Transplant International

CONSENSUS STATEMENT

Consensus statement on normothermic regional perfusion in donation after circulatory death: Report from the European Society for Organ Transplantation's Transplant Learning Journey

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SUMMARY

Normothermic regional perfusion (NRP) in donation after circulatory death (DCD) is a safe alternative to *in situ* cooling and rapid procurement. An increasing number of countries and centres are performing NRP, a technically and logistically challenging procedure. This consensus document provides evidence-based recommendations on the use of NRP in uncontrolled and controlled DCDs. It also offers minimal ethical, logistical and technical requirements that form the foundation of a safe and effective NRP programme. The present article is based on evidence and opinions formulated by a panel of European experts of Workstream 04 of the Transplantation Learning Journey project, which is part of the European Society for Organ Transplantation.

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†TLJ 2.0 WS04 – Collaborators members are presented in Appendix 1.

Introduction

This consensus statement originated from the observation that normothermic regional perfusion (NRP) in donation after circulatory death (DCD) is increasingly used in Europe, while little has been published regarding ethical, logistical and technical aspects associated with its use [1, 2]. In the absence of Level 1 evidence, it was unclear whether NRP should be recommended in uncontrolled DCD (uDCD) or controlled DCD (cDCD) given that all abdominal, and sometimes thoracic, organs are exposed to the technology and what is good for one organ may compromise another. With the recent recommendations to include expansion of cDCD in the proposed 'World Health Organisation Global Consultation on the science of organ donation and transplantation' and to utilize either *in situ* or *ex situ* perfusion techniques in cDCD, NRP is likely to find wider implementation [3].

Cessation of circulatory and respiratory function at normothermia in DCD results in warm ischemic injury of organs before preservation. When oxygenated blood flow is temporarily re-established by NRP following circulatory arrest, previously depleted energy substrates are restored, by-products of anaerobic metabolism are cleared, and endogenous antioxidants are induced, helping to improve organ quality and viability before preservation [4]. In contrast to *in situ* cooling and rapid procurement (ISP), NRP allows assessment of organ function [4]. The potential of NRP to improve historically poor DCD results and expand restrictive donor and organ selection criteria has led to its expansion in the past decade, particularly in Europe. Currently, NRP is permitted in DCD organ recovery in eight European countries and mandatory in three [1].

This consensus statement seeks to guide transplant professionals in the implementation and application of NRP in both uDCD and cDCD. It covers evidence supporting use of NRP as well as ethical, logistical and technical concerns. We have attempted to be as inclusive as possible in addressing clinically relevant conditions that may impact implementation and application of NRP, but given the rapidly evolving nature of this field, we recognize the likelihood of omissions.

Box 1. European Society for Organ Transplantation (ESOT) and the Transplantation Learning Journey (TLJ) projectWorkstreams within the TLJ project help to achieve the primary aim of ESOT – to improve patient access to (and outcomes in) transplantation. TLJ Workstreams facilitate objective discussion of scientific and clinical research, and expert opinion, to ensure that all perspectives on a topic are considered, with clinically relevant end goals in mind.

ESOT seeks to progress transplantation research, practice and education, and to collaborate with other international bodies, to ensure that policies and regulations are globally consistent and relevant, and based on strong scientific, ethical and clinical foundations.

ESOT TLJ 2.0 TRANSPLANTATION LEARNING JOURNEY

ESOT EUROPEAN SOCIETY FOR ORGAN TRANSPLANTATION

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In December 2019, the European Society for Organ Transplantation (ESOT) established a Workstream of European experts (Appendix S1) to create this consensus statement within the Transplantation Learning Journey project (Box 1). The Workstream lead met with the Evidence Review Team (ERT) to outline key questions amenable to formal evidence review and to determine literature search strategy (Appendix S2). Additionally, Workstream core members formulated relevant questions that were unlikely to be supported by systematic evidence review to be discussed with expert groups (Appendix S2). The ERT searched PubMed, Embase and Cochrane libraries to identify relevant studies published through August 2020 and identified 105 for inclusion [2]. In this document, NRP includes any form of abdominal (A-NRP) or thoraco-abdominal (TA-NRP) regional perfusion, making use of extracorporeal membrane oxygenation at temperatures >20°C. Recommendations with supporting evidence identified by the systematic review were graded on strength of recommendation (1 or 2 for strong or conditional, respectively) and evidence (A, B, C or D for strong, moderate, weak and very weak, respectively), following the Grades of Recommendation Assessment, Development and Evaluation (GRADE) [5]. Recommendations for topics not addressed in formal evidence review were based on other published evidence and Workstream consensus that was achieved by completion of questionnaires and a series of videoconferences; these guideline statements were 'not graded' and should not be interpreted as being stronger recommendations than Level 1 or 2. The recommendations formulated by the Workstream are summarized in Table 1.

Recommendations on the use of NRP in DCD

- We recommend the use of A-NRP in uDCD procedures, in preference to ISP and static cold storage, when ethical, technical and logistical requirements are met (1C).
- Solid organ grafts from uDCD NRP donors need to be used with caution, weighing risk of patients' continued waiting against risk for adverse graft outcome (1B).

Kidneys from uDCDs may increase transplantation rates [6]. However, the uDCD process is challenging and unpredictable, with a narrow window for intervention before irreversible organ damage occurs [6]. Solid organ transplantation from uDCD without some form

Table 1. Recommendations on the use of normothermic regional perfusion in donation after circulatory death and relevant ethical, logistical and technical aspects.

Recommendation	Strength of recommendation and evidence*
We recommend the use of A-NRP in uDCD procedures, in preference to ISP and static cold storage, when ethical, technical and logistical requirements are met.	1C
Solid organ grafts from uDCD NRP donors need to be used with caution, weighing risk of patients' continued waiting against risk for adverse graft outcome.	1B
We recommend the use of A-NRP in cDCD procedures, in preference to ISP and static cold storage, when ethical, technical and logistical requirements are met.	1B
We recommend the use of TA-NRP be further explored and developed with strict follow-up of all transplanted organs.	2D
We recommend further research on the necessity of *ex situ* organ perfusion following NRP.	not graded
We recommend comparison of donor conversion rates and organ utilization rates after NRP with those of ISP in DCD and DBD, in well-designed studies.	not graded
We recommend (inter)national registries to include standardized reporting of NRP aspects.	not graded
We recommend future studies report on outcomes of all organs from NRP donors and include an ISP (matched) comparator group, when possible.	not graded

A-NRP, abdominal normothermic regional perfusion; cDCD, controlled donation after circulatory death; DBD, donation after brain death; DCD, donation after circulatory death; ISP, *in situ* cooling and rapid procurement; TA-NRP, thoraco-abdominal normothermic regional perfusion; uDCD, uncontrolled donation after circulatory death.

*Strength of recommendation (1 or 2 for strong or conditional, respectively) and evidence (A, B, C or D for strong, moderate, weak and very weak, respectively), following the Grades of Recommendation Assessment, Development and Evaluation (GRADE) [5].

of regional perfusion is uncommon. Few reports of ISP in livers from uDCDs reflect low utilization rates and variable graft and patient survival [7]. For kidney, high primary non-function (PNF) rates with ISP are described [6]. When legally permissible, NRP allows preservation manoeuvres to be started and maintained for hours with minimal donor disfigurement while approval for organ donation is sought. Viability testing during NRP could reduce PNF rates, though well-defined viability criteria have not been specified. Nevertheless, high liver and kidney PNF rates are reported, even with NRP (Table S1). Although some registry analyses suggest NRP decreases kidney PNF and delayed graft function, quality and certainty of evidence are low (Table S1) [2]. In comparison to donation after brain death (DBD) grafts, transplantation of uDCD livers and kidneys after NRP is associated with inferior graft and patient survival (Table S1) [2]. Experience with uDCD lung transplantation in NRP settings is limited, and early and late outcomes may be inferior to those of cDCD lung transplants [2]. Given these data, solid organ grafts from uDCD NRP donors need to be used with caution, weighing risk of patients' continued waiting to risks of receiving a uDCD graft.

We recommend the use of A-NRP in cDCD procedures, in preference to ISP and static cold storage, when ethical, technical and logistical requirements are met (1B).

Current evidence shows, with high certainty, that NRP in cDCD decreases risk of ischaemic cholangiopathy (Table S2) [2]. The risk of anastomotic biliary strictures and early allograft dysfunction is also reduced, with similar graft and patient outcomes, though quality of evidence is low (Table S2) [2, 8]. Spanish national data suggest NRP improves short-term outcomes of cDCD kidneys compared with ISP (Table S2) [2, 9]. Initial experience with pancreas transplantation after NRP shows feasibility, but more data on safety and effectiveness are needed (Table S2) [2]. Lung transplantation after topical cooling in combination with A-NRP requires technical experience to avoid compromising perfusion of abdominal organs after lungs have been procured and A-NRP continues (see further).

We recommend the use of TA-NRP be further explored and developed with strict follow-up of all transplanted organs (2D).

When NRP involves abdomen and chest, the heart is reperfused, allowing robust functional assessment and DCD heart transplantation. Experience with heart transplantation after TA-NRP is limited to small case series in cDCD, with outcomes comparable to those after ISP (Table S2) [2]. Successful heart transplantation after TA-NRP with short cold ischaemic times and without *ex situ* normothermic perfusion has been described [2, 10]. There is one published report mentioning transplantation of lungs after TA-NRP (Table S2) [2, 10]. Reporting of outcomes of these cases and careful comparison with ISP DCD lungs is important. There is theoretical concern that lungs might experience negative outcomes following TA-NRP, since cardiopulmonary bypass, to which TA-NRP bears resemblance, has a negative impact on the lung. There is currently no evidence to suggest that abdominal organs are disadvantaged during TA-NRP compared with A-NRP when technical criteria are met. Nevertheless, the procedure is more complex. If the heart is left to support the circulation but functions poorly or requires high-dose inotropes, adequate perfusion to abdominal organs is at risk. Contingency plans to quickly convert to A-NRP or ISP are needed to safeguard abdominal organs should an issue arise during TA-NRP.

We recommend further research on the necessity of *ex situ* organ perfusion following NRP (not graded).

With increasing evidence that *ex situ* organ perfusion improves outcomes in DCD livers and kidneys retrieved after ISP [11–14] and that it allows for additional viability testing [15, 16], the necessity and effect of *ex situ* perfusion after NRP need to be investigated. Most NRP studies have been performed with static cold storage. Nevertheless, a considerable number of kidneys, especially from uDCD, have undergone *ex situ* hypothermic perfusion, though no outcome comparison with cold storage is available [2]. Indeed, kidneys might benefit from improved preservation after NRP, as PNF (in uDCD) and delayed graft function rates in DCD remain high [13, 17]. Most livers have also been cold stored [2], though the Italian experience includes the use of oxygenated hypothermic perfusion [18]. *Ex situ* perfusion might allow better uDCD liver selection, given high PNF rates after NRP with static cold storage. For the heart, static cold storage has been reported when the cardiac cold ischaemia time was short, with the donor at or very close to the recipient centre, and only after assessment during TA-NRP [2, 10]. If cold storage was safe, it would avoid considerable cost and complexity of *ex situ* heart perfusion after TA-NRP.

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We recommend comparison of donor conversion rates and organ utilization rates after NRP with those of ISP in DCD and DBD, in well-designed studies (not graded).

In comparison to DBD, DCD results in lower donor conversion rates (DCR) and organ utilization rates (OUR) [19–21]. NRP is thought to increase utilization rates because organ viability can be assessed and recovery is less hurried [22]. Although preliminary analysis suggests improved abdominal OURs with NRP [23], our systematic search could not identify any study designed to investigate this, and no direct comparisons with ISP were available [2]. As calculation of DCR relies on the definition of potential, eligible, actual and utilized donors, we recommend using the definitions of Domínguez-Gil et al. [24].

- We recommend (inter)national registries to include standardized reporting of NRP aspects (not graded).
- We recommend future studies report on outcomes of all organs from NRP donors and include an ISP (matched) comparator group, when possible (not graded).

In the absence of randomized controlled trials, quality of published evidence is limited and risk of publication bias is high [2]. Nevertheless, evidence suggests loss of equipoise for the liver, with data suggesting reduced biliary complications and early allograft dysfunction with NRP and no evidence of detrimental effects for other abdominal organs [2, 8]. Together with challenges related to donor interventional research, this likley explains observed reticence to performing expensive and challenging randomized controlled trials comparing ISP and NRP in cDCD [25, 26]. In addition, many clinically relevant questions are impractical as primary outcomes of randomized controlled trials. Well-designed and maintained (inter)national registries might provide the basis for rigorous observational studies, applying appropriate statistical methods allowing causal inference [27]. These registries would benefit from standardized data collection for all organs recovered from NRP donors and standardized outcome definitions to allow more straightforward data comparisons and meta-analyses. Established registries could be updated to include essential information (Appendix S3) and adapted to include information on *ex situ* perfusion [28]. Specific NRP registries are needed to investigate detailed questions concerning viability assessment, ideal perfusate composition and management during NRP.

Ethical considerations when implementing NRP

As NRP is an integral part of DCD procedures, DCD ethical considerations apply [29–32]. We reiterate those general considerations and add specific issues that should be discussed in any institution with active or planned NRP programmes, keeping in mind that compliance with national, professional and institutional guidelines is essential and may further direct ethical discussions [33].

We recommend developing 'donor identification' protocols to identify potential DCD donors, attuned to national guidance and donor legislation (consent and authorization) (not graded).

The decision to cease resuscitation manoeuvres in or withdraw life-sustaining therapy (WLST) should be made in accordance with national and professional guidance on end-of-life decisions. Such decisions should be made independently of considerations regarding organ donation. Developing donor identification protocols avoids potential conflict of interest by treating physicians, increases the number of potential donors, avoids delay in referral of potential donors, allows clear and transparent communication with relatives and avoids the unnecessary use of resources.

With regard to antemortem interventions during end-of-life care, guidance should include statements on antemortem insertion of guidewires and/or cannulae to facilitate NRP after determination of death (not graded).

End-of-life care should be continued in the best interest of the dying patient, and antemortem interventions should follow national legislation and professional guidelines. Antemortem interventions in the potential donor are ethically acceptable if they do not add risk, harm or discomfort to the patient or relatives. Each institution should develop specific guidance on at least the following antemortem interventions:

• sedatives/analgesics: at all times, patients' comfort should be guaranteed and balanced against expected discomfort, without intention to hasten death or shorten warm ischaemia [34, 35];
• heparin administration;
• antemortem insertion of guidewires or cannulae: facilitates starting NRP after determination of death but might induce pain, damage body integrity and induce haemorrhage (especially as heparinization is needed when cannulae are inserted); protocol needed on whether to remove guidewires/cannulae should the potential donor not proceed to actual donation.

• NRP can only start after declaration of death (not graded);
• We recommend that any NRP technique ensures that brain perfusion is not restored (not graded).

It is fundamental that NRP procedures are in accordance with the dead donor rule (organs can only be retrieved after determination of death, and death should never result from organ recovery) [36–38]. Definition of circulatory arrest and determination of death should be performed according to medical, professional and national standards [39–41].

From an ethical viewpoint, the definition of death in DCD settings is generally accepted as the 'permanent' rather than the 'irreversible' cessation of circulation [42–47]. 'Permanent' means that no efforts are made to restart circulation and autoresuscitation is no longer possible. This point is commonly accepted to be achieved after 5 minutes of continuous apnoea, circulatory loss and unresponsiveness, but in some countries, legislation requires a longer observational period [45].

In NRP settings, 'permanent' has an additional dimension, since NRP restores circulation to a limited vascular region [48]. Brain reperfusion would negate permanence, and any NRP technique needs to ensure brain reperfusion does not occur [49, 50]. Technical adaptations to the NRP procedure have been proposed [48, 51]. Transparent protocols, in accordance with the latest standards in medical care, are needed.

We recommend that contingency plans to quickly modify or abort an NRP procedure be in place (not graded).

Because of the nature of DCD procedures and the technical complexity of NRP, protocols for cessation or rapid alteration of the planned procedure are needed. From an ethical perspective, certain situations are to be anticipated in any NRP protocol. First, the risk of autoresuscitation during the no-touch period, inherent to all DCD procedures, needs to be considered. Clear criteria for what is considered autoresuscitation and transparent communication when there is suspicion of autoresuscitation are needed. Autoresuscitation might lead to prolonged agonal periods or abortion of the procedure. In case of persistent circulation, a clear protocol should be in place to continue end-of-life care in the best interest of the patient.

Secondly, when the patient has been declared dead, NRP has been started and all efforts to permanently exclude brain perfusion are in place, signs of brain reperfusion could, theoretically, be detected. A clear protocol on how to define brain reperfusion during NRP is needed; contingency plans to modify or abort the procedure are crucial.

Minimal logistic requirements for NRP

We recommend that centres setting up an NRP programme should

• Seek regulatory support and national guidelines (not graded);
• Include WLST protocols, as an integral part of end-of-life care, into NRP protocols (not graded);
• Maintain open communication with relatives and seek consent in accordance with local legislation (not graded);
• Rigorously train all involved in NRP (not graded);
• Develop an NRP (electronic) case report form (not graded);
• Monitor NRP activity, considering efficiency, efficacy, DCR and OURs, and post-transplant outcomes of all organs (not graded).

Legal provisions, (inter)national guidelines, and recommendations regarding end-of-life care, declaration of death and DCD are essential [1]. Implementing NRP warrants discussion with organ allocation services, as there might be implications for organ allocation (Table S3).

As in any donation procedure, communication with relatives is important, and consent/authorization needs to be sought. Most countries with NRP programmes

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specifically mention use of NRP in interviews with relatives (Table S3). This conversation needs to discuss timing (e.g. prolonging antemortem care, as organizing a donation procedure takes time) and location of WLST (intensive care and operating room).

Detailed protocols, standard operating procedures, and checklists for coordinators and perfusionists are essential to ensure the presence of appropriate materials, drugs and tissue samples. Protocols should be tailored to ensure essential equipment, unlikley to be present in the donor hospital, is brought by the NRP team. Case report forms and checklists are helpful to record and coordinate the NRP process. These should, at a minimum, contain information on donor identity, NRP type, cannulation site, withdrawal time (from WLST to start NRP), warm ischaemic times (WIT) (functional WIT from systolic blood pressure <50 mmHg to start NRP, asystolic WIT), time from incision to NRP, regional perfusion flows and pressures, timing and dose of drugs administered during NRP, temperatures and duration of NRP.

Training of all involved is essential, and team training is preferred. Continuing education could be established via (inter)national or regional courses, with specific training oriented towards transplant coordinators, nurses, surgeons, perfusionists, intensivists/internists and anaesthesiologists involved in DCD management. We advocate simulation training, wet-labs and attendance at a minimum of 5 NRP cases to understand the process. In some countries, NRP can only be performed in designated hospitals. Mobile NRP teams, using portable devices, have also been piloted (Table S3) [52]. Mobile teams require close collaboration with the donor hospital. Organizing team (de)briefings facilitates open communication and enhances safety and efficacy of the procedure. Programmes should continuously monitor their NRP activity (efficiency, efficacy, DCR and OURs, post-transplant outcomes).

Minimal basic technical requirements for NRP

We recommend that A-NRP is established and maintained by a team that includes at least two surgeons, a scrub nurse, a circulating nurse and a perfusionist (not graded).

Typically, an NRP team includes at least two surgeons or an intensivist to perform cannulation; a scrub nurse, a circulating nurse and a perfusionist in charge of setting up and running the NRP circuit. Belgium and the Netherlands recommend two perfusionists. In Spain, where antemortem cannulation is permitted in many donor hospitals, cannulation may also be performed by an interventional radiologist before WLST (Table S4).

- We recommend that the NRP circuit includes a minimum of a centrifugal pump, membrane oxygenator and heat exchanger, with sufficient crystalloid solution to fill circuit tubing (not graded).
- We recommend that donor cross-matched packed red blood cells be added to the perfusate to maintain haemoglobin >8 g/dl and sufficient heparin be added to ensure anticoagulation in therapeutic range (not graded).

A reservoir and leucocyte filter can also be included in the circuