding. All states allow determinations of death by either neurological or circulatory criteria, and many have enacted the language of the UDDA. The Dead Donor Rule is also not legally binding but an underlying moral principle to organ transplantation.

³⁹ The Uniform Law Commission has suspended its deliberations on the UDDA as of 9/22/23, indicating that the UDDA may not be updated at all for the foreseeable future.

⁴⁰ 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."

⁴¹ "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.

⁴² 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

⁴³ "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.

⁴⁴ The extent to which, in deference to transparency, the public is made aware of transplant practices (including whether centers participate in NRP) varies on a case-by-case basis, an issue which is beyond the scope of this paper.

⁴⁵ "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-metra-system-p200035>.

⁴⁶ "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>.

⁴⁷ 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.

83 ethical implications.^{48,49,50} Transplant centers and OPOs have developed a patchwork of approaches and
 84 decisions related to NRP in the U.S., creating fragmentation and inconsistency in protocols for treatment
 85 of potential organ donors. Many questions remain at this time about the science of NRP as it relates to
 86 potential blood flow to the brain, particularly in a retrograde fashion through collateral flow to the
 87 spinal cord.⁵¹ While some studies reflect rapid progress in identifying the potential for cerebral flow to
 88 be minimal during NRP when vessels are occluded,^{52,53} and although this paper acknowledges that the
 89 potential for a donor being sensate at the time of organ procurement may be low, more research is
 90 needed to confirm that the perfusion of the brain or brainstem during NRP does not occur.

91
 92 Appendix A (page 31) provides an overview of all relevant terms and acronyms that are defined in this
 93 paper; it may be referenced throughout where technical terms are used. Finally, an overview of
 94 presenters and topics discussed by the Workgroup is included in Appendix B (page 35).

96 Overview of Ethical Findings

97 Ethical principles guiding transplantation provide a system of checks and balances.⁵⁴ This is spelled out
 98 in the OPTN Final Rule according to which utility, justice, and respect for persons are “the major ethical
 99 principles to be balanced to achieve an equitable outcome in the allocation of organs for
 100 transplantation.”⁵⁵ Another important cornerstone of organ transplantation is public trust, since no
 101 transplant would occur without the endorsement of society and the generosity of individual donors and
 102 their families.

103
 104 The **Dead Donor Rule** states that donors must meet criteria for death at the time of donation, to ensure
 105 that persons donating organs do not die by or for donation.⁵⁶ The Dead Donor Rule is a fundamental
 106 tenet of trust in the organ donation system. Adherence to this is critical despite the need to reduce
 107 ischemic time and optimize perfusion to improve transplant outcomes. NRP raises questions about

⁴⁸ 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.

⁴⁹ 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.

⁵⁰ 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.

⁵¹ Bernat, James., et al. "Understanding the Brain-based Determination of Death When Organ Recovery is Performed with DCDD In Situ Normothermic Regional Perfusion." *Transplantation* ():10.1097/TP.0000000000004642, May 12, 2023. | DOI: 10.1097/TP.0000000000004642

⁵² 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.

⁵³ 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.

⁵⁴ 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/>.

⁵⁵ "Final Rule." OPTN: Organ Procurement and Transplantation Network - OPTN. <https://optn.transplant.hrsa.gov/about/final-rule/>.

⁵⁶ 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.

108 whether the act of ligating the arteries or using an occluding balloon prior to perfusion with the
 109 knowledge and intent of restarting regional circulation constitutes a violation of the Dead Donor Rule, as
 110 well as a violation of the UDDA, by rendering the initial determination of death by circulatory criteria
 111 invalid (as circulation was restarted successfully), and without a determination of death by brain death
 112 criteria.⁵⁷

113
 114 To provide assurance, the following question should be asked: Does regional postmortem circulatory
 115 restoration imply that the criteria for meeting death, legitimately established at the time death was
 116 declared according to accepted DCD practices, is overturned following that restoration?⁵⁸ Has adequate
 117 brain monitoring been conducted to examine brain function in circumstances where the carotid and
 118 vertebral arteries cannot be perfused? Would such function be restored, or even somewhat improved, if
 119 these arteries were not occluded?⁵⁹ Evidence demonstrating lack of blood flow to the brain would be
 120 instructive to address concerns about harm, but may not address the larger question about whether the
 121 act of occluding the arteries itself violates the Dead Donor Rule. While there are differing ethical
 122 opinions regarding the implications of NRP and the Dead Donor Rule, assurance that the Dead Donor
 123 Rule has not been violated must be met to be consistent with current ethical practice.

124
 125 NRP has further implications on the requirement of non-maleficence, or do no harm. It is currently
 126 unclear if NRP results in collateral blood flow to the brain, including the brainstem. Also, it is not fully
 127 clear if collateral blood flow, if it does exist, poses any risk to the donor in the form of experiencing pain.
 128 The detection of brain or brainstem flow may be tested through transcranial Dopplers, angiograms, or
 129 tissue oxygenation measurements as a step to clarify the nature of collateral blood flow, but at the
 130 moment there is a lack of good data for these measurements, certainly precluding any possibility of
 131 arriving at consensus in the transplantation community that in NRP non-maleficence is not violated.

132
 133 Another important ethical consideration is whether and how NRP upholds **respect for persons** (which
 134 includes respect for autonomy). This entails demonstrating a proactive and transparent process of
 135 informed decision-making. The principle of respect for autonomy refers to one's capacity to self-
 136 determine and have a say over what happens to oneself.⁶⁰ In order for NRP to adhere to the principle of
 137 autonomy, clearer guidelines and standards are needed to ensure that patients, health care agents, and
 138 families approached about organ donation understand and can opt to, or not to, proceed with NRP.⁶¹
 139 The paper also acknowledges the potential benefit to demonstrating respect for the principle of
 140 autonomy in that NRP facilitates the fulfillment of potential donor wishes to give the gift of life.

141

⁵⁷ National Conference of Commissioners on Uniform State Laws. *Uniform Determination of Death Act*. 1980.

⁵⁸This 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/l1cfcvm3/20221021_ethics_meeting-summary_draft.pdf.

⁵⁹ 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

⁶⁰ 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/>.

⁶¹That 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.

142 Lastly, the principle of **utility** is a highly relevant consideration to any ethical analysis of NRP. The
 143 principle of utility takes into account all possible goods and harms that can be envisioned, considering
 144 the quantity and probability of the various outcomes. Current evidence suggests that the *in situ* manner
 145 in which NRP organs are acquired yields optimal results for the recipient by maximizing the number of
 146 organs procured, as well as the quality and longevity of these organs.⁶² The alternative methods of *ex*
 147 *vivo* machine perfusion also have positive impacts on organ utilization while avoiding the central
 148 controversy of perfusing organs and creating blood flow in the body of someone who was declared dead
 149 by circulatory criteria, but the utility benefits for hearts may be lessened by increased post-transplant
 150 graft failure.⁶³ In developing this paper, the available attestations on the part of transplant professionals
 151 working in, and intimately familiar with, NRP were considered.⁶⁴ It is of central importance to consider
 152 potential recipients whose lives stand to be improved for the better as a result of NRP, and this
 153 mattered a great deal in the overall ethical analysis.

154
 155 As previously mentioned, all of the ethical principles considered are important to consider in tandem, to
 156 which end the analysis has taken the approach that fulfilling the expectations for normative justification
 157 for any one principle is *necessary, but not sufficient*, for arriving at a conclusion about NRP.

158 Background

159 *NRP Procedure*⁶⁵

160
 161 Currently, there are two major classifications of NRP, abdominal (A-NRP) and thoraco-abdominal NRP
 162 (TA-NRP). A-NRP involves perfusing the liver, kidney and pancreas and other tissue in the lower part of
 163 the body using cannulas inserted below the diaphragm, either into the iliac artery and vein or into the
 164 abdominal aorta.⁶⁶ TA-NRP involves perfusing the thoracic organs in addition to abdominal ones, and
 165 also implies blood flow through the heart; both forms of NRP involve occlusion of arteries to the brain,
 166 although it is less likely that blood flow reach the brain due to A-NRP perfusing organs further from the
 167 brain and not perfusing the heart.⁶⁷ A distinction between TA-NRP and A-NRP is that regional perfusion
 168 is localized for A-NRP and does not include perfusion to the heart. In A-NRP, cross-clamp or ligation of
 169 the aorta eliminates perfusion to the upper body, and not specifically to the carotid vessels or the brain.
 170 However, considerations about restoration of circulation are still present in both TA- and A- NRP, and
 171 the potential for blood flow to the brain with A-NRP still exists. Plausibly, A-NRP may be less of a
 172 concern, but more data is still needed to demonstrate blood flow to the brain does not occur.

173
 174 The development of NRP in the U.S. emerged as a patchwork, with each center/OPO adopting different
 175 approaches, some with rigorous ethical oversight through institutional review boards (IRBs) and formal

⁶²Jochmans, 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.

⁶³ 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.

⁶⁴ Summaries of the Committee's deliberations are available here: <https://optn.transplant.hrsa.gov/about/committees/ethics-committee/>

⁶⁵ A note that portions of this section are highly technical and a reminder that all relevant terms are defined in Appendix A, page 30.

⁶⁶Basmaji, 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.

⁶⁷ 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.

176 ethics consultations, others with more informal oversight. No objective, formal ethical evaluations have
 177 occurred, similar to prior reports issued by the Institute of Medicine with DCD donation.⁶⁸ It is important
 178 to note that any actions taken prior to and including declaration of death are those taken solely by the
 179 non-OPO, critical care team. Details of how NRP is performed vary but typically reflect utilization of
 180 standard DCD protocols. The ethically salient elements are as follows:⁶⁹

181 **Elements of NRP that apply to both TA- and A-NRP:**
 182

1	<u>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.</u>
2	<u>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.</u>
3	<u>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.</u>
4	<u>Any interventions that are performed before the death of the patient (e.g., liver biopsy, bronchoscopy, placement of vascular catheters, administration of heparin) are done with the authorization of the patient or patient’s surrogate.</u>
5	<u>Life support is withdrawn, and standard end-of-life comfort measures are initiated.</u>
6	<u>When and if the patient becomes pulseless, the patient is monitored for a period of time (typically 5 minutes in the US), and if autoresuscitation does not occur in that time, death is declared by a physician independent of the transplant team based on determination of death by circulatory criteria.⁷⁰</u>

⁶⁸ 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.

⁶⁹ 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.

⁷⁰ 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.

183 At this point in the process of NRP organ procurement, TA-NRP and A-NRP procedures diverge. The
 184 relevant elements are noted below:⁷¹

185 **Elements of NRP: comparing TA- and A- NRP**

<u>TA-NRP</u>	<u>A-NRP</u>
<u>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.</u>	<u>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.</u>
<u>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,⁷² 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.</u>	<u>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.</u>
<u>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.</u>	<u>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.</u> ⁷³

⁷¹ Basmaji, John, et al. "Paving the Road..." *Critical Care Explorations* 3, no. 11 (2021), e0553. doi:10.1097/cce.0000000000000553.

⁷² 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.

⁷³ 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>

186 Historical Perspective⁷⁴

187 To appreciate the current ethical discussions regarding NRP, it is helpful to understand the context from
 188 which it arose. In 1993, the University of Pittsburgh developed a protocol that provided a path to obtain
 189 organs from individuals deemed dead by cessation of circulation or donors after circulatory death (DCD)
 190 to address a growing need for transplantation.⁷⁵ The growth of DCD donors, and its subsequent
 191 acceptance by the medical community and society, was promoted in two Institute of Medicine reports
 192 that outlined the ethical and medical issues of non-heart beating donors.^{76,77} One report identified that
 193 the demand for organ transplantation had increased by 212% in the prior decade and that organs from
 194 DCD donors could increase organ transplantation by 25%.⁷⁸ Important contributions outlined the
 195 practice of separating the organ procurement teams from physicians charged with the management of
 196 the terminally ill patients and their death declaration.⁷⁹ They also defined the 5 minute “standoff”
 197 period from death declaration to procurement, that would minimize the chances of spontaneous cardiac
 198 restoration.⁸⁰ Early experience with DCD liver and kidney transplants demonstrated that these
 199 transplants were safe and had a significant survival benefit for recipients compared to remaining on the
 200 waitlist.⁸¹

201
 202 The ethical underpinning of DCD transplantation relies on the fact that it adheres to the Dead Donor
 203 Rule, in that the donation itself was not the cause of death, and that it was consistent with the UDDA
 204 definition that the donor had irreversible cessation of circulatory and respiratory function, interpreted in
 205 this case as “permanent” cessation of circulatory function.⁸² An essential corollary is the implicit
 206 understanding that no attempts would be made to resuscitate the donor and as such, the lack of
 207 circulation to the brain also causes irreversible cessation of all functions of the brain, including the
 208 brainstem.^{83,84}

209
 210 The first challenge to the irreversibility clause of the UDDA came from the use of DCD hearts in three
 211 pediatric heart transplant recipients.⁸⁵ If circulatory cessation is irreversible, then how is restarting

⁷⁴ A note that portions of this section are highly technical and a reminder that all relevant terms are defined in Appendix A, page 30.

⁷⁵ 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

⁷⁶ 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

⁷⁷ 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.

⁷⁸ 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

⁷⁹ Ibid.

⁸⁰ Ibid.

⁸¹ D’Alessandro AM, et al. Donation after cardiac death: the University of Wisconsin experience. *Ann Transplant* 2004;9(1):68-71

⁸² See footnote 5.

⁸³ 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

⁸⁴ 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.”

⁸⁵ 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.

212 cardiac function in the recipient permissible?⁸⁶ Although ethical debates continue regarding DCD heart
 213 transplantation, its expansion has been allowed by the notion that despite challenging the irreversibility
 214 of asystole, no attempts were made to resuscitate the donor and thus progressive deterioration of brain
 215 function proceeded consistent with the UDDA definition of brain death.⁸⁷ In response to this concern,
 216 terminology was modified to reflect the currently accepted terminology of "Donation after Circulatory
 217 Death" instead of "Donation after Cardiac Death."⁸⁸ Indisputable in this debate was the agreement that
 218 attempts at reversing asystole in the donor, even after death declaration, were not consistent with the
 219 process of withdrawing support in a terminally ill patient.⁸⁹

220
 221 The use of ECMO in a DCD donor was protocolized in the U.S. by the University of Michigan and was
 222 originally performed for intra-abdominal organs only.⁹⁰ The use of an intra-aortic occlusion balloon
 223 above the diaphragm eliminated cardiopulmonary resuscitation and thus the NRP procedure was
 224 deemed "regional" and reportedly consistent with the principle that there were no attempts to
 225 resuscitate a donor following the death declaration. During TA-NRP, the aortic arch vessels are ligated to
 226 address concerns that ECMO or cardio-pulmonary bypass may result in cerebral circulation.⁹¹ Some
 227 protocols in Europe use a venting procedure to expose arch vessels to atmospheric pressure to further
 228 reduce the chances of collateral cerebral perfusion.⁹² TA-NRP protocols in Spain use Bispectral index
 229 (BIS) monitoring to confirm lack of frontal lobe brain activity following the initiation of ECMO.⁹³

230
 231 NRP poses significant questions, and its use has not had an *a priori* consensus in terms of its legality,
 232 ethical foundation, or societal acceptance. This is critical, as its further expansion may lead to improved
 233 survival for many patients waiting for transplant. However, a lack of transparency and failure to address
 234 gaps in knowledge have the potential to impact societal credibility in the overall transplant system.
 235 Spontaneous cardiac restoration has been observed in TA-NRP when cardio-pulmonary bypass was
 236 used, which then directly calls into question the defined event of death declaration prior to the standoff
 237 period.⁹⁴ From a physiological perspective it is also unknown to what extent collateral circulation results
 238 in perfusion of the posterior brain and brainstem.⁹⁵ Anatomically, there is substantial variability in how

⁸⁶ 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.

⁸⁷ 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.

⁸⁸ "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.

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

⁹⁰ 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.

⁹¹ Dalsgaard, Frederik F., et al. "Clamping of the Aortic Arch Vessels..." *Transplantation* 106, no. 9 (2022), 1763-1769. doi:10.1097/tp.0000000000004047.

⁹² 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.

⁹³ 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.

⁹⁴ 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.

⁹⁵ 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.

239 the spinal cord receives circulation and our current knowledge challenges the assertion that ligation of
 240 aortic arch vessels is sufficient to eliminate perfusion of the entire brain and brainstem, as required by
 241 the UDDA.⁹⁶

242
 243 The ethical integrity of DCD donation is highly dependent on the societal acceptance that imminently
 244 dying individuals may have cardiopulmonary support withdrawn and, following the act of dying, they
 245 could donate organs to help others. Implicit is that the individual is not experiencing harm from the
 246 organ procurement as they are declared dead by accepted definitions. Unknown in NRP is if the issues
 247 regarding brain/brainstem circulation have been scientifically investigated, if organ resuscitation
 248 practices conducted in NRP result in inadvertent harm, and if there are in fact potential violations of the
 249 Dead Donor Rule.⁹⁷

250 251 Need for Ethical Review

252 As the use of NRP has expanded, so have concerns that its pursuit may violate ethical principles
 253 governing organ transplantation and legal boundaries.⁹⁸ The UDDA, which provides part of the legal
 254 framework for organ transplantation in the United States, defines death as “**An individual who has**
 255 **sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible**
 256 **cessation of all functions of the entire brain, including the brain stem.**”⁹⁹ A 2021 statement by the
 257 American College of Physicians (ACP) expressed concern that NRP does not comply with the UDDA
 258 because it entails recirculation of blood in the body after death is declared, violating irreversibility, and
 259 potentially the Dead Donor Rule.¹⁰⁰ Additional concerns related to nonmaleficence include unknown
 260 implications of circulation and potential blood flow to the brain.

261
 262 Those in favor of NRP consider that the procedure does not violate irreversibility because the circulation
 263 is localized, or “regional.” Under this view, the UDDA may need to be clarified to expand the
 264 interpretation of irreversibility understood as permanence to allow for regional recirculation.¹⁰¹
 265 However, proponents argue that no ethical norm is violated and this may be merely a legal
 266 clarification.¹⁰² Proponents of NRP consider respect for persons (patient autonomy in choosing to
 267 donate) and utility (increased use of organs and improved outcomes for recipients) as strong ethical
 268 reasons to pursue NRP.¹⁰³ While still considering it necessary to have appropriate protocols and
 269 informed decision making, supporters of NRP do not consider that the Dead Donor Rule is violated or
 270 that harm is being done to donors because the procedure occurs after circulatory death has been

⁹⁶ Griep, Randall B., and Eva B. Griep. "Spinal Cord Perfusion and Protection During Descending Thoracic and Thoracoabdominal Aortic Surgery: The Collateral Network Concept." *The Annals of Thoracic Surgery* 83, no. 2 (2007), S865-S869. doi:10.1016/j.athoracsur.2006.10.092.; Griep, Eva B., et al. "The anatomy of the spinal cord collateral circulation." *The Annals of Thoracic Surgery* 1, no. 3 (2012), 350-357. doi: [10.3978/j.issn.2225-319X.2012.09.03](https://doi.org/10.3978/j.issn.2225-319X.2012.09.03)

⁹⁷ 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.

⁹⁸ 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>

⁹⁹ National Conference of Commissioners on Uniform State Laws. *Uniform Determination of Death Act*. 1980.

¹⁰⁰ 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.

¹⁰¹ 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.

¹⁰² Ibid.

¹⁰³ Ibid.

271 declared.¹⁰⁴ Given the varying perspectives within the community, a workgroup was convened of
 272 experts with diverse and diverging opinions and backgrounds to conduct a robust and balanced review
 273 of ethical implications, as described in the “Deliberative Process section” below.

274
 275 *Deliberative Process*

276 In *circumstances* where no *a priori* agreement exists on the hierarchy of principles or values governing
 277 ethical decision-making, people turn to a procedural justice approach. This type of approach (in contrast
 278 to distributive justice approaches) stems from the following: if diverse stakeholders are engaged and the
 279 process is transparent, and if stakeholders can agree at the outset on the terms for a fair deliberative
 280 process, then the outcome arising from the deliberation must be seen and accepted as fair.¹⁰⁵

281 For such a new technology as NRP, with its complexity and potential for controversy, it was considered
 282 imperative to create a deliberative process for review that was thorough and inclusive of all relevant
 283 perspectives. To that end, a diverse workgroup was formed with expertise on NRP, organ donation,
 284 ethics, donor family experience, organ procurement, and transplantation to assess the ethical
 285 justification for NRP. The Workgroup included supporters and skeptics of NRP, as well as representatives
 286 from all key transplant communities, and diverse medical specialties.¹⁰⁶ Guest presentations included
 287 proponents and critics of NRP.

288
 289 The Ethics Committee started its deliberation with presentations from both European surgical teams
 290 engaged in the practice of NRP and the American College of Physicians (ACP), which had recently issued
 291 a position statement critical of NRP.¹⁰⁷ The Workgroup reviewed protocols presented by U.S. transplant
 292 programs engaged in the practice, and sought out the perspectives of intensivists, neurological experts,
 293 anesthesiologists, researchers and clinical experts in determination of death, and European transplant
 294 clinicians.¹⁰⁸ Members updated a shared literature review with 60 relevant publications and participated
 295 in Workgroup subgroups to consider the particular implications of irreversibility, patient autonomy, and
 296 physician intent. The Workgroup met 15 times from July 2022 to March 2023, and members provided
 297 regular updates on progress and discussions to the Committee. An informal survey of the Workgroup
 298 indicated that throughout the course of Workgroup review, most respondents had changed their mind
 299 regarding whether NRP could be appropriately and ethically pursued in the current environment.¹⁰⁹ This
 300 finding suggests that the deliberations of the group and the presentations it received influenced
 301 evolving perspectives of Workgroup members as they understood more about the practice of NRP and
 302 associated ethical implications. The discussions within the Workgroup directly led to the generation of
 303 initial drafts of the white paper, which were updated in iterative fashion based on feedback from the
 304 Workgroup and Committee. Further review by the Committee developed the paper, which was shared
 305 with the community and subsequently updated, reflecting adherence to a deliberative and thorough
 306 ethical analysis.

¹⁰⁴ 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.

¹⁰⁵ Summaries of the Committee's and Workgroup's deliberations are available here: <https://optn.transplant.hrsa.gov/about/committees/ethics-committee/>

¹⁰⁶ Ibid.

¹⁰⁷ A full list of presenters and topics reviewed by the workgroup can be found in Appendix B.

¹⁰⁸ Ibid.

¹⁰⁹ 84% of Workgroup members participated in the survey.

307 Ethical Implications of NRP

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

311 *Do No Harm (nonmaleficence)*

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

322
323 **Argument that NRP does not violate the Dead Donor Rule (DDR) and does not harm the donor:**

324
325 Proponents of NRP contend that NRP is a modification of standard DCD donation, which has been in use
 326 since 1992, and which is now a well-accepted approach to organ procurement.¹¹⁰ In DCD donation in the
 327 US, death is declared (if it occurs) following a predetermined duration of pulselessness, provided that
 328 autoresuscitation has not occurred.¹¹¹ The 5-minute interval has been supported by evidence that
 329 autoresuscitation does not typically occur beyond this time interval, provided that there have been no
 330 prior attempts to resuscitate the patient.¹¹²

331
332 Proponents further explain that NRP does not violate the DDR because the restoration of circulation is
 333 only regional (excluding the brain in TA-NRP, and excluding the brain and thoracic organs in A-NRP), and
 334 consider the fact that circulation is restored *in situ* rather than *ex vivo* to be ethically irrelevant.¹¹³ The
 335 arteries that supply the brain are clamped or otherwise occluded, and arteries that lie distal to the
 336 occlusion are vented to atmospheric pressure to divert any potential collateral blood flow away from
 337 the brain in an effort to minimize the risk of cerebral reperfusion.¹¹⁴

338
339 On the question of whether re-establishing circulation invalidates the determination of death, Parent et
 340 al makes a parallel point on the legal issue: “The law is silent on whether subsequent acts can invalidate
 341 a declaration of death. Regardless, occluding cerebral circulation... does not cause death—the patient

¹¹⁰ 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.

¹¹¹ Manara, A.R., et al. "Donation after circulatory death." *British Journal of Anaesthesia* 108 (2012), i108-i121. doi:10.1093/bja/aer357.

¹¹² 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.

¹¹³ 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.

¹¹⁴ *Ibid.*

342 has already been pronounced dead by standard cDCD criteria.”¹¹⁵ Moreover, proponents describe the
 343 importance of intention: “Resuscitation efforts require attempting to restart the heart for life-saving/
 344 prolonging purposes. In undertaking cDCD NRP, there is no intention or attempt to resuscitate because
 345 doing so would be medically ineffective... Perfusing the thoracic and abdominal organs after circulatory
 346 determination of death... does not alter the fact that... continued care would be medically ineffective
 347 and inconsistent with a meaningful existence.”¹¹⁶ Their presumption is that the intent to restart
 348 circulation merely for the purposes of regional reperfusion for donation does not constitute
 349 resuscitation. They note that the DDR is not violated in that the occlusion of the arteries ensure that the
 350 process of brain death continues unabated after circulatory death determination has been achieved.

351
 352 On the question of potential harm to the donor, many argue that the donor is insensate because
 353 clamping the aortic arch vessels ensures a lack of cerebral blood flow that most closely mimics the level
 354 of blood flow to a brain in a standard DCD donor. As such, they perceive the conditions for NRP to be
 355 similar to those for DCD, where it is assumed that the donor is insensate and no harm is incurred by the
 356 procedure. This assumption could be confirmed by use of anesthetics on the donor, a practice which is
 357 not unique to NRP but raises questions beyond the purview of this paper to fully consider.¹¹⁷ Do no
 358 harm and respect for persons do raise questions about whether anesthesia is appropriate.

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

361 Yet, many raise concerns that the patient has been declared dead on the basis of the permanent
 362 cessation of circulation, with the full intent and understanding that regional circulation will be restored,
 363 invalidating the prior determination.¹¹⁸ It is important to note that at that time of donation the patient
 364 may no longer meet criteria needed for declaration of circulatory death nor have they been
 365 demonstrated to meet the accepted criteria for the neurologic determination of death- which has not
 366 been assessed.¹¹⁹
 367 Although it is impractical for the team to pursue tests needed to confirm neurologic determination of
 368 death, without this, the patient donor does not meet either standard for circulatory or neurologic
 369 determination of death at the time of organ procurement. A reasonable person may ask: since the
 370 patient has been declared dead after the established duration of pulselessness, why is it necessary to
 371 ligate the aortic arch vessels? There is no single proffered answer to this question. Those in favor of NRP
 372 suggest that occluding the aortic arch vessels is something that occurs after death has been declared,
 373 which consequently has no ethical relevance, and as such ought simply to be characterized as an
 374 additional step of efficiency to bring about an already agreed upon outcome. Since, according to this

¹¹⁵ 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.

¹¹⁶ Ibid. "cDCD" refers to controlled DCD scenarios in which life support is withdrawn in accordance with potential donor/family decisions.

¹¹⁷ Cappucci, S. P., Smith, W. S., Schwartzstein, R., White, D. B., Mitchell, S. L., & Fehnel, C. R. (2022). End-of-life care in the potential donor after circulatory death: A systematic review. *The Neurohospitalist*, 13(1), 61-68. <https://doi.org/10.1177/19418744221123194>

¹¹⁸ 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.

¹¹⁹ One could argue that determination of death in DCD (including DCD NRP) donation is premised on the condition that no attempt will be made to restore circulation after the onset of pulselessness. Intention notwithstanding, NRP arguably violates this condition, by using ECMO to restore circulation to the body's vital organs, except the brain. From this perspective, the problem is not so much that the determination of death has been reversed, but rather that it was arguably not valid in the first place, since a central requirement of DCD donation was violated. It is also true that others consider that the determination of death is not premised on the condition described above, and that nonmaleficence is maintained as long as the donor is insensate.

375 logic, there is a tacit agreement by all parties that CPR will not be applied once the heart stops beating,
 376 DCD, including DCD-NRP, can, indeed, reliably be characterized as “permanent” even before occlusion is
 377 considered. In other words, occlusion merely makes explicit that which is already implicit. It is a prior act
 378 of omission, namely, the decision not to resuscitate, as opposed to any subsequent act of commission,
 379 because of which death follows. The decision to occlude is no more than one of economy and
 380 expedience, which ensures permanent cessation of circulation to the brain. It is not a decision to ensure
 381 that death takes place, as if there would otherwise have been any doubt.

382
 383 Those who think NRP does run afoul of the “do no harm” principle ask: has any convincing evidence
 384 been put forth to demonstrate that brain death has occurred at the time circulatory death is declared? If
 385 not, it is arguably reasonable to assume that brain death criteria have not been met at the time
 386 circulatory death is declared. In situ reperfusion via ECMO without the additional step of occlusion
 387 serves, if anything, to move in a direction *away* from brain death. In light of this, any overt act
 388 preventing blood from getting to the brain is arguably its own determinative act of commission. In this
 389 case, one could reasonably conclude that the occlusion of these key vessels takes place in order to add
 390 an extra layer of assurance that dying is not thwarted, or that dying is sped up. As such, occlusion cannot
 391 rightly be characterized as merely a decision of “economy.”

392 It bears mentioning that in calling attention to these disparate explanations for why occlusion of the
 393 aortic arch vessels takes place in NRP, this analysis does not opine on which is more plausible. It does
 394 take the view, however, that the decision to occlude warrants scrutiny and better understanding.
 395 Moreover, how one understands the motive behind the decision to occlude will be revealing in the
 396 context of any rendered ethical analysis of NRP. Indeed, for the proponent of NRP, for whom the initial
 397 declaration of death based on circulatory criteria should be unquestionably trusted and therefore never
 398 second-guessed, intent is what governs the analysis and the perspective that the DDR is not violated.¹²⁰
 399 That all parties have agreed that death is an inevitability, and that nothing should be done to undo this,
 400 takes precedence. While these intentions are undoubtedly sincere, they are a problematic defense
 401 against those who see NRP as a work-around to the DDR. Skeptics may argue that declaring the patient
 402 dead on the basis of the permanent loss of cardiorespiratory function is misleading, since that function
 403 is immediately restored, clearly showing that its loss was not permanent, nor irreversible.¹²¹ Similarly,
 404 while proponents clearly do not intend to restore brain perfusion with ECMO, this is at least a
 405 theoretical possibility, and promises to terminate the procedure if this were to occur, can be alarming in
 406 the views of skeptics. Finally, proponents also allude to the near certainty that these patients will
 407 become brain dead, if they are not already, without acknowledging that brain death is a complex
 408 diagnosis that can only be made over a course of at least several hours.¹²² From the perspective of one
 409 who has concerns about any taken human action which might impact the reliability upon which death
 410 criteria are invoked, more attention should be paid to compliance with the principle of “do no harm,” in
 411 which case right intent (like informed decision making), is a necessary, but not sufficient, element in the
 412 ethical analysis. Intent does not have overriding priority in the ethical analysis.

413
 414 On the role of intention and justifying ligation through cautiousness, Glazier/Capron consider that “the
 415 legal standard for determining death is bare of intent: a patient is dead when circulation neither can nor

¹²⁰ 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.

¹²¹ 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.

¹²² 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.

416 will resume. That the patient is in a state where meaningful existence is not possible, that trying to
 417 induce spontaneous resumption of circulation would be futile, or even that the NRP protocol is
 418 consistent with the donor's wishes, are all irrelevant to whether the patient is deceased under US law,
 419 which turns on the person's physical condition not on anyone's intention."¹²³

420
 421 On the question of harm to the donor: potential for harm to the donor stems from being uncertain if
 422 occluding the arch vessels is sufficient to prevent blood flow to the brain and ensure that the donor is
 423 insensate. This should be tested for, and more studies to confirm that NRP donors are insensate are
 424 needed.¹²⁴

425
 426 Additional potential harms to public trust and dissenting healthcare providers are described under
 427 "utility" (page 20).

428 Respect for Persons

430 The ethical principle of respect for persons includes the belief that people with decision making ability
 431 should be allowed to make important, personal decisions for themselves, so long as those decisions do
 432 not impose harm to others. "This principle embraces the moral requirements of honesty and fidelity to
 433 commitments made, and respect for autonomy."¹²⁵ With NRP, the ethical principle of respect for
 434 persons suggests we have a duty to honor the potential donor's first-person authorization for donation
 435 for ante-mortem interventions required for donation to occur.

436
 437 Respect for persons requires honoring the potential donor's and their family's preferences for receiving
 438 information about NRP, as well as the intentions and wishes to become a donor, and to make the best
 439 possible use of this donation. Moreover, respect for persons acknowledges the importance of donor
 440 families in acting as surrogate or authorized decision-makers, acting in accordance with the preferences,
 441 values, and expectations of donor candidate patients. In this vein, some consider that NRP promotes
 442 autonomy.

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

449
 450 However, concern for overwhelming families in itself doesn't override the responsibility to avoid
 451 situations in which families are later distressed to learn information they felt should have been
 452 presented to them initially and might have affected their donation decision. Given the paucity of data
 453 about public support for NRP, including among different groups and cultural or religious identities, and

¹²³ 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.

¹²⁴ There is currently one available paper that found no cerebral blood flow in two human donors when ligation of arteries occurred during NRP. These data are promising, but the Committee considers more robust data are needed to confirm its implications. Reference: Frontera J., Lewis A., James L., Melmed, K., Parent, B., Raz, E., Hussain, S., Smith, D., Moazami, N., "Thoracoabdominal Normothermic Regional Perfusion in Donation after Circulatory Death Does Not Restore Brain Blood Flow." *J Heart Lung Transplant*. 2023 May 19;S1053-2498(23)01862-4. doi: 10.1016/j.healun.2023.05.010. Online ahead of print.

¹²⁵ 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/>.

454 the unsettled legal implications, the analysis prioritizes the balance between these competing priorities
 455 accordingly.

456 Informed decision making is not equivalent to informed consent, and applies under authorization in the
 457 context of organ donation. This process of informed decision making may be similar to how families
 458 make decisions about timing of donation and restrictions around type of organs procured. Informed
 459 decision making implies that sufficient information about organ donation to make decisions as they
 460 pertain to core preferences and values will be provided. On the question of informed decision making,
 461 some opine that standards applicable to the authorization process for DCD donation are sufficient,
 462 because both TA- and A- NRP uses similar premortem interventions.^{126,127} Yet others, concerned with
 463 whether regional restoration of circulation negates the original determination of death, consider crucial
 464 differences must be disclosed to potential donors and families regarding recirculation and the potential
 465 restoration of any cerebral perfusion.¹²⁸ For some, these distinctions are meaningful in a way that may
 466 contradict their values and beliefs, and may alter their propensity to participate in NRP. Without
 467 sufficient public polling, outreach to communities of different faiths and cultures, etc., it is challenging to
 468 know how widely acceptable NRP is, and what elements must be included in informed decision making.
 469 Some critics of NRP argue that achieving informed consent or authorization to NRP is simply not possible
 470 if ligating arteries constitutes the cause of death, because an individual cannot give consent or
 471 authorization for something that causes their death. With these potential exceptions and limitations
 472 identified, the following section provides an overview of informed decision making for optimizing
 473 respect for persons in conversations with patients and their families who may be approached about
 474 organ donation and NRP specifically.

475 *Informed Decision Making*

476 This paper acknowledges the challenges faced by OPOs in approaching potential donors and donor
 477 families, and the difficulty in explaining the components needed for informed decision making (for
 478 procedures pre- and post-mortem) and balancing the need for adequately informing potential donor
 479 patients and families with the understanding that many families, grief-stricken, do not wish to hear
 480 details of these procedures. To uphold commitments to autonomy, and to maintain public trust in the
 481 organ donation and transplant system, it is critical to be transparent about methods used to facilitate
 482 organ donation and facilitate an informed decision-making process with the donor and/or surrogate
 483 decision maker. Transplant professionals should avoid evasive and paternalistic attitudes toward
 484 bereaved family members that preclude sharing of information and instead focus on an informed
 485 decision making process with clear goals for upholding transparency, respect for the rights and interests
 486 of the donor and/or their surrogate decision maker, and good stewardship of gifted organs.^{129,130} This is

¹²⁶ While there is a difference between informed consent and authorization in this context, without greater information, these differences may be meaningless to members of the general public. This analysis errs on the side of transparency to support maintaining public trust, which is the bedrock of any successful organ donation system.

¹²⁷ Parent, Brendan, et al. "Ethical and logistical concerns..." *American Journal of Transplantation* 20, no. 6 (2020), 1508-1512. doi:10.1111/ajt.15772.

¹²⁸ 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.

¹²⁹ 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.

¹³⁰ Gries, Cynthia J., et al. "An Official American Thoracic Society/International Society for Heart and Lung

487 especially true for NRP, as feelings regarding this specific procedure may differ from other more
 488 established forms of organ procurement. More research is needed to better articulate these.

489
 490 The basis for informed decision making for NRP, rests on the foundational principles of authorization for
 491 DCD, which include, among other things:

- 492
- 493 1. Informed decision making for ante-mortem procedures and authorization for post-mortem
 494 procedures must be obtained. The potential donor's clinical care team and OPO staff obtaining
 495 this permission should be "capable of disclosing information accurately, interacting
 496 compassionately with grieving families, and answering all relevant questions... optimal
 497 requestors will be those persons who are able to be transparent and are best able to relay
 498 information to families in a comprehensive, compassionate, and even-handed manner."¹³¹
 - 499 2. Ideally, the trained requestor for potential donation is a member of the OPO staff with specific
 500 training and education to support conversations about NRP with donor family members and
 501 hospital staff.¹³²
 - 502 3. "If patients have provided first-person consent for organ donation, those obtaining consent
 503 from surrogates for ante-mortem procedures ... should consider using language that frames the
 504 conversation around a default assumption of donation."¹³³ If the donor family declines ante-
 505 mortem interventions that may be necessary for NRP, options for proceeding with standard DCD
 506 should be discussed.
 - 507 4. Authorization from potential donor or surrogate decision maker must be obtained for ante-
 508 mortem interventions to maximize transplantable organs as part of the consent for donation.¹³⁴
 509 These include heparin administration, bronchoscopy, liver biopsy, placement of cannulae, prep
 510 and drape of the donor, and transport to a separate location or operating room for recovery as
 511 applicable.¹³⁵
 - 512 5. The requestor must include an explanation of the hands-off period after circulatory cessation.

513
 514 In addition to the elements of informed decision making included for a DCD recovery as described
 515 above, NRP raises questions about the need to disclose additional information about the recovery
 516 procedure. Recommendations for NRP include a reiteration of the purpose and function of the hands-off

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.

¹³¹ 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.

¹³² 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.

¹³³ 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.

¹³⁴ 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>.

¹³⁵ 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.

517 waiting period, as well as a description of the steps of the procurement procedure.¹³⁶ For TA-NRP, this
 518 includes the ligation of vessels to prevent cerebral circulation and the reperfusion of targeted organs
 519 before they are removed from the body. Disclosure for TA-NRP should also include a statement that
 520 heart function may be restored to provide blood flow to organs.¹³⁷ Both TA- and A- NRP should include
 521 informed decision-making discussions that identify the potential restoration of any cerebral perfusion.

522
 523 Experienced requestors understand that the needs and preferences of donor family members and
 524 surrogate decision makers may be different based on the unique circumstances of each case. The
 525 informed decision-making process for organ donation has the obligation to refrain from burdening the
 526 donor family during their time of suffering any more than is absolutely necessary. Information must be
 527 clear and easy to understand to meet legal standards including whether the proposed protocol is
 528 understood and whether justification for failure to disclose risk is acceptable.¹³⁸ Considering strongly
 529 held beliefs in the transplant community regarding the ethical, moral, and legal ramifications of NRP, it is
 530 especially critical that the potential donor family be educated about the unique procedures associated
 531 with NRP.

532
 533 Although OPOs must abide with consideration for not burdening donor families with unnecessary or
 534 unwanted details, the ethical principle of respect for persons supports giving the surrogate decision
 535 maker the option to opt out of detailed information about the recovery procedure, while requiring that
 536 some key pieces of information are always explained. In the case of NRP, this likely includes describing
 537 clearly that although the donor is declared dead by circulatory death criteria, circulation will be restored
 538 regionally (A-NRP) and this may include the heart (TA-NRP), at a time the patient donor has not been
 539 assessed to meet the criteria for brain death. It may be especially important in the case of NRP to
 540 provide comprehensive support to donor families following the donation event, such that if questions or
 541 concerns about the recovery method arise after the fact, donor families have access to information and
 542 support. The analysis acknowledges that in rare circumstances the potential donor's surrogate may
 543 decline, after serious efforts are undertaken, to hear the information that will ensure Informed decision
 544 making is provided. Such "noninformed decision making" should be fully documented and should not
 545 preclude proceeding with the NRP protocol.¹³⁹ Requestor training should specifically include these
 546 elements.

547
 548 This paper strongly recommends that local hospitals' ethics committees review NRP practices to
 549 promote and support transparency within the surrounding community. A clear process for anonymous
 550 reporting of complaints or concerns by staff should be developed. In rare occasions potential donors
 551 may be moved to another hospital or to an OPO recovery center, if the donor care unit is within a
 552 licensed hospital. It is especially important in such instances that informed decision making, including
 553 review of the NRP procedure, occurs prior to any transfer of a potential donor. Another consideration
 554 relevant to transfers is assurance of local ethics committee review, which may be more challenging for
 555 smaller hospitals.

556

¹³⁶ 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.

¹³⁷ 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.

¹³⁸ Showalter, Stuart J. *The Law of Healthcare Administration*, 9th ed. Chicago: Health Administration Press, 2020. NCh. p. 411

¹³⁹ 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.

557 Uncontrolled NRP

558 Uncontrolled scenarios are those in which circulatory death occurs unexpectedly, not after the planned
 559 withdrawal of life support.¹⁴⁰ While the process of organ recovery following the decision for donation is
 560 largely the same in uncontrolled NRP as in controlled NRP (hands-off period, occlusion of vessels, and so
 561 on), uncontrolled NRP presents additional ethical concerns related to respect for persons and non-
 562 maleficence.¹⁴¹

563
 564 The transition between living patient and organ donor in uncontrolled NRP is rapid and potentially
 565 confusing for both potential donor families and clinical teams. This raises concerns about compressed
 566 timing and difficulty of informed consent discussions with potential donor families. Putting potential
 567 donor families in a situation where they do not fully understand the implications of what they are
 568 consenting to is extremely risky.

569
 570 The potential for teams to make decisions that do not fully honor respect for persons or potentially
 571 cause harm is greater given the rapidity and urgency of uncontrolled settings. Trust in clinical teams and
 572 in donation processes are a cornerstone to the organ transplantation system. There is a greater
 573 potential for harm or concern for autonomy where there is a lack of procedures and protocols to ensure
 574 safety and maintain trust. The transplant community owes itself and the general public assurance that
 575 no harm will occur and respect for persons is maintained. The potential for harm is greater in
 576 uncontrolled scenarios, and additional caution should be reflected accordingly.

577
578 Utility

579 Utility is a foundational principle that guides the United States' transplant system. Applied to organ
 580 donation and allocation, utility "specifies that allocation should maximize the expected net amount of
 581 overall good (that is, good adjusted for accompanying harms), thereby incorporating the principle of
 582 beneficence (do good) and the principle of non-maleficence (do no harm)."¹⁴²

583
584 Potential Increases to Utility

585 NRP is a promising development in the field of organ transplantation, since it has the potential to
 586 substantially improve both the number and the quality of organs that are available for transplantation,
 587 and in particular for the heart, which may be difficult to effectively procure by standard DCD
 588 donation.¹⁴³ The number of organs would likely be increased by enabling the transplantable organs to be
 589 resuscitated in situ, such that otherwise unusable organs could become transplantable. Similarly, in situ
 590 resuscitation has the potential to increase the function and the quality of the organs before they are
 591 removed for transplantation, which should improve graft function and survival in the long run.¹⁴⁴

592

¹⁴⁰ 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>

¹⁴¹ 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.

¹⁴² 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/>.

¹⁴³ 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.

¹⁴⁴ *Ibid.*

593 Preliminary data are promising, but contingent on further evidence. Initial studies show there is an
 594 overall increase in the average number of organs transplanted per donor with NRP compared to
 595 controlled DCD (cDCD) (3.3 versus 2.6).¹⁴⁵ Specifically, TA-NRP is positively associated with hearts being
 596 recovered and available for transplant, and has been successfully performed with triple organ
 597 transplants and pediatric heart transplants.^{146,147,148,149,150} A study showed NRP may improve utilization
 598 of livers that had been previously declined.¹⁵¹

599
 600 Some data show potential for improved outcomes and graft survival. For livers procured through NRP,
 601 decreased rates of early allograft dysfunction, 30-day graft loss, ischemic cholangiopathy, and
 602 anastomotic strictures were found compared to cDCD livers; A-NRP shows positive results in preventing
 603 ischemic type biliary lesions.^{152,153,154} Compared with static cold storage, NRP shows improved outcomes
 604 for liver transplants.¹⁵⁵ Research has also shown decreased delayed graft function (DGF), decreased 1-
 605 year graft loss, and improved 12-month kidney function for NRP kidneys compared to cDCD kidneys.¹⁵⁶
 606 NRP kidneys are also associated with lower DGF compared to cold perfusion techniques.¹⁵⁷

¹⁴⁵ 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.

¹⁴⁶ 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.

¹⁴⁷ Kwon, J. H., Usry, B., Hashmi, Z. A., Bhandari, K., Carnicelli, A. P., Tedford, R. J., Welch, B. A., Shorbaji, K., & Kilic, A. (2023). Donor utilization in heart transplant with donation after circulatory death in the United States. *American Journal of Transplantation*. <https://doi.org/10.1016/j.ajt.2023.07.019>

¹⁴⁸ Kagawa, H., Goodwin, M., Stehlik, J., Campsen, J., Baker, T., & Selzman, C. (2023). A case report of triple organ transplantation from a donor after circulatory death using thoraco-abdominal Normothermic regional perfusion. <https://doi.org/10.2139/ssrn.4464191>

¹⁴⁹ Beckerman, Z., Overbey, D., Bryner, B. S., Schroder, J. N., Andersen, N. D., Carboni, M. P., Casalinova, S., & Turek, J. W. (2023). Infant heart transplant following donation after circulatory death using normothermic regional perfusion and distant transport, first reported case in North America. *JTCVS Techniques*, 20, 156-157. <https://doi.org/10.1016/j.xjtc.2023.04.001>

¹⁵⁰ Biniwale, R., Lahar, S., Balasubramanya, S., Caraccio, C., Ngang, B., Barone, H., Stimpson, E., Dela Cruz, K., Alejos, J. C., Williams, R., Halnon, N., Reardon, L., Si, M., Shemin, R., Ardehali, A., & Van Arsdell, G. (2023). Pediatric heart transplantation from donation after circulatory death using normothermic regional perfusion and cold storage from a distant donor: First US experience. *JTCVS Techniques*, 20, 158-161. <https://doi.org/10.1016/j.xjtc.2023.05.010>

¹⁵¹ Schurink, I. J., De Goeij, F. H., Habets, L. J., Van de Leemkolk, F. E., Van Dun, C. A., Oniscu, G. C., Alwayn, I. P., Polak, W. G., Huurman, V. A., & De Jonge, J. (2022). Salvage of declined extended-criteria DCD livers using in situ Normothermic regional perfusion. *Annals of Surgery*, 276(4), e223-e230. <https://doi.org/10.1097/sla.0000000000005611>

¹⁵² 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

¹⁵³ Durán, M., Calleja, R., Hann, A., Clarke, G., Ciria, R., Nutu, A., Sanabria-Mateos, R., Ayllón, M. D., López-Cillero, P., Mergental, H., Briceño, J., & Perera, M. T. (2023). Machine perfusion and the prevention of ischemic type biliary lesions following liver transplant: What is the evidence? *World Journal of Gastroenterology*, 29(20), 3066-3083. <https://doi.org/10.3748/wjg.v29.i20.3066>

¹⁵⁴ Schurink, I. J., De Goeij, F. H., Habets, L. J., Van de Leemkolk, F. E., Van Dun, C. A., Oniscu, G. C., Alwayn, I. P., Polak, W. G., Huurman, V. A., & De Jonge, J. (2022). Salvage of declined extended-criteria DCD livers using in situ Normothermic regional perfusion. *Annals of Surgery*, 276(4), e223-e230. <https://doi.org/10.1097/sla.0000000000005611>

¹⁵⁵ Liang, A., Cheng, W., Cao, P., Cai, S., Zhang, L., Zhong, K., & Nie, Y. (2023). Effects of machine perfusion strategies on different donor types in liver transplantation: A systematic review and meta-analysis. *International Journal of Surgery*. <https://doi.org/10.1097/js9.0000000000000661>

¹⁵⁶ 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>

¹⁵⁷ Ghoneima, A. S., Sousa Da Silva, R. X., Gosteli, M. A., Barlow, A. D., & Kron, P. (2023). Outcomes of kidney perfusion techniques in transplantation from deceased donors: A systematic review and meta-analysis. *Journal of Clinical Medicine*, 12(12), 3871. <https://doi.org/10.3390/jcm12123871>

607 One area that the transplant community should monitor closely is the impact on lung utilization. There
 608 are some data suggesting positive outcomes for lungs and heart-lungs procured with NRP.^{158,159,160}
 609 However, there is concern about lower utilization of lungs when NRP is the procurement method.¹⁶¹
 610 While initial data suggest that heart, liver, and kidney utilization are positively impacted by NRP, further
 611 research should clarify how lungs are impacted.

612
 613 NRP may also increase utility for donor families, who may receive comfort from the knowledge that
 614 their loved one was able to save a greater number of lives with fewer complications. As previously
 615 noted, data on public attitudes toward NRP are limited. However, it is known that families experience
 616 psychosocial distress when their loved one is a DCD donor whose death does not occur in time to allow
 617 the donation of organs.¹⁶² Other studies suggest that the public is open to expanding donor protocols
 618 (imminent death donation) in a way that maximizes the chance that a donor will be able successfully
 619 donate.¹⁶³

620

621 Potential to decrease utility

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

625

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

632 Potential Harm to Public Trust

633 Loss or decline in public trust in organ transplantation may be a direct harm of NRP. This harm may be
 634 amplified given the current societal challenges regarding misinformation of scientific and health

¹⁵⁸ Gomes, B., Ribeiro, R., Alvarez, J., Ribeiro, R., Honjeu, A., Gazzalle, A., Bissoondath, V., Yu, F., Adamson, M., Meineri, M., Rao, V., Badiwala, M., Keshavjee, S., & Cypel, M. (2020). Normothermic regional perfusion (NRP) during heart DCD recovery: Is lung quality impacted? A pre-clinical study. *The Journal of Heart and Lung Transplantation*, 39(4), S353-S354. <https://doi.org/10.1016/j.healun.2020.01.415>

¹⁵⁹ Tanaka, S., Campo-Canaveral de la Cruz, J., & Crowley Carrasco, S. (2020). Effect on the donor lungs of using abdominal normothermic regional perfusion in controlled donation after circulatory death. *European Journal of Cardio-Thoracic Surgery*, 59(2), 359-366. <https://doi.org/10.1093/ejcts/ezaa398>

¹⁶⁰ Spencer, P. J., Saddoughi, S. A., Choi, K., Dickinson, T. A., Richman, A., Reynolds, F. A., & Villavicencio, M. A. (2023). Heart-lung transplantation from donation after circulatory death using mobile Normothermic regional perfusion. *ASAIO Journal*. <https://doi.org/10.1097/mat.0000000000002029>

¹⁶¹ Francois, S., Popa, S., Shaver, C., Mallea, J., Hartwig, M., Patel, Y., Tucker, W., Zofkie, B., Shelton, R., Benjamin, J., Brown, A., & Bacchetta, M. (2023). (1234) comparison of lung utilization from nrp-dcd vs non-nrp Dcd using Evlp. *The Journal of Heart and Lung Transplantation*, 42(4), S527. <https://doi.org/10.1016/j.healun.2023.02.1444>

¹⁶² 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.

¹⁶³ 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.

635 information.¹⁶⁴ While loss of trust in the organ donation process is a harm in itself, it may also have a
 636 secondary effect of decreasing the number of people willing to consent to deceased or living donation.
 637 Additionally, given the lack of consensus among leading legal scholars about the legality of NRP, the
 638 potential for lawsuits associated with potential DDR and UDDA violations could further magnify the
 639 public relations challenge of sustaining public support for the mission of organ procurement and
 640 transplantation.¹⁶⁵ These lawsuits may not only undermine public support, but they may also strain the
 641 transplant system and community in response.

642

643 Moral distress among transplant clinicians

644 The ethical and legal concerns described above have raised concerns among clinicians and other health
 645 care providers, including some clinicians at centers that perform NRP, that can be characterized as moral
 646 distress: the perception that a clinician must engage in an action as part of their clinical role that they
 647 believe to be morally wrong.¹⁶⁶ In the absence of greater clarity from the UDDA, and without better
 648 understanding the scope and extent of potential harms particularly to the potential donors (pre-
 649 mortem) and of donor families, either by virtue of the NRP procedure itself, or merely by not sufficiently
 650 informing the potential donor patient and family of the ethically salient distinctions imposed by NRP,
 651 these clinicians may suffer moral injury. A number of clinicians have reached out to members of the NRP
 652 Workgroup and Ethics Committee to express their concerns about NRP.¹⁶⁷ These concerns were often
 653 related privately, and there are not public data on clinician attitudes on NRP particularly within the
 654 United States. It is also important to acknowledge, in the interest of being able to help patients in need
 655 and respect donors, some clinicians and other health care providers expressed during public comment
 656 that they may feel moral distress at not being able to perform NRP and avoid non-utilization of an organ.

657

658 Conclusions

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

663

664 The OPTN shares the enthusiasm of the transplant community in developing and implementing solutions
 665 to improve the transplant system and reduce wait times and deaths for patients awaiting organ
 666 transplantation. This analysis also affirms the sacred trust and commitment of the transplant community
 667 to organ donors and donor families. Finally, the paper underscores that the transplant community is

¹⁶⁴ 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.

¹⁶⁵ 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.

¹⁶⁶ 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.

¹⁶⁷ Summaries of the Committee's deliberations are available here: <https://optn.transplant.hrsa.gov/about/committees/ethics-committee/>

668 entrusted to preserve and foster public trust and support in organ donation through ensuring donation
669 procedures that are ethical and transparent.

670

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

673

674 ● There are serious ethical concerns that NRP is not consistent with the Dead Donor Rule. There
675 may be differences in the degree to which these ethical concerns apply to A-NRP versus TA-NRP.

676 ● Nonmaleficence must not be violated in the pursuit of NRP, even if positive utility outcomes
677 could result.

678 ● Consistent and transparent protocols, including adequate informed decision making with
679 patients (pre-mortem) and of families approached about donation, are necessary pre-conditions
680 for any ethical pursuit of NRP.

681 ● Uncontrolled scenarios for any form of NRP should not be performed at this time because of
682 added concern regarding nonmaleficence and respect for person

1 Addendum

2 Addendum: The Uniform Determination of Death Act and NRP

3 This white paper concerns the ethics of NRP and does not purport to provide an opinion on the
 4 legality of NRP in any U.S. state, a topic outside the committee's charge. At the same time, given that
 5 the Uniform Determination of Death Act (UDDA) is currently being considered for revision,¹⁶⁸ it is
 6 important to at least briefly discuss the implications of the current text of the UDDA and its possible
 7 revisions for NRP.

8

9 What is the UDDA?

10 The UDDA is a uniform act promulgated by the Uniform Law Commission (ULC). The UCL, also
 11 known as the National Conference of Commissioners on Uniform State Laws, established in 1892, is
 12 made up of a non-partisan group of experts that formulates model legislation in many areas of the law
 13 from various fields of law.¹⁶⁹ The process also pushes the individual states towards uniformity, a goal
 14 that is particularly important in areas like the determination of death because "[a]n individual should
 15 not be simultaneously dead and alive pursuant to the laws of two different states. It should not be
 16 possible to 'statutorily resurrect' a person from state A merely by applying law of state B."¹⁷⁰ The other
 17 uniform law that is most relevant to organ donation is the Uniform Anatomical Gift Act.¹⁷¹

18

19 The UDDA specifically traces its origin to 1978, when Congress enacted legislation creating the
 20 President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral
 21 Research, which had as part of its charge study "the matter of defining death, including the advisability
 22 of developing a uniform definition of death."¹⁷² It produced a report and draft legislation (in
 23 consultation with American Medical Association (AMA) and American Bar Association (ABA)) and
 24 recommended that all states adopt it.

25

26 The UDDA provides that: "An individual who has sustained either (1) irreversible cessation of
 27 circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain,
 28 including the brain stem, is dead. A determination of death must be made in accordance with accepted
 29 medical standards."¹⁷³

30

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

¹⁶⁸ 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.

¹⁶⁹ "About Us - Uniform Law Commission." Uniform Law Commission. <https://www.uniformlaws.org/aboutulc/overview>.

¹⁷⁰ 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.

¹⁷¹ National Conference of Commissioners on Uniform State Laws. *Anatomical Gift Act*. 2006.

¹⁷² President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, 42 USC, 1981.

¹⁷³ National Conference of Commissioners on Uniform State Laws. *Uniform Determination of Death Act*. 1980.

34 used only where an individual's respiratory and circulatory functions were maintained by artificial
 35 means.”¹⁷⁴
 36

37 *What Implications Does the UDDA have for NRP?*

38 The meaning of the term “irreversible” in the UDDA has long been contested and at least some
 39 of the debate as to whether NRP is in tension with the UDDA turns on how the term is understood.
 40

41 Alexandra Glazier and Alex Capron read the wording so as to make at least some forms of NRP
 42 incompatible with the UDDA. As they write: “For years the term ‘irreversible’ (cannot be changed) has
 43 been interpreted as ‘permanent’ (will not change). Accordingly, an individual is dead under US law when
 44 circulation has ceased and will not return through either autoresuscitation or medical intervention.”¹⁷⁵
 45 They then respond to an argument that this proves too much because the same might be said of DCD by
 46 arguing that with NRP “after death is declared, circulation resumes with artificial support” and that this
 47 “contradicts the legal requirement that death depends on circulation having permanently ceased.”¹⁷⁶
 48

49 By contrast, Les James et al. argue that irreversibility as defined by the Uniform Determination
 50 of Death Act specifically relates to the function of the organ within the person: “After an organ has lost
 51 the ability to function within the organism, electrical and metabolic activity at the level of individual cells
 52 or even groups of cells may continue for a period of time.”¹⁷⁷ During NRP, the organs’ inability to
 53 function within the organism was confirmed with the determination of death. The [views of their
 54 opponents] mistakenly applies a rigid and impractical conception of irreversibility to NRP, without
 55 recognizing that the same conception would undermine most determinations of death. If we support
 56 determinations of death in accordance with accepted medical standards, then we should accept that
 57 NRP respects nonmaleficence, because it causes no harm to individuals.¹⁷⁸
 58

59 Matthew DeCamp, Joseph J. Fins, and Lois Snyder Sulmasy in turn criticize these authors for
 60 insisting that the:
 61

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

65 . . . James et al suggest NRP is no different than standard donation after circulatory
 66 determination of death (DCD). Their text proves our point by describing, yet not acknowledging,
 67 the morally salient differences between standard DCD and NRP. Instead of using cold perfusate
 68 before explantation, NRP restarts the circulation of warm blood that stopped moments before.
 69 Recognizing the alarming fact that this will restart brain circulation, active steps are taken to
 70 ensure brain death, improperly shifting lanes from circulatory death to brain death. But brain
 71 death could not possibly be declared based on the timeframe and existing requirements for
 72 doing so.”¹⁷⁹

¹⁷⁴ Klein, Daniel. Uniform Determination of Death Act. American Law Reports, 7th Edition, Art. 5, 2020.

¹⁷⁵ 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.

¹⁷⁶ Ibid.

¹⁷⁷ 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.

¹⁷⁸ Ibid.

¹⁷⁹ 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.

73 They further argue that: “The technical details of NRP can obfuscate the straightforward point
 74 that a person is not dead based solely on a declaration. Consider a counterexample: In standard DCD,
 75 after a 5-min “hands-off period,” death is declared. But what if, just before explantation,
 76 autoresuscitation occurs, and the heart restarts (a known phenomenon)?¹⁸⁰ Would explantation
 77 proceed? It should not. Was this patient dead, then raised from the dead? No. What happened proved
 78 the prior declaration wrong. The patient was not dead. Restarting circulation invalidated the prior
 79 declaration of death. Likewise in NRP.”¹⁸¹

80
 81 A major part of the debate concerns the relevance of the intention of the transplant team in
 82 performing NRP. One argument is that even when NRP restores circulation, the transplant team is not
 83 attempting to resuscitate because that would be medically ineffective and its sole goal is to preserve the
 84 organs, such that this does not reverse the loss of function (or otherwise put the loss of function
 85 remains permanent). The same is true of the individual who has authorized organ donation, they intend
 86 any restoration of circulation solely for the purpose of maintaining the viability of the organs not for
 87 resuscitation and this should not disturb the conclusion that function has been irreversibly (or
 88 permanently) lost.

89
 90 Glazier and Capron respond by drawing a distinction between the ethical significance of
 91 intention versus its legal significance (or lack thereof) under the UDDA.¹⁸² They argue that:

92
 93 “Although intentions may be important when evaluating the ethical acceptability of
 94 physicians’ actions, the legal standard for determining death is bare of intent: a patient is dead
 95 when circulation neither can nor will resume. That the patient is in a state where meaningful
 96 existence is not possible, that trying to induce spontaneous resumption of circulation would be
 97 futile, or even that the NRP protocol is consistent with the donor's wishes, are all irrelevant to
 98 whether the patient is deceased under US law, which turns on the person's physical condition
 99 not on anyone's intention.”¹⁸³

100
 101 A further complication in assessing what the UDDA means for NRP is the circulation of blood
 102 flow to the brain. Glazier and Capron argue that if an NRP protocol calls for the occluding of the carotids,
 103 the transplant team:

104
 105 “may indeed intend to improve organ viability but it is also true that preventing oxygen
 106 from reaching the brain removes the risk that in some DCDD patients the restoration of blood
 107 flow to the brain could prompt at least temporary resumption of functions that are inconsistent
 108 with either or both the neurological or the circulatory respiratory standard for determining
 109 death. An ambitious district attorney might convincingly argue that physicians following the NRP
 110 protocol also intended to render irreversible any brain functions that had not permanently
 111 ceased, thus ensuring the patient's death.”¹⁸⁴

¹⁸⁰ 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.

¹⁸¹ Ibid.

¹⁸² 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.

¹⁸³ Ibid.

¹⁸⁴ Ibid.

112 As Harry Peled et al. put it “Although it is true that the intent of NRP is to produce permanent
 113 cessation of brain circulation, if brain blood flow does occur, the permanence requirement was never
 114 met, and therefore, the declaration of death was not valid.”¹⁸⁵

115
 116 Rendering matters more complicated, not all NRP protocols are the same as to the risk of blood
 117 recirculation. As Basmaji et al note that there are two types of NRP:

118
 119 “abdominal NRP (A-NRP) and thoracoabdominal NRP (TA-NRP). A-NRP supports the
 120 liver, kidney, and pancreas, whereas TA-NRP supports the heart, lungs, and abdominal organs. In
 121 A-NRP, cannulas are inserted either into the iliac artery and vein or into the abdominal aorta
 122 and inferior vena cava, whereas the thoracic aorta is occluded at the level of the diaphragm. In
 123 TA-NRP, the cannulas are placed in the right atrium and the iliac artery or abdominal aorta (6). A
 124 critical anatomic difference exists between these two NRP modalities: A-NRP excludes blood
 125 flow into the thoracic aorta but TA-NRP does not.”¹⁸⁶

126
 127 They are not the same when it comes to the risk of brain reperfusion:

128
 129 “Unlike TA-NRP, A-NRP excludes the thoracic aorta from the extracorporeal circuit,
 130 preventing collateral flow via the internal thoracic, intercostal, and thoracic spinal arteries.
 131 Surgical techniques, such as selective cannulation of the aorta and inferior vena cava as well as
 132 manual transection of the lumbar collaterals, eliminate the possibility of collateral flow via the
 133 inferior epigastric and lumbar arteries, respectively. Although neither technique “definitively”
 134 rules out the possibility of brain reperfusion, A-NRP is the safer modality in this respect.”¹⁸⁷

135
 136 Thus for those for whom the possibility of brain reperfusion is relevant to whether the UDDA’s
 137 criteria for declaring death have been met, the details of the NRP protocol might matter.

138 UDDA Revisions

139
 140
 141 The ULC was considering potential revisions to the UDDA; those discussions have ceased as of
 142 September 2023. This paper will not speculate upon any potential future revisions.¹⁸⁸

¹⁸⁵ Peled H, Mathews S, Rhodes D, et al. “Normothermic Regional...” *Critical Care Med* 2022;50(11):1644-1648, doi:10.1097/ccm.0000000000005632

¹⁸⁶ 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.

¹⁸⁷ Ibid.

¹⁸⁸ The Drafting Committee to Revise the Uniform Determination of Death Act, a Committee of the Uniform Law Commission, was previously meeting to determine if revisions to the UDDA are appropriate.

1 Appendix A: Relevant Terms and Acronyms

2 Ethical Terms – Definitions

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

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

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

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

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

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

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

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

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

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

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

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

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

33

34 Medical Terms - Definitions

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

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

38 **Anastomotic strictures**: Narrowing of an anastomosis.

39 **Anesthetic**: a substance that reduces sensitivity to pain

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

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

42 **Atrial cannula**: a cannula inserted into an artery

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

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

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

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

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

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

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

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

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

59 **Coronary arteries:** Main blood flow vessels to the heart.

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

63 **Distal:** further away from

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

67 **Ex vivo:** outside the body

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

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

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

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

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

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

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

83 **Insensate:** unable to feel pain

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

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

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

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

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

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

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

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

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

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

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

106 **Postmortem:** after death

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

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

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

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

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

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

119

120 Acronyms

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

124 **A-NRP:** Abdominal NRP

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

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

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

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

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

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

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

146 **OPO:**

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

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

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

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

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

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

1 Appendix B: Review of Presentations to Workgroup

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

3
4

Presentations to Workgroup:

<u>Organization Name</u>	<u>Presenter Names</u>	<u>Presentation details/ethical perspective:</u>
<u>University of Minnesota</u>	<u>Cindy Martin, MD</u> <u>Andrew Shaffer, MD</u> <u>Jennifer Needle, MD, MPH</u> <u>Joel WU, JD, MPH, MA</u>	<u>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 occurred¹⁸⁹</u>
<u>New England Donor Services</u>	<u>Alex Glazier, JD, MPH</u>	<u>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 met¹⁹⁰</u>
<u>European Society of Organ Transplant (ESOT)</u>	<u>Amelia Hessheimer, MD</u>	<u>Presentation focused on importance of public trust, honoring donor family wishes, the potential for monitoring cerebral activity, defining death, and sharing models of growth¹⁹¹</u>
<u>University Hospitals Leuven</u>	<u>Arne Neyrinck, MD, PhD</u>	<u>Anesthesiologist perspective on TA-NRP developments in Europe.¹⁹²</u>
<u>University of Cambridge</u>	<u>Christopher JE Watson, MD</u>	<u>Provided an update on the efforts and efforts of NRP in the UK.¹⁹³</u>
<u>Geisel School of Medicine - Dartmouth</u>	<u>James Bernat, MD</u>	<u>Dr. Bernat shared his expertise as a neurologist, specifically focusing on declaration of brain death¹⁹⁴</u>
<u>St. Jude Heritage Fullerton</u>	<u>Harry Peled, MD</u>	<u>Dr. Peled shared the perspective of an intensivist (a physician who provides specialized care for critically ill patients) in relation to NRP¹⁹⁵</u>
<u>American College of Physicians (ACP)</u>	<u>Matthew DeCamp, MD</u>	<u>Dr. DeCamp shared concerns raised by the ACP about the implications of ligating arteries to the brain post circulatory death declaration in NRP donors.¹⁹⁶</u>

¹⁸⁹ OPTN Ethics Committee NRP Workgroup, *Meeting Summary*, August 4, 2022.

¹⁹⁰ OPTN Ethics Committee NRP Workgroup, *Meeting Summary*, August 11, 2022.

¹⁹¹ OPTN Ethics Committee NRP Workgroup, *Meeting Summary*, September 8, 2022.

¹⁹² OPTN Ethics Committee. *Meeting Summary*, March 22, 2022

¹⁹³ OPTN Ethics Committee NRP Workgroup, *Meeting Summary*, September 8, 2022.

¹⁹⁴ OPTN Ethics Committee NRP Workgroup, *Meeting Summary*, September 22, 2022.

¹⁹⁵ OPTN Ethics Committee NRP Workgroup, *Meeting Summary*, December 8, 2022.

¹⁹⁶ OPTN Ethics Committee. *Meeting Summary*, March 22, 2022

1 Appendix C: Workgroup Members

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

4 Workgroup Members

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

#

Appendix A: Post-Public Comment Changes

New language that was proposed following public comment is underlined and highlighted (example); language that is proposed for removal following public comment is struck through and highlighted (example).

Ethical Analysis of Normothermic Regional Perfusion

Executive Summary

~~This white paper~~ outlines conditions for ethical practice of donation in the United States, and implications for normothermic regional perfusion (NRP).¹⁹⁷ ~~The Committee is aware that m~~Many viewpoints exist on NRP, and ~~while that~~ the analysis espoused here may not accord with the views of some, ~~although~~ all were taken into account in the analysis. The purpose of this paper is to provide mission and scope of the Committee, is to support the transplant community and the OPTN Board of Directors ~~with by~~ providing ethical analysis and guidance at the systems-level to support the sustainability of organ donation and transplantation in the United States and to maintain public trust. ~~This Committee analysis recognizes both~~ the importance of increasing utility for candidates waiting for a transplant, and ~~notes~~ the importance of maintaining public trust and adhering to longstanding ethical and legal norms, ~~which that~~ underpin support and sustainability of the entire transplant system.

Importantly, this white paper is not a referendum on clinicians, centers, or OPOs that engage in the practice of NRP. The analysis committee assumes at the outset, ~~without reservation~~, that all stakeholders in the transplant community currently engaged in the practice of NRP have good intentions and, ~~to the extent that they~~ engage in NRP, ~~do so~~ responsibly, ~~and~~ attempting to do so in accordance with their transplant center's stated protocols. Of the many protocols and testimonials ~~that the workgroup and Committee~~ reviewed in development of this white paper, none undertook the pursuit of NRP lightly: all were thoughtful, well-intended, and followed protocols that were well-developed.

~~Normothermic regional perfusion (NRP)~~ is a technique for perfusion either of abdominal organs (A-NRP) or thoracic and abdominal organs (TA-NRP) in a person's body after declaration of circulatory death, and includes occlusion of vessels to prevent brain perfusion.¹⁹⁸ ~~This papere~~ OPTN Ethics Committee reviews the ethical implications of NRP according to established ethical principles guiding donation and transplantation, including: the principle of nonmaleficence (do no harm), respect for persons (which includes respect for autonomy), and utility. The principle of nonmaleficence is important for maintaining public trust and requires compliance with the Dead Donor Rule, which requires that patients must be

¹⁹⁷ The analysis benefited from 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,~~ ~~There are~~ Committee notes some important differences in basic premises underlying differences between donation practices between the United States and some European contexts, which include: support for interventions related to donation, adherence to the Dead Donor Rule, determinations of death criteria, differences in policies regarding provision of analgesics as part of organ donation practices, and differences in public attitudes and expectations regarding donation practices.

¹⁹⁸ 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.

dead at the time of organ procurement (i.e. meet criteria for brain or circulatory death) and that organ donation does not cause death.¹⁹⁹ This paper concludes that:

- NRP has great potential to improve utility for candidates with end-stage organ disease awaiting organ transplantation, and as such should be strongly considered. Utility is necessary, but insufficient to demonstrate that a practice is ethical.
- It is unclear whether NRP complies with the Dead Donor Rule. Circulation²⁰⁰ is restored regionally in the person after circulatory death has been declared, giving rise to questions that are **morally** meaningful as to whether the person continues to meet criteria required for determination of death—in this case permanent²⁰¹ cessation of circulation— at the time donation takes place. To clarify, this concern implies that a person legitimately meets criteria for determining death owing to permanent cessation of circulation at the time of death declaration, but that this criterion is violated subsequently when circulation is restored (at the time of donation).
 - **There may be differences in the degree to which the seriousness of these ethical concerns apply to A-NRP versus TA-NRP.**
- NRP raises concerns about the potential for harm if the assumption that the donor is insensate is incorrect following restoration of circulation following occlusion of the arteries.²⁰²
 - **This concern that the donor may still be sensate** may be mitigated by studies demonstrating that blood flow to the brain during regional perfusion is minimal (e.g. using transcranial Doppler, angiogram studies, or tissue oxygenation measurement).
 - It may also be mitigated by **the** use of certain medications during NRP. However, use of such medications may further undermine compliance with the Dead Donor Rule.
- In the interest of public trust, respect for persons, and transparency, informed decision making **for NRP** should include disclosure of recirculation through the heart (TA-NRP) and the potential restoration of any cerebral perfusion (TA-NRP and A-NRP), as well as considerations of meaningful differences from other donation approaches.^{203,204}

¹⁹⁹ 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.

²⁰⁰ 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].

²⁰¹ 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>.

²⁰² By “insensate” this paper means unable to feel pain.

²⁰³ 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.

²⁰⁴ “Transparency” in this context implies that unique elements of NRP are communicated in a plain-language way to individuals impacted by the donation process.

- This could be addressed by: Clear requirements and guidelines for disclosure, and explanation of morally relevant components of NRP, and standardization and oversight of consistency within the authorization process are necessary components of informed decision making.
- The paper emphasizes the importance of encouraging engagement with donor families to ensure the level of information shared reflects their individual preferences.
- Uncontrolled scenarios for NRP raise additional very serious concerns for respect for persons and proceeding too quickly from therapeutic treatment to organ recovery.²⁰⁵

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

Uniqueness of NRP

NRP entails restoring blood flow through a portion of a person’s body after that person has been declared dead by loss of circulatory function, which by definition requires permanent cessation of circulation. ²⁰⁶ 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. ²⁰⁷
Unlike other machine perfusion techniques, NRP is the only one that perfuses the organs <i>in situ</i> , i.e. while they are in the body. ²⁰⁸
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. ²⁰⁹ In DCD, criteria for circulatory death are maintained observed, so neurological testing is not needed as this person already meets criteria for death determination. For NRP, neurological criteria are not demonstrated to have been met, while at the same time, criteria for circulatory death are not demonstrated to be maintained following the process of reperfusion. neither of these occur.

Scope of White Paper

The OPTN Ethics Committee “aims to guide the policies and practices of the OPTN related to organ donation, procurement, distribution, allocation and transplantation so they are consistent with ethical principles.”²¹⁰ White papers are developed for informational purposes and are intended to guide OPTN

²⁰⁵ 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>

²⁰⁶ 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>.

²⁰⁷ 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

²⁰⁸ “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/>.

²⁰⁹ 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.

²¹⁰ “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.

operations. As such, it is beyond the scope of this paper to speculate regarding potential future changes to the Uniform Determination of Death Act (UDDA), and to opine on whether NRP complies with current law.^{211,212} The Addendum (page 25) provides background on the UDDA and its relevance for the NRP discussion. **This paper's scope does not include reviewing the ethical foundations of DCD, which have been considered extensively elsewhere.**^{213,214,215,216,217} The focus of this white paper is to fully explore and map the relevant ethical principles applied to NRP and the ensuing implications for the OPTN and broader transplant community.

Introduction

There has been an increasing interest in machine perfusion techniques to improve organ quality and utilization, and multiple machines that perfuse organs *ex vivo* (outside the body) have received FDA approval within the last five years.^{218,219} NRP is unique in perfusing organs *in situ* (in the body), which involves ligating the major blood vessels to the brain prior to restoration of circulatory blood flow; in contrast, other machine perfusion techniques are *ex vivo* (outside the body). While NRP has expanded significantly in the United States since 2020, no formal ethical analysis or guidance has been issued by the OPTN regarding the implications for *in situ* organ perfusion.²²⁰ Many other countries that have pursued NRP or have decided against it have provided additional guidance and consideration of its

²¹¹ It is important to note that the UDDA is not itself legally binding. Each state may consider the UDDA in enacting its laws, which are legally binding. **All states allow determinations of death by either neurological or circulatory criteria, and many have enacted the language of the UDDA.** The Dead Donor Rule is also not legally binding but an underlying moral principle to organ transplantation.

²¹² The Uniform Law Commission has suspended its deliberations on the UDDA as of 9/22/23, indicating that the UDDA may not be updated at all for the foreseeable future.

²¹³ 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."

²¹⁴ "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.

²¹⁵ 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

²¹⁶ "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.

²¹⁷ **The extent to which, in deference to transparency, the public is made aware of transplant practices (including whether centers participate in NRP) varies on a case-by-case basis, an issue which is beyond the scope of this paper.**

²¹⁸ "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-metra-system-p200035>.

²¹⁹ "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>.

²²⁰ Croome, Kristopher P., et al. "American Society of Transplant Surgeons recommendations on best practices in donation after circulatory death organ procurement." *American Journal of Transplantation* 23, no. 2 (2023), 171-179. doi:10.1016/j.ajt.2022.10.009.

ethical implications.^{221,222,223} Transplant centers and OPOs have developed a patchwork of approaches and decisions related to NRP in the U.S., creating fragmentation and inconsistency in protocols for treatment of potential organ donors. Many questions remain at this time about the science of NRP as it relates to potential blood flow to the brain, particularly in a retrograde fashion through collateral flow to the spinal cord.²²⁴ While some studies reflect rapid progress in identifying the potential for cerebral flow to be minimal during NRP when vessels are occluded,^{225,226} and although **this paper the Committee** acknowledges that the potential for **a donor being sensate at the time of organ procurement harm** may be low, more research is needed to confirm that the perfusion of the brain or brainstem during NRP does not occur.

Appendix A (page **319**) provides an overview of all relevant terms and acronyms that are defined in this paper; it may be referenced throughout where technical terms are used. Finally, an overview of presenters and topics discussed by the Workgroup is included in Appendix B (page **352**).

Overview of Ethical Findings

Ethical principles guiding transplantation provide a system of checks and balances.²²⁷ This is spelled out in the **OPTN** Final Rule according to which utility, justice, and respect for persons are “the major ethical principles to be balanced to achieve an equitable outcome in the allocation of organs for transplantation.”²²⁸ Another important cornerstone of organ transplantation is public trust, since no transplant would occur without the endorsement of society and the generosity of individual donors and their families.

The **Dead Donor Rule** states that donors must meet criteria for death at the time of donation, to ensure that persons donating organs do not die by or for donation.²²⁹ The Dead Donor Rule is a fundamental tenet of trust in the organ donation system. Adherence to this is critical despite the **paradoxical** need to

²²¹ 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.

²²² 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.

²²³ 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.

²²⁴ Bernat, James., et al. "Understanding the Brain-based Determination of Death When Organ Recovery is Performed with DCDD In Situ Normothermic Regional Perfusion." *Transplantation* ():10.1097/TP.0000000000004642, May 12, 2023. | DOI: 10.1097/TP.0000000000004642

²²⁵ 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.

²²⁶ 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.

²²⁷ 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/>.

²²⁸ "Final Rule." OPTN: Organ Procurement and Transplantation Network - OPTN. <https://optn.transplant.hrsa.gov/about/final-rule/>.

²²⁹ 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.

reduce ischemic time and optimize perfusion to improve transplant outcomes. NRP raises questions about whether the act of ligating the arteries or using an occluding balloon prior to perfusion with the knowledge and intent of restarting regional circulation constitutes a violation of the Dead Donor Rule, as well as a violation of the UDDA, by rendering the initial **determination of** death by circulatory criteria invalid (as circulation was restarted successfully), and without a determination of death by brain death criteria.²³⁰

To provide assurance, the **following** question should be asked: Does regional postmortem circulatory restoration imply that the criteria for meeting death, legitimately established at the time death was declared **according to accepted DCD practices**, is overturned following that restoration?²³¹ Has adequate brain monitoring been conducted to examine brain function in circumstances where the carotid and vertebral arteries cannot be perfused? Would such function be restored, or even somewhat improved, if these arteries were not occluded?²³² Evidence demonstrating lack of blood flow to the brain would be instructive to address concerns about harm, but may not address the larger question about whether the act of occluding the arteries itself violates the Dead Donor Rule. While there are differing ethical opinions regarding the implications of NRP and the Dead Donor Rule, assurance that the Dead Donor Rule has not been violated must be met to be consistent with current ethical practice.

NRP has further implications on the requirement of non-maleficence, or do no harm. **Non-maleficence requires demonstrating that the performance of NRP occurs without harm to the donor and it is currently unclear if NRP results in collateral blood flow to the brain or brainstem. Also not clear is if the existence and extent of collateral blood flow poses risk to the donor in the form of experiencing pain. It is currently unclear if NRP results in collateral blood flow to the brain, including the brainstem. Also, it is not fully clear if collateral blood flow, if it does exist, poses any risk to the donor in the form of experiencing pain.** The detection of brain or brainstem flow may be tested through transcranial Dopplers, angiograms, or tissue oxygenation measurements as a step to clarify the nature of collateral blood flow, **but at the moment there is a lack of good data for these measurements, certainly precluding any possibility of arriving at consensus in the transplantation community that in NRP non-maleficence is not violated.** Still unclear is if there is an association of collateral blood flow with a potential sense state which will require consensus to assure that the non-maleficence standard is not violated.

Another important ethical consideration is whether and how NRP upholds **respect for persons (which includes respect for** autonomy). This entails demonstrating a proactive and transparent process of informed decision-making. The principle of **respect for** autonomy refers to one's capacity to self-determine and have a say over what happens to oneself.²³³ **Autonomy implies "respect for persons"**

²³⁰ National Conference of Commissioners on Uniform State Laws. *Uniform Determination of Death Act*. 1980.

²³¹This 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.

²³² 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

²³³ 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/>.

insofar as it signals decision-making that preserves the dignity of the decision-maker.²³⁴ In order for NRP to adhere to the principle of autonomy, clearer guidelines and standards are needed to ensure that patients, health care agents, and families approached about organ donation understand and can opt to, or not to, proceed with NRP.²³⁵ The paper also acknowledges the potential benefit to demonstrating respect for persons the principle of autonomy in that NRP facilitates the fulfillment of potential donor wishes to give the gift of life.

Lastly, the principle of utility is a highly relevant consideration to any ethical analysis of NRP. The principle of utility takes into account all possible goods and harms that can be envisioned, considering the quantity and probability of the various outcomes. Current evidence suggests that the *in situ* manner in which NRP organs are acquired yields optimal results for the recipient by maximizing the number of organs procured, as well as the quality and longevity of these organs.²³⁶ The alternative methods of *ex vivo* machine perfusion also have positive impacts on organ utilization while avoiding the central controversy of perfusing organs and creating blood flow in the body of someone who was declared dead by circulatory criteria, but the utility benefits for hearts may be lessened by increased post-transplant graft failure.²³⁷ In developing this paper, its deliberations, the Committee considered the available attestations on the part of transplant professionals working in, and intimately familiar with, NRP were considered.²³⁸ It is of central importance to the Committee to consider potential recipients whose lives stand to be improved for the better as a result of NRP, and this mattered a great deal in the overall ethical analysis.

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

Background

*NRP Procedure*²³⁹

Currently, there are two major classifications of NRP, abdominal (A-NRP) and thoraco-abdominal NRP (TA-NRP). A-NRP involves perfusing the liver, kidney and pancreas and other tissue in the lower part of the body using cannulas inserted below the diaphragm, either into the iliac artery and vein or into the abdominal aorta.²⁴⁰ TA-NRP involves perfusing the thoracic organs in addition to abdominal ones, and

²³⁴ Ibid.; Beauchamp, Tom L., and James F. Childress. *Principles of Biomedical Ethics*. New York: Oxford University Press, USA, 2009. ICh.

²³⁵ 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.

²³⁶ 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.

²³⁷ 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.

²³⁸ Summaries of the Committee's deliberations are available here: <https://optn.transplant.hrsa.gov/about/committees/ethics-committee/>

²³⁹ A note that portions of this section are highly technical and a reminder that all relevant terms are defined in Appendix A, page 30.

²⁴⁰ 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.

also implies blood flow through the heart; both forms of NRP involve occlusion of arteries to the brain to prevent perfusion to the brain, although it is less likely that blood flow reach the brain due to A-NRP perfusing organs further from the brain and not perfusing the heart.²⁴¹ A distinction between TA-NRP and A-NRP is that regional perfusion is localized for A-NRP and does not include perfusion to the heart. In A-NRP, cross-clamp or ligation of the aorta eliminates perfusion to the upper body, and not specifically to the carotid vessels or the brain. However, considerations about restoration of circulation are still present in both TA- and A- NRP, and the potential for blood flow to the brain with A-NRP still exists. Plausibly, A-NRP may be less of a concern, but more data is still needed to demonstrate blood flow to the brain does not occur.

The development of NRP in the U.S. emerged as a patchwork, with each center/OPO adopting different approaches, some with rigorous ethical oversight through institutional review boards (IRBs) and formal ethics consultations, others with more informal oversight. No objective, formal ethical evaluations have occurred, similar to prior reports issued by the Institute of Medicine with DCD donation.²⁴² It is important to note that any actions taken prior to and including declaration of death are those taken solely by the non-OPO, critical care team. Details of how NRP is performed vary but typically reflect utilization of standard DCD protocols. The ethically salient elements are as follows:²⁴³

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) are done with the authorization of the patient or patient’s surrogate.
5	Life support is withdrawn, and standard end-of-life comfort measures are initiated.
6	When and if the patient becomes pulseless, the patient is monitored for a period of time (typically 5 minutes in the US), and if autoresuscitation does not occur in that time, death is declared by an independent physician independent of the transplant team based on determination of death by circulatory criteria. ²⁴⁴

²⁴¹ 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.

²⁴² 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.

²⁴³ 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.

²⁴⁴ Institute of Medicine (US) Committee on Non-Heart-Beating Transplantation II: The Scientific and Ethical Basis for Practice and Protocols. "Non-Heart-Beating Organ Transplantation." *Washington (DC): National Academies Press (US); 2000*, 2000. doi:10.17226/9700.

At this point in the process of NRP organ procurement, TA-NRP and A-NRP procedures diverge. The **Committee notes the** relevant elements **are noted** below:²⁴⁵

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, ²⁴⁶ 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. ²⁴⁷

²⁴⁵ Basmaji, John, et al. "Paving the Road..." *Critical Care Explorations* 3, no. 11 (2021), e0553. doi:10.1097/cce.0000000000000553.

²⁴⁶ 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.

²⁴⁷ The American Academy of Neurology (AAN) identifies brain death determination by “demonstration of complete loss of consciousness (coma), brainstem reflexes, and the independent capacity for the ventilatory drive (apnea), in the absence of any factors that imply possible reversibility.” Reference: Russell, James A. Epstein, Leon G., Greer, David M., Kirschen, Matthew., Rubin, Michael, A., Lewis, Ariane. “Brain death, the determination of brain death, and member guidance for brain death accommodation requests: AAN position statement.” *American Academy of Neurology*, January 2, 2019, DOI: <https://doi.org/10.1212/WNL.0000000000006750>

*Historical Perspective*²⁴⁸

To appreciate the current ethical discussions regarding NRP, it is helpful to understand the context from which it arose. In 1993, the University of Pittsburgh developed a protocol that provided a path to obtain organs from individuals deemed dead by cessation of circulation or donors after circulatory death (DCD) to address a growing need for transplantation.²⁴⁹ The growth of DCD donors, and its subsequent acceptance by the medical community and society, was promoted in two Institute of Medicine reports that outlined the ethical and medical issues of non-heart beating donors.^{250,251} One report identified that the demand for organ transplantation had increased by 212% in the prior decade and that organs from DCD donors could increase organ transplantation by 25%.²⁵² Important contributions outlined the practice of separating the organ procurement teams from physicians charged with the management of the terminally ill patients and their death declaration.²⁵³ They also defined the 5 minute “standoff” period from death declaration to procurement, that would minimize the chances of spontaneous ~~re-animation cardiac restoration~~.²⁵⁴ Early experience with DCD liver and kidney transplants demonstrated that these transplants were safe and had a significant survival benefit ~~for recipients~~ compared to remaining on the waitlist.²⁵⁵

The ethical underpinning of DCD transplantation relies on the fact that it adheres to the Dead Donor Rule, in that the donation itself was not the cause of death, and that it was consistent with the UDDA definition that the donor had irreversible cessation of circulatory and respiratory function, interpreted in this case as “permanent” cessation of circulatory function.²⁵⁶ An essential corollary is the implicit understanding that no attempts would be made to resuscitate the donor and as such, the lack of circulation to the brain also causes irreversible cessation of all functions of the brain, including the brainstem.^{257,258}

²⁴⁸ A note that portions of this section are highly technical and a reminder that all relevant terms are defined in Appendix A, page 30.

²⁴⁹ 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

²⁵⁰ 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

²⁵¹ 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.

²⁵² 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

²⁵³ Ibid.

²⁵⁴ Ibid.

²⁵⁵ D'Alessandro AM, et al. Donation after cardiac death: the University of Wisconsin experience. *Ann Transplant* 2004;9(1):68-71

²⁵⁶ See footnote 5.

²⁵⁷ 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

²⁵⁸ OPTN Ethics Committee NRP Workgroup, *Meeting Summary*, September 22, 2022. Available here:

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

The first challenge to the irreversibility clause of the UDDA came from the use of DCD hearts in three pediatric heart transplant recipients.²⁵⁹ If circulatory cessation is irreversible, then how is restarting cardiac function in the recipient permissible?²⁶⁰ Although ethical debates continue regarding DCD heart transplantation, its expansion has been allowed by the notion that despite challenging the irreversibility of asystole, **higher brain functions in the donor are not impacted and are no attempts were made to resuscitate the donor and thus progressive deterioration of brain function proceeded** consistent with the UDDA definition of brain death.²⁶¹ **In response to this concern,** terminology was **therefore** modified to reflect the currently accepted terminology of “Donation after Circulatory Death” instead of “Donation after Cardiac Death.”²⁶² Indisputable in this debate was the agreement that attempts at reversing asystole in the donor, even after death declaration, were not consistent with the process of withdrawing support in a terminally ill patient.²⁶³

The use of ECMO in a DCD donor was protocolized in the U.S. by the University of Michigan and was originally performed for intra-abdominal organs only.²⁶⁴ The use of an intra-aortic occlusion balloon above the diaphragm eliminated cardiopulmonary resuscitation and thus the NRP procedure was deemed “regional” and reportedly consistent with the principle that there were no attempts to resuscitate a donor following the death declaration. During TA-NRP, the aortic arch vessels are ligated to address concerns that ECMO or cardio-pulmonary bypass may result in cerebral circulation.²⁶⁵ Some protocols in Europe use a venting procedure to expose arch vessels to atmospheric pressure to further reduce the chances of collateral cerebral perfusion.²⁶⁶ TA-NRP protocols in Spain uses **Bispectral index (BIS)** monitoring to confirm lack of frontal lobe brain activity following the initiation of ECMO.²⁶⁷

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

²⁵⁹ 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.

²⁶⁰ 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.

²⁶¹ 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.

²⁶² "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.

²⁶³ 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.

²⁶⁴ 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.

²⁶⁵ Dalsgaard, Frederik F., et al. "Clamping of the Aortic Arch Vessels..." *Transplantation* 106, no. 9 (2022), 1763-1769. doi:10.1097/tp.0000000000004047.

²⁶⁶ 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.

²⁶⁷ 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.

declaration prior to the standoff period.²⁶⁸ From a physiological perspective, it is also unknown to what extent collateral circulation results in perfusion of the posterior brain and brainstem.²⁶⁹ Anatomically, there is substantial variability in how the spinal cord receives circulation and our current knowledge challenges the assertion that ligation of aortic arch vessels is sufficient to eliminate perfusion of the entire brain and brainstem, as required by the UDDA.²⁷⁰

The ethical integrity of DCD donation is highly dependent on the societal acceptance that **imminently dying terminally ill** individuals may have cardiopulmonary support withdrawn and, following the act of dying, they could donate organs to help others. Implicit **in the act of dying** is that the individual is not experiencing harm from the organ procurement as they are declared dead by accepted definitions. Unknown in NRP is if the issues regarding brain/brainstem circulation have been scientifically investigated, if organ resuscitation practices conducted in NRP result in inadvertent harm, and if there are in fact potential violations of the Dead Donor Rule.²⁷¹

Need for Ethical Review

As the use of NRP has expanded, so have concerns that its pursuit may violate ethical principles governing organ transplantation and legal boundaries.²⁷² The UDDA, which provides part of the legal framework for organ transplantation in the United States, defines death as **“An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem.”**²⁷³ A 2021 statement by the American College of Physicians (ACP) expressed concern that NRP does not comply with the UDDA because it entails recirculation of blood in the body after death is declared, violating irreversibility, and potentially the Dead Donor Rule.²⁷⁴ Additional concerns related to nonmaleficence include unknown implications of circulation and potential blood flow to the brain.

Those in favor of NRP consider that the procedure does not violate irreversibility because the circulation is localized, or “regional.” Under this view, the UDDA may need to be clarified to expand the interpretation of irreversibility understood as permanence to allow for regional recirculation.²⁷⁵ However, proponents argue that no ethical norm is violated and this may be merely a legal clarification.²⁷⁶ Proponents of NRP consider respect for persons (patient autonomy in choosing to

²⁶⁸ 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.

²⁶⁹ 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.

²⁷⁰ Griep, Randall B., and Eva B. Griep. “Spinal Cord Perfusion and Protection During Descending Thoracic and Thoracoabdominal Aortic Surgery: The Collateral Network Concept.” *The Annals of Thoracic Surgery* 83, no. 2 (2007), S865-S869. doi:10.1016/j.athoracsur.2006.10.092.; Griep, Eva B., et al. “The anatomy of the spinal cord collateral circulation.” *The Annals of Thoracic Surgery* 1, no. 3 (2012), 350-357. doi: [10.3978/j.issn.2225-319X.2012.09.03](https://doi.org/10.3978/j.issn.2225-319X.2012.09.03)

²⁷¹ 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.

²⁷² 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>

²⁷³ National Conference of Commissioners on Uniform State Laws. *Uniform Determination of Death Act*. 1980.

²⁷⁴ 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.

²⁷⁵ 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.

²⁷⁶ Ibid.

donate) and utility (increased use of organs and improved outcomes for recipients) as strong ethical reasons to pursue NRP.²⁷⁷ While still considering it necessary to have appropriate protocols and informed decision making, supporters of NRP do not consider that the Dead Donor Rule is violated or that harm is being done to donors because the procedure occurs after circulatory death has been declared.²⁷⁸ Given the varying perspectives within the community, a workgroup was convened **and the importance of maintaining public trust, the Committee convened an NRP Workgroup** of experts with diverse and diverging opinions and backgrounds to conduct a robust and balanced review of ethical implications, as described in the “Deliberative Process section” below.

Deliberative Process

In circumstances where no *a priori* agreement exists on the hierarchy of principles or values governing ethical decision-making **exist**, people turn to a procedural justice approach. This type of approach (in contrast to distributive justice approaches) stems from the following: if diverse stakeholders are engaged and the process is transparent, and if stakeholders can agree at the outset on the terms for a fair deliberative process, then the outcome arising from the deliberation must be seen and accepted as fair.²⁷⁹

For such a new technology as NRP, with its complexity and potential for controversy, **the Committee it was considered it imperative to create a deliberative process for review that was thorough and inclusive of all relevant perspectives. To that end, the Committee brought together a diverse workgroup was formed** with expertise on NRP, organ donation, ethics, donor family experience, organ procurement, and transplantation to assess the ethical justification for NRP. The Workgroup included supporters and skeptics of NRP, as well as representatives from all key transplant communities, and diverse medical specialties.²⁸⁰ **Committee leadership sought out and obtained membership on the Workgroup that was diverse in perspective and experience.** Guest presentations included proponents and critics of NRP.

The **Ethics** Committee started its deliberation with presentations from both European surgical teams engaged in the practice of NRP and the American College of Physicians (ACP), which had recently issued a position statement critical of NRP.²⁸¹ The Workgroup reviewed protocols presented by U.S. transplant programs engaged in the practice, and sought out the perspectives of intensivists, neurological experts, anesthesiologists, researchers and clinical experts in determination of death, and European transplant clinicians.²⁸² Members updated a shared literature review with 60 relevant publications and participated in Workgroup subgroups to consider the particular implications of irreversibility, patient autonomy, and physician intent. The Workgroup met 15 times from July 2022 to March 2023, and members provided regular updates on progress and discussions to the Committee. An informal survey of the Workgroup indicated that throughout the course of Workgroup review, most respondents had changed their mind regarding whether NRP could be appropriately and ethically pursued in the current environment.²⁸³ This finding suggests that the deliberations of the group and the presentations it received influenced

²⁷⁷ Ibid.

²⁷⁸ 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.

²⁷⁹ Summaries of the Committee's and Workgroup's deliberations are available here: <https://optn.transplant.hrsa.gov/about/committees/ethics-committee/>

²⁸⁰ Ibid.

²⁸¹ A full list of presenters and topics reviewed by the workgroup can be found in Appendix B.

²⁸² Ibid.

²⁸³ 84% of Workgroup members participated in the survey.

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

Ethical Implications of NRP

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

Do No Harm (nonmaleficence)

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

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

Proponents of NRP contend that NRP is a modification of standard DCD donation, which has been in use since 1992, and which is now a well-accepted approach to organ procurement.²⁸⁴ In DCD donation in the US, death is declared (if it occurs) following a predetermined duration of pulselessness, provided that autoresuscitation has not occurred.²⁸⁵ The 5-minute interval has been supported by evidence that autoresuscitation does not typically occur beyond this time interval, provided that there have been no prior attempts to resuscitate the patient.²⁸⁶

Proponents further explain that NRP does not violate the DDR because the restoration of circulation is only regional (excluding the brain in TA-NRP, and excluding the brain and thoracic organs in A-NRP), and consider the fact that circulation is restored *in situ* rather than *ex vivo* to be ethically irrelevant.²⁸⁷ The arteries that supply the brain are clamped or otherwise occluded, and arteries that lie distal to the

²⁸⁴ 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.

²⁸⁵ Manara, A.R., et al. "Donation after circulatory death." *British Journal of Anaesthesia* 108 (2012), i108-i121. doi:10.1093/bja/aer357.

²⁸⁶ 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.

²⁸⁷ Wall, Anji E., et al. "Applying the ethical framework for donation after circulatory death to thoracic normothermic regional perfusion procedures." *American Journal of Transplantation* 22, no. 5 (2022), 1311-1315. doi:10.1111/ajt.16959.

occlusion are vented to atmospheric pressure to divert any potential collateral blood flow away from the brain in an effort to minimize the risk of cerebral reperfusion.²⁸⁸

On the question of whether re-establishing circulation invalidates the determination of death, Parent et al makes a parallel point on the legal issue: “The law is silent on whether subsequent acts can invalidate a declaration of death. Regardless, occluding cerebral circulation... does not cause death—the patient has already been pronounced dead by standard cDCD criteria.”²⁸⁹ Moreover, proponents describe the importance of intention: “Resuscitation efforts require attempting to restart the heart for life-saving/prolonging purposes. In undertaking cDCD NRP, there is no intention or attempt to resuscitate because doing so would be medically ineffective... Perfusing the thoracic and abdominal organs after circulatory determination of death... does not alter the fact that... continued care would be medically ineffective and inconsistent with a meaningful existence.”²⁹⁰ Their presumption is that the intent to restart circulation merely for the purposes of regional reperfusion for donation does not constitute resuscitation. They note that the DDR is not violated in that the occlusion of the arteries ensure that the process of brain death continues unabated after circulatory death determination has been achieved.

On the question of potential harm to the donor, many argue that the donor is insensate because clamping the aortic arch vessels ensures a lack of cerebral blood flow that most closely mimics the level of blood flow to a brain in a standard DCD donor. As such, they perceive the conditions for NRP to be similar to those for DCD, where it is assumed that the donor is insensate and no harm is incurred by the procedure. This assumption could be confirmed by use of anesthetics on the donor, a practice which is not unique to NRP but raises questions beyond the purview of this paper to fully consider.²⁹¹ Do no harm and respect for persons do raise questions about whether anesthesia is appropriate.

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

Yet, many raise concerns that the patient has been declared dead on the basis of the permanent cessation of circulation, with the full intent and understanding that regional circulation will be restored, invalidating the prior determination.²⁹² It is important to note that at that time of donation the patient may no longer meet criteria needed for declaration of circulatory death nor have they been demonstrated to meet the accepted criteria for the neurologic determination of death- which has not been assessed.²⁹³

²⁸⁸ Ibid.

²⁸⁹ 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.

²⁹⁰ Ibid. “cDCD” refers to controlled DCD scenarios in which life support is withdrawn in accordance with potential donor/family decisions.

²⁹¹ Cappucci, S. P., Smith, W. S., Schwartzstein, R., White, D. B., Mitchell, S. L., & Fehnel, C. R. (2022). End-of-life care in the potential donor after circulatory death: A systematic review. *The Neurohospitalist*, 13(1), 61-68. <https://doi.org/10.1177/19418744221123194>

²⁹² 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.

²⁹³ One could argue that determination of death in DCD (including DCD NRP) donation is premised on the condition that no attempt will be made to restore circulation after the onset of pulselessness. Intention notwithstanding, NRP arguably violates this condition, by using ECMO to restore circulation to the body's vital organs, except the brain. From this perspective, the problem is not so much that the determination of death has been reversed, but rather that it was arguably not valid in the first place, since a central requirement of DCD donation was violated. It is also true that others consider that the determination of death is not premised on the condition described above, and that nonmaleficence is maintained as long as the donor is insensate.

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

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

It bears mentioning that in calling attention to these disparate explanations for why occlusion of the aortic arch vessels takes place in NRP, this analysis e Committee does not opine on which is more plausible. The Committee it does take the view, however, that the decision to occlude warrants scrutiny and better understanding. Moreover, the Committee maintains that how one understands the motive behind the decision to occlude will be revealing in the context of any rendered ethical analysis of NRP. Indeed, for the proponent of NRP, for whom the initial declaration of death based on circulatory criteria should be unquestionably trusted and therefore never second-guessed, intent is what governs the analysis and the perspective that the DDR is not violated.²⁹⁴ That all parties have agreed that death is an inevitability, and that nothing should be done to undo this, takes precedence. While these intentions are undoubtedly sincere, they are a problematic defense against those who see NRP as a work-around to the DDR. Skeptics may argue that declaring the patient dead on the basis of the permanent loss of cardiorespiratory function is misleading, since that function is immediately restored, clearly showing that its loss was not permanent, nor irreversible.²⁹⁵ Similarly, while proponents clearly do not intend to restore brain perfusion with ECMO, this is at least a theoretical possibility, and promises to terminate the procedure if this were to occur, can be alarming in the views of skeptics. Finally, proponents also allude to the near certainty that these patients will become brain dead, if they are not already, without

²⁹⁴ 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.

²⁹⁵ 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.

acknowledging that brain death is a complex diagnosis that can only be made over a course of at least several hours.²⁹⁶ From the perspective of one who has concerns about any taken human action which might impact the reliability upon which death criteria are invoked, more attention should be paid to compliance with the principle of “do no harm,” in which case right intent (like informed decision making), is a necessary, but not sufficient, element in the ethical analysis. Intent does not have overriding priority in the ethical analysis.

On the role of intention and justifying ligation through cautiousness, Glazier/Capron consider that “the legal standard for determining death is bare of intent: a patient is dead when circulation neither can nor will resume. That the patient is in a state where meaningful existence is not possible, that trying to induce spontaneous resumption of circulation would be futile, or even that the NRP protocol is consistent with the donor's wishes, are all irrelevant to whether the patient is deceased under US law, which turns on the person's physical condition not on anyone's intention.”²⁹⁷

On the question of harm to the donor: potential for harm to the donor stems from being uncertain if occluding the arch vessels is sufficient to prevent blood flow to the brain and ensure that the donor is insensate. This should be tested for, and more studies to confirm that NRP donors are insensate are needed.²⁹⁸

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

Respect for Persons

The ethical principle of respect for persons **includes refers to** the belief that people **with decision making ability** should be allowed to make **important, personal** decisions for themselves, so long as those decisions do not impose harm to others. “This principle embraces the moral requirements of honesty and fidelity to commitments made, and respect for autonomy.”²⁹⁹ With NRP, the ethical principle of respect for persons suggests we have a duty to honor the potential donor’s first-person authorization for donation for ante-mortem interventions required for donation to occur.

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

²⁹⁶ 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.

²⁹⁷ 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.

²⁹⁸ There is currently one available paper that found no cerebral blood flow in two human donors when ligation of arteries occurred during NRP. These data are promising, but the Committee considers more robust data are needed to confirm its implications. Reference: Frontera J., Lewis A., James L., Melmed, K., Parent, B., Raz, E., Hussain, S., Smith, D., Moazami, N., “Thoracoabdominal Normothermic Regional Perfusion in Donation after Circulatory Death Does Not Restore Brain Blood Flow.” *J Heart Lung Transplant*. 2023 May 19;S1053-2498(23)01862-4. doi: 10.1016/j.healun.2023.05.010. Online ahead of print.

²⁹⁹ OPTN Ethics Committee. *Ethical Principles...* OPTN, 2015. <https://optn.transplant.hrsa.gov/professionals/by-topic/ethical-considerations/ethical-principles-in-the-allocation-of-human-organs/>.

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

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

Informed decision making is not equivalent to informed consent, and applies under authorization in the context of organ donation. This process of informed decision making may be similar to how families make decisions about timing of donation and restrictions around type of organs procured. Informed decision making implies that sufficient information about organ donation to make decisions as they pertain to core preferences and values will be provided. On the question of informed decision making, some opine that standards applicable to the authorization process for DCD donation are sufficient, because both TA- and A- NRP uses similar premortem interventions.^{300,301} Yet others, concerned with whether regional restoration of circulation negates the original determination of death, consider crucial differences must be disclosed to potential donors and families regarding recirculation and the potential restoration of any cerebral perfusion.³⁰² For some, these distinctions are meaningful in a way that may contradict their values and beliefs, and may alter their propensity to participate in NRP. Without sufficient public polling, outreach to communities of different faiths and cultures, etc., it is challenging to know how widely acceptable NRP is, and what elements must be included in informed decision making. Some critics of NRP argue that achieving informed consent or authorization to NRP are is simply not possible if ligating arteries constitutes the cause of death, because an individual cannot give consent or authorization for something that causes their death. With these potential exceptions and limitations identified, the following section provides an overview of informed decision making for optimizing respect for persons in conversations with patients and their families who may be approached about organ donation and NRP specifically.

Informed Decision Making

This paper e Committee acknowledges the challenges faced by OPOs in approaching potential donors candidates and potential donor families, and the difficulty in explaining the components needed for informed decision making (for procedures pre- and post-mortem) and balancing the need for adequately informing potential donor patients and families with the understanding that many families,

³⁰⁰ While there is a difference between informed consent and authorization in this context, without greater information, these differences may be meaningless to members of the general public. This analysis errs on the side of transparency to support maintaining public trust, which is the bedrock of any successful organ donation system.

³⁰¹ Parent, Brendan, et al. "Ethical and logistical concerns..." *American Journal of Transplantation* 20, no. 6 (2020), 1508-1512. doi:10.1111/ajt.15772.

³⁰² 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.

grief-stricken, do not wish to hear details of these procedures. To uphold commitments to autonomy, and to maintain public trust in the organ donation and transplant system, it is critical to be transparent about methods used to facilitate organ donation and facilitate an informed decision-making process with the donor and/or surrogate decision maker. Transplant professionals should avoid evasive and paternalistic attitudes toward bereaved family members that preclude sharing of information and instead focus on an informed decision making process with clear goals for upholding transparency, respect for the rights and interests of the donor and/or their surrogate decision maker, and good stewardship of gifted organs.^{303,304} This is especially true for NRP, as feelings regarding this specific procedure may differ from other more established forms of organ procurement. More research is needed to better articulate these.

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

1. The withdrawal of life sustaining treatment (WLST) conversation must occur before any discussion of donation. The should occur only with the potential donor's clinical care team, *not* OPO staff. The donation conversation, whenever possible, should not occur until after an informed decision has been made to withdraw life sustaining treatment. The Committee acknowledges that this effort is impacted when families spontaneously raise questions about the opportunity to donate organs before or in tandem with the WLST conversation.³⁰⁵
2. Informed decision making for ante-mortem procedures and authorization for post-mortem procedures must be obtained by the potential patient donor's clinical care team, The potential donor's clinical care team and OPO staff obtaining this permission should be "Capable of disclosing information accurately, interacting compassionately with grieving families, and answering all relevant questions... optimal requestors will be those persons who are able to be transparent and are best able to relay information to families in a comprehensive, compassionate, and even-handed manner."³⁰⁶
3. Ideally, the trained requestor for potential donation is a member of the OPO staff with specific training and education to support conversations about NRP with donor family members and hospital staff.³⁰⁷

³⁰³ 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.

³⁰⁴ 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.

³⁰⁵ 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.

³⁰⁶ 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.

³⁰⁶ 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.

³⁰⁷ 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.

4. "If patients have provided first-person consent for organ donation, those obtaining consent from surrogates for ante-mortem procedures ... should consider using language that frames the conversation around a default assumption of donation."³⁰⁸ If the donor family declines ante-mortem interventions that may be necessary for NRP, options for proceeding with standard DCD should be discussed.
5. Authorization from potential patient donor or surrogate decision maker must be obtained for ante-mortem interventions to maximize transplantable organs as part of the consent for donation.³⁰⁹ These include heparin administration, bronchoscopy, liver biopsy, placement of cannulae, prep and drape of the donor, and transport to a separate location or operating room for recovery as applicable.³¹⁰
6. The requestor must include an explanation of the hands-off period after circulatory cessation.

In addition to the elements of informed decision making included for a DCD recovery as described above, NRP raises questions about the need to disclose additional information about the recovery procedure. Recommendations for NRP include a reiteration of the purpose and function of the hands-off waiting period, as well as a description of the steps of the procurement procedure.³¹¹ For TA-NRP, this includes the ligation of vessels to prevent cerebral circulation and the reperfusion of targeted organs before they are removed from the body. Disclosure for TA-NRP should also include a statement that heart function may be restored to provide blood flow to organs.³¹² The Committee also considers that Both TA- and A- NRP should include in informed decision-making discussions that identify the identification of the potential restoration of any cerebral perfusion.

Experienced requestors understand that the needs and preferences of donor family members and surrogate decision makers may be different based on the unique circumstances of each case. The informed decision-making process for organ donation has the obligation to refrain from burdening the donor family during their time of suffering any more than is absolutely necessary. Information must be clear and easy to understand to meet legal standards including whether the proposed protocol is understood and whether justification for failure to disclose risk is acceptable.³¹³ Considering strongly held beliefs in the transplant community regarding the ethical, moral, and legal ramifications of NRP, it is especially critical that the potential donor family be educated about the unique procedures associated with NRP.

Although OPOs must abide with consideration for not burdening potential donor families with unnecessary or unwanted details, the ethical principle of respect for persons supports giving the

³⁰⁸ 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.

³⁰⁹ 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>.

³¹⁰ 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.

³¹¹ 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.

³¹² 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.

³¹³ Showalter, Stuart J. *The Law of Healthcare Administration*, 9th ed. Chicago: Health Administration Press, 2020. NCh. p. 411

surrogate decision maker the option to opt out of detailed information about the recovery procedure, while requiring that some key pieces of information are always explained. In the case of NRP, this likely includes describing clearly that although the donor is declared dead by circulatory death criteria, circulation will be restored regionally (A-NRP) and this may include the heart (TA-NRP), at a time the patient donor has not been assessed to meet the criteria for brain death. It may be especially important in the case of NRP to provide comprehensive support to donor families following the donation event, such that if questions or concerns about the recovery method arise after the fact, donor families have access to information and support. The analysis acknowledges Committee accepts that in rare circumstances the potential donor's surrogate may decline, after serious efforts are undertaken, to hear the information that will ensure Informed decision making is provided. Such "noninformed decision making" should be fully documented and should not preclude proceeding with the NRP protocol.³¹⁴ Requestor training should specifically include these elements.

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

Uncontrolled NRP

Uncontrolled scenarios are those in which circulatory death occurs unexpectedly, not after the planned withdrawal of life support.³¹⁵ While the process of organ recovery following the decision for donation is largely the same in uncontrolled NRP as in controlled NRP (hands-off period, occlusion of vessels, and so on), uncontrolled NRP presents additional ethical concerns related to respect for persons and non-maleficence.³¹⁶

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

An additional complication to uncontrolled NRP stems from the use of ECMO. If a clinical team has decided against using ECMO to prolong life (due to low chance of recovery or quality of life judgment), but then ECMO is used to resume circulation after the hands-off period, this presents significant concern regarding respect for persons. Uncontrolled NRP is additionally challenged by the need to balance clinical decisions with factors relevant to organ preservation and informed consent, all of which need to be conducted in a setting of high acuity.

³¹⁴ 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.

³¹⁵ 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>

³¹⁶ 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.

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

Utility

Utility is a foundational principle that guides the United States' transplant system. Applied to organ donation and allocation, utility "specifies that allocation should maximize the expected net amount of overall good (that is, good adjusted for accompanying harms), thereby incorporating the principle of beneficence (do good) and the principle of non-maleficence (do no harm)."³¹⁷

Potential Increases to Utility

NRP is a promising development in the field of organ transplantation, since it has the potential to substantially improve both the number and the quality of organs that are available for transplantation, and in particular for the heart, which may be difficult to effectively procure by standard DCD donation.³¹⁸ The number of organs would likely be increased by enabling the transplantable organs to be resuscitated in situ, such that otherwise unusable organs could become transplantable. Similarly, in situ resuscitation has the potential to increase the function and the quality of the organs before they are removed for transplantation, which should improve graft function and survival in the long run.³¹⁹

Preliminary data are promising, but contingent on further evidence. Initial studies show there is an overall increase in the average number of organs transplanted per donor with NRP compared to controlled DCD (cDCD) (3.3 versus 2.6).³²⁰ Specifically, **for heart: TA-NRP is positively associated with hearts being recovered and available for transplant, and has been successfully performed with triple organ transplants and pediatric heart transplants.** Increased number of hearts available for transplant

³¹⁷ 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/>.

³¹⁸ 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.

³¹⁹ Ibid.

³²⁰ 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.

(applies to TA-NRP only).^{321, 322, 323, 324, 325} A study showed NRP may improve utilization of livers that had been previously declined.³²⁶

Some data show potential for improved outcomes and graft survival. For livers procured through NRP, decreased rates of early allograft dysfunction, 30-day graft loss, ischemic cholangiopathy, and anastomotic strictures were found compared to cDCD livers; A-NRP shows positive results in preventing ischemic type biliary lesions.^{327, 328, 329} Compared with static cold storage, NRP shows improved outcomes for liver transplants.³³⁰ And for kidney: Research has also shown decreased delayed graft function (DGF), and decreased 1-year graft loss, and improved 12-month kidney function for NRP kidneys compared to cDCD kidneys.³³¹ NRP kidneys are also associated with lower DGF compared to cold perfusion techniques.³³²

³²¹ 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.

³²² Kwon, J. H., Usry, B., Hashmi, Z. A., Bhandari, K., Carnicelli, A. P., Tedford, R. J., Welch, B. A., Shorbaji, K., & Kilic, A. (2023). Donor utilization in heart transplant with donation after circulatory death in the United States. *American Journal of Transplantation*. <https://doi.org/10.1016/j.ajt.2023.07.019>

³²³ Kagawa, H., Goodwin, M., Stehlik, J., Campsen, J., Baker, T., & Selzman, C. (2023). A case report of triple organ transplantation from a donor after circulatory death using thoraco-abdominal Normothermic regional perfusion. <https://doi.org/10.2139/ssrn.4464191>

³²⁴ Beckerman, Z., Overbey, D., Bryner, B. S., Schroder, J. N., Andersen, N. D., Carboni, M. P., Casalinova, S., & Turek, J. W. (2023). Infant heart transplant following donation after circulatory death using normothermic regional perfusion and distant transport, first reported case in North America. *JTCVS Techniques*, 20, 156-157. <https://doi.org/10.1016/j.xjtc.2023.04.001>

³²⁵ Biniwale, R., Lahar, S., Balasubramanya, S., Caraccio, C., Ngang, B., Barone, H., Stimpson, E., Dela Cruz, K., Alejos, J. C., Williams, R., Halnon, N., Reardon, L., Si, M., Shemin, R., Ardehali, A., & Van Arsdell, G. (2023). Pediatric heart transplantation from donation after circulatory death using normothermic regional perfusion and cold storage from a distant donor: First US experience. *JTCVS Techniques*, 20, 158-161. <https://doi.org/10.1016/j.xjtc.2023.05.010>

³²⁶ Schurink, I. J., De Goeij, F. H., Habets, L. J., Van de Leemkolk, F. E., Van Dun, C. A., Oniscu, G. C., Alwayn, I. P., Polak, W. G., Huurman, V. A., & De Jonge, J. (2022). Salvage of declined extended-criteria DCD livers using in situ Normothermic regional perfusion. *Annals of Surgery*, 276(4), e223-e230. <https://doi.org/10.1097/sla.0000000000005611>

³²⁷ 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

³²⁸ Durán, M., Calleja, R., Hann, A., Clarke, G., Ciria, R., Nutu, A., Sanabria-Mateos, R., Ayllón, M. D., López-Cillero, P., Mergental, H., Briceño, J., & Perera, M. T. (2023). Machine perfusion and the prevention of ischemic type biliary lesions following liver transplant: What is the evidence? *World Journal of Gastroenterology*, 29(20), 3066-3083. <https://doi.org/10.3748/wjg.v29.i20.3066>

³²⁹ Schurink, I. J., De Goeij, F. H., Habets, L. J., Van de Leemkolk, F. E., Van Dun, C. A., Oniscu, G. C., Alwayn, I. P., Polak, W. G., Huurman, V. A., & De Jonge, J. (2022). Salvage of declined extended-criteria DCD livers using in situ Normothermic regional perfusion. *Annals of Surgery*, 276(4), e223-e230. <https://doi.org/10.1097/sla.0000000000005611>

³³⁰ Liang, A., Cheng, W., Cao, P., Cai, S., Zhang, L., Zhong, K., & Nie, Y. (2023). Effects of machine perfusion strategies on different donor types in liver transplantation: A systematic review and meta-analysis. *International Journal of Surgery*. <https://doi.org/10.1097/js9.0000000000000661>

³³¹ 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>

³³² Ghoneima, A. S., Sousa Da Silva, R. X., Gosteli, M. A., Barlow, A. D., & Kron, P. (2023). Outcomes of kidney perfusion techniques in transplantation from deceased donors: A systematic review and meta-analysis. *Journal of Clinical Medicine*, 12(12), 3871. <https://doi.org/10.3390/jcm12123871>

One area that the transplant community should monitor closely is the impact on lung utilization. There are some data suggesting positive outcomes for lungs and heart-lungs procured with NRP.^{333,334,335} However, there is concern about lower utilization of lungs when NRP is the procurement method.³³⁶ While initial data suggest that heart, liver, and kidney utilization are positively impacted by NRP, further research should clarify how lungs are impacted.

NRP may also increase utility for donor families, who may receive comfort from the knowledge that their loved one was able to save a greater number of lives with fewer complications. As previously noted, data on public attitudes toward NRP are limited. However, it is known that families experience psychosocial distress when their loved one is a DCD donor whose death does not occur in time to allow the donation of organs.³³⁷ Other studies suggest that the public is open to expanding donor protocols (imminent death donation) in a way that maximizes the chance that a donor will be able successfully donate.³³⁸

Potential to decrease utility

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

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

Potential Harm to Public Trust

Loss or decline in public trust in organ transplantation may be a direct harm of NRP. This harm may be amplified given the current societal challenges regarding misinformation of scientific and health

³³³ Gomes, B., Ribeiro, R., Alvarez, J., Ribeiro, R., Honjeu, A., Gazzalle, A., Bissoondath, V., Yu, F., Adamson, M., Meineri, M., Rao, V., Badiwala, M., Keshavjee, S., & Cypel, M. (2020). Normothermic regional perfusion (NRP) during heart DCD recovery: Is lung quality impacted? A pre-clinical study. *The Journal of Heart and Lung Transplantation*, 39(4), S353-S354. <https://doi.org/10.1016/j.healun.2020.01.415>

³³⁴ Tanaka, S., Campo-Canaveral de la Cruz, J., & Crowley Carrasco, S. (2020). Effect on the donor lungs of using abdominal normothermic regional perfusion in controlled donation after circulatory death. *European Journal of Cardio-Thoracic Surgery*, 59(2), 359-366. <https://doi.org/10.1093/ejcts/ezaa398>

³³⁵ Spencer, P. J., Saddoughi, S. A., Choi, K., Dickinson, T. A., Richman, A., Reynolds, F. A., & Villavicencio, M. A. (2023). Heart-lung transplantation from donation after circulatory death using mobile Normothermic regional perfusion. *ASAIO Journal*. <https://doi.org/10.1097/mat.0000000000002029>

³³⁶ Francois, S., Popa, S., Shaver, C., Mallea, J., Hartwig, M., Patel, Y., Tucker, W., Zofkie, B., Shelton, R., Benjamin, J., Brown, A., & Bacchetta, M. (2023). (1234) comparison of lung utilization from nrp-dcd vs non-nrp Dcd using Evlp. *The Journal of Heart and Lung Transplantation*, 42(4), S527. <https://doi.org/10.1016/j.healun.2023.02.1444>

³³⁷ 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.

³³⁸ 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.

information.³³⁹ While loss of trust in the organ donation process is a harm in itself, it may also have a secondary effect of decreasing the number of people willing to consent to deceased or living donation. Additionally, given the lack of consensus among leading legal scholars about the legality of NRP, the potential for lawsuits associated with potential DDR and UDDA violations could further magnify the public relations challenge of sustaining public support for the mission of organ procurement and transplantation.³⁴⁰ These lawsuits may not only undermine public support, but they may also strain the transplant system and community in response.

Moral distress among transplant clinicians

The ethical and legal concerns described above have raised concerns among clinicians and other health care providers, including some clinicians at centers that perform NRP, that can be characterized as moral distress: the perception that a clinician must engage in an action as part of their clinical role that they believe to be morally wrong.³⁴¹ In the absence of greater clarity from the UDDA, and without better understanding the scope and extent of potential harms particularly to the potential patient donors (pre-mortem) and of donor families, either by virtue of the NRP procedure itself, or merely by not sufficiently informing the potential donor patient and family of the ethically salient distinctions imposed by NRP, these clinicians may suffer moral injury. A number of clinicians have reached out to members of the NRP Workgroup and Ethics Committee to express their concerns about NRP.³⁴² These concerns were often related privately, and there are not public data on clinician attitudes on NRP particularly within the United States. **It is also important to acknowledge, in the interest of being able to help patients in need and respect donors, some clinicians and other health care providers expressed during public comment that they may feel moral distress at not being able to perform NRP and avoid non-utilization of an organ.**

Conclusions

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

Theis OPTN 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 analysis Committee** also affirms the sacred trust and commitment of the transplant community to organ donors and donor families. Finally, the **paper 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.

³³⁹ 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.

³⁴⁰ 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.

³⁴¹ 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.

³⁴² Summaries of the Committee's deliberations are available here: <https://optn.transplant.hrsa.gov/about/committees/ethics-committee/>

It is with these commitments and understandings, and based on the analysis described herein, that this paper Committee concludes that the OPTN should proceed, but proceed cautiously regarding the practice of NRP for organ procurement. The following ethical issues require consideration and resolution:

- Assurance: There are serious ethical concerns that NRP is not consistent with the Dead Donor Rule. There may be differences in the degree to which the seriousness of these ethical concerns apply to A-NRP versus TA-NRP.
- Nonmaleficence must not be violated in the pursuit of NRP, even if positive utility outcomes could result.
- Standardized, Consistent and transparent protocols, including adequate informed decision making with patients (pre-mortem) and of families approached about donation, are necessary pre-conditions for any ethical pursuit of NRP.
- 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.

1 Addendum

2 Addendum: The Uniform Determination of Death Act and NRP

3
4 This white paper concerns the ethics of NRP and does not purport to provide an opinion
5 on the legality of NRP in any U.S. state, a topic outside the committee's charge. At the same
6 time, given that the Uniform Determination of Death Act (UDDA) is currently being considered
7 for revision,³⁴³ it is important to at least briefly discuss the implications of the current text of the
8 UDDA and its possible revisions for NRP.

9 10 *What is the UDDA?*

11
12 The UDDA is a uniform act promulgated by the Uniform Law Commission (ULC). The
13 UCL, also known as the National Conference of Commissioners on Uniform State Laws,
14 established in 1892, is made up of a non-partisan group of experts that formulates model
15 legislation in many areas of the law from **in** various fields of law.³⁴⁴ The process also pushes the
16 individual states towards uniformity, a goal that **is** particularly important in areas like the
17 determination of death because "[a]n individual should not be simultaneously dead and alive
18 pursuant to the laws of two different states. It should not be possible to 'statutorily resurrect' a
19 person from state A merely by applying law of state B."³⁴⁵ The other uniform law that is most
20 relevant to organ donation is the Uniform Anatomical Gift Act.³⁴⁶

21
22 The UDDA specifically traces its origin to 1978, when Congress enacted legislation
23 creating the President's Commission for the Study of Ethical Problems in Medicine and
24 Biomedical and Behavioral Research, which had as part of its charge study "the matter of
25 defining death, including the advisability of developing a uniform definition of death."³⁴⁷ It
26 produced a report and draft legislation (in consultation with American Medical Association
27 (AMA) and American Bar Association (ABA)) and recommended that all states adopt it.

28
29 The UDDA provides that: "An individual who has sustained either (1) irreversible
30 cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of
31 the entire brain, including the brain stem, is dead. A determination of death must be made in
32 accordance with accepted medical standards."³⁴⁸

33
34 Many states have adopted the UDDA, albeit some with modification. "As of 2016, the
35 UDDA had been adopted by 38 states, either word for word or with similar wording. Another
36 nine states had adopted the UDDA, but with an express qualification that the neurological

³⁴³ 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.

³⁴⁴ "About Us - Uniform Law Commission." Uniform Law Commission. <https://www.uniformlaws.org/aboutulc/overview>.

³⁴⁵ 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.

³⁴⁶ National Conference of Commissioners on Uniform State Laws. *Anatomical Gift Act*. 2006.

³⁴⁷ President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, 42 USC, 1981.

³⁴⁸ National Conference of Commissioners on Uniform State Laws. *Uniform Determination of Death Act*. 1980.

37 criteria for death could be used only where an individual's respiratory and circulatory functions
38 were maintained by artificial means."³⁴⁹

39
40 *What Implications Does the UDDA have for NRP?*

41
42 The meaning of the term "irreversible" in the UDDA has long been contested and at
43 least some of the debate as to whether NRP is in tension with the UDDA turns on how the term
44 is understood.

45
46 Alexandra Glazier and Alex Capron read the wording so as to make at least some forms
47 of NRP incompatible with the UDDA. As they write: "For years the term 'irreversible' (cannot be
48 changed) has been interpreted as 'permanent' (will not change). Accordingly, an individual is
49 dead under US law when circulation has ceased and will not return through either
50 autoresuscitation or medical intervention."³⁵⁰ They then respond to an argument that this
51 proves too much because the same might be said of DCD by arguing that with NRP "after death
52 is declared, circulation resumes with artificial support" and that this "contradicts the legal
53 requirement that death depends on circulation having permanently ceased."³⁵¹

54
55 By contrast, Les James et al. argue that irreversibility as defined by the Uniform
56 Determination of Death Act specifically relates to the function of the organ within the person:
57 "After an organ has lost the ability to function within the organism, electrical and metabolic
58 activity at the level of individual cells or even groups of cells may continue for a period of
59 time."³⁵² During NRP, the organs' inability to function within the organism was confirmed with
60 the determination of death. The [views of their opponents] mistakenly applies a rigid and
61 impractical conception of irreversibility to NRP, without recognizing that the same conception
62 would undermine most determinations of death. If we support determinations of death in
63 accordance with accepted medical standards, then we should accept that NRP respects
64 nonmaleficence, because it causes no harm to individuals.³⁵³

65
66 Matthew DeCamp, Joseph J. Fins, and Lois Synder Sulmasy in turn criticize these authors
67 for insisting that the:

68
69 "pronouncement of death, biologic reality notwithstanding, is what makes someone
70 dead and that this declaration is sufficient to permit organ procurement. They misunderstand
71 and misapply basic ethical principles and US law.

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

³⁴⁹ Klein, Daniel. Uniform Determination of Death Act. American Law Reports, 7th Edition, Art. 5, 2020.

³⁵⁰ 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.

³⁵¹ Ibid.

³⁵² 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.

³⁵³ Ibid.

78 death could not possibly be declared based on the timeframe and existing requirements for
79 doing so.”³⁵⁴

80
81 They further argue that: “The technical details of NRP can obfuscate the straightforward
82 point that a person is not dead based solely on a declaration. Consider a counterexample: In
83 standard DCD, after a 5-min “hands-off period,” death is declared. But what if, just before
84 explantation, autoresuscitation occurs, and the heart restarts (a known phenomenon)?³⁵⁵
85 Would explantation proceed? It should not. Was this patient dead, then raised from the dead?
86 No. What happened proved the prior declaration wrong. The patient was not dead. Restarting
87 circulation invalidated the prior declaration of death. Likewise in NRP.”³⁵⁶

88
89 A major part of the debate concerns the relevance of the intention of the transplant
90 team in performing NRP. One argument is that even when NRP restores circulation, the
91 transplant team is not attempting to resuscitate because that would be medically ineffective
92 and its sole goal is to preserve the organs, such that this does not reverse the loss of function (or
93 otherwise put the loss of function remains permanent). The same is true of the individual who
94 has authorized organ donation, they intend any restoration of circulation solely for the purpose
95 of maintaining the viability of the organs not for resuscitation and this should not disturb the
96 conclusion that function has been irreversibly (or permanently) lost.

97
98 Glazier and Capron respond by drawing a distinction between the ethical significance of
99 intention versus its legal significance (or lack thereof) under the UDDA.³⁵⁷ They argue that:

100
101 “Although intentions may be important when evaluating the ethical acceptability of
102 physicians’ actions, the legal standard for determining death is bare of intent: a patient is dead
103 when circulation neither can nor will resume. That the patient is in a state where meaningful
104 existence is not possible, that trying to induce spontaneous resumption of circulation would be
105 futile, or even that the NRP protocol is consistent with the donor's wishes, are all irrelevant to
106 whether the patient is deceased under US law, which turns on the person's physical condition
107 not on anyone's intention.”³⁵⁸

108
109 A further complication in assessing what the UDDA means for NRP is the circulation of
110 blood flow to the brain. Glazier and Capron argue that if an NRP protocol calls for the occluding
111 of the carotids, the transplant team:

112
113 “may indeed intend to improve organ viability but it is also true that preventing oxygen
114 from reaching the brain removes the risk that in some DCDD patients the restoration of blood
115 flow to the brain could prompt at least temporary resumption of functions that are inconsistent
116 with either or both the neurological or the circulatory respiratory standard for determining
117 death. An ambitious district attorney might convincingly argue that physicians following the NRP

³⁵⁴ 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.

³⁵⁵ 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.

³⁵⁶ *Ibid.*

³⁵⁷ 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.

³⁵⁸ *Ibid.*

118 protocol also intended to render irreversible any brain functions that had not permanently
119 ceased, thus ensuring the patient's death."³⁵⁹

120

121 As Harry Peled et al. put it "Although it is true that the intent of NRP is to produce
122 permanent cessation of brain circulation, if brain blood flow does occur, the permanence
123 requirement was never met, and therefore, the declaration of death was not valid."³⁶⁰

124

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

127

128 "abdominal NRP (A-NRP) and thoracoabdominal NRP (TA-NRP). A-NRP supports the
129 liver, kidney, and pancreas, whereas TA-NRP supports the heart, lungs, and abdominal organs. In
130 A-NRP, cannulas are inserted either into the iliac artery and vein or into the abdominal aorta
131 and inferior vena cava, whereas the thoracic aorta is occluded at the level of the diaphragm. In
132 TA-NRP, the cannulas are placed in the right atrium and the iliac artery or abdominal aorta (6). A
133 critical anatomic difference exists between these two NRP modalities: A-NRP excludes blood
134 flow into the thoracic aorta but TA-NRP does not."³⁶¹

135

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

137

138 "Unlike TA-NRP, A-NRP excludes the thoracic aorta from the extracorporeal circuit,
139 preventing collateral flow via the internal thoracic, intercostal, and thoracic spinal arteries.
140 Surgical techniques, such as selective cannulation of the aorta and inferior vena cava as well as
141 manual transection of the lumbar collaterals, eliminate the possibility of collateral flow via the
142 inferior epigastric and lumbar arteries, respectively. Although neither technique "definitively"
143 rules out the possibility of brain reperfusion, A-NRP is the safer modality in this respect."³⁶²

144

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

148

149 *UDDA Revisions*

150

151 The ULC was is currently considering potential revisions to the UDDA; those discussions
152 have ceased as of September 2023. upon which This paper will not speculate upon any potential
153 future revisions.³⁶³

³⁵⁹ Ibid.

³⁶⁰ Peled H, Mathews S, Rhodes D, et al. "Normothermic Regional..." *Critical Care Med* 2022;50(11):1644-1648, doi:10.1097/ccm.0000000000005632

³⁶¹ 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.

³⁶² Ibid.

³⁶³ The Drafting Committee to Revise the Uniform Determination of Death Act, a Committee of the Uniform Law Commission, is currently was previously meeting to determine if revisions to the UDDA are appropriate.

1 Appendix A: Relevant Terms and Acronyms

2

3 *Ethical Terms – Definitions*

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

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

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

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

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

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

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

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

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

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

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

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

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

34

35 *Medical Terms - Definitions*

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

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

39 **Anastomotic strictures:** Narrowing of an anastomosis.

40 **Anesthetic:** a substance that reduces sensitivity to pain

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

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

43 **Atrial cannula:** a cannula inserted into an artery

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

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

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

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

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

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

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

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

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

60 **Coronary arteries:** Main blood flow vessels to the heart.

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

64 **Distal:** further away from

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

68 **Ex vivo:** outside the body

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

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

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

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

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

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

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

84 **Insensate:** unable to feel pain

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

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

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

- 93 **Laparotomy:** a medical procedure that cuts into the abdominal cavity, used in NRP to gain access to
 94 abdominal organs
- 95 **Life support:** can refer to a variety of medical interventions aimed at keeping someone alive while their
 96 normal body processes are not functioning properly, including cardiopulmonary resuscitation (CPR),
 97 defibrillation, and ECMO
- 98 **Ligation:** a medical procedure that involves completely occluding a blood vessel or tubular structure by
 99 the act of a ligature
- 100 **Liver biopsy:** when a piece of the liver is removed for examination
- 101 **Machine perfusion (ex vivo):** refers to a process of keeping donated organs viable through circulation of
 102 blood or perfusate outside the body with a machine
- 103 **Neuronal hypoxemia:** when not enough oxygen is reaching the neurons of the brain
- 104 **Occlusion:** a blockage of a blood vessel or passageway in the body, can be complete or partial.
- 105 **Perfusion:** The act of providing flow of fluid, blood, or other substances into a blood vessel and/or
 106 organ.
- 107 **Postmortem:** after death
- 108 **Resuscitation:** refers to the act of restoring someone from unconsciousness or the act of re-invigorating
 109 something that is dying
- 110 **Spontaneous reanimation:** see autoresuscitation
- 111 **Standoff period:** a period of time between circulatory arrest and final declaration of death, to ensure
 112 that there is no spontaneous irreversibility. In the US, standoff periods typically range from 2-10
 113 minutes, with 5 minutes being a common hospital procedure.
- 114 **Sternotomy:** a medical procedure that opens up the chest via a transection of the breastbone (sternum)
- 115 **Tissue oxygenation measurement:** measures the average oxygen saturation of hemoglobin in the red
 116 blood cells, which carry oxygenated blood to the body's tissues.
- 117 **Transcranial doppler:** a type of ultrasound that measures blood flow through the blood vessels in the
 118 brain
- 119 **Uncontrolled NRP:** use of NRP after unexpected cardiac arrest, in contrast to the typical use of NRP
 120 following controlled withdraw of life sustaining therapy

121

Acronyms

- 123 **ACP:** American College of Physicians. The ACP issued a statement in 2021 expressing concern about the
 124 ethical and legal ramifications of NRP due to potential violation of the dead donor rule and
 125 irreversibility.
- 126 A-NRP:
- 127 **DBD:** Donation after Brain Death. Most organ donors are DBD donors but an increasing proportion are
 128 DCD.
- 129 **DCD:** Donation after Circulatory Death. Circulatory death is determined after waiting a set time period
 130 following withdrawal of life support (cDCD or controlled DCD) or waiting a certain amount of time for
 131 circulatory functions to cease (uDCD or uncontrolled DCD). Note: all organ transplant teams are
 132 separate from the medical teams determining death). While DCD has historically accounted for a smaller
 133 proportion of organ transplants, that percentage is growing steadily as outcomes and techniques have
 134 improved.
- 135 **DGF:** delayed graft function. A common complication of transplant where the transplant does not
 136 function right away.
- 137 **ECMO:** extracorporeal membrane oxygenation. A medical technique that oxygenates blood outside the
 138 body using tubing to pump blood through a lung machine. In NRP, ECMO is used to keep the heart
 139 beating and oxygenated after donor death and before transplant.

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

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

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

148 **OPO:**

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

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

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

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

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

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

- 1 **Appendix B: Review of Presentations to Workgroup**
- 2 No changes post public comment.
- 3 **Appendix C: Workgroup Members**
- 4 No changes post public comment.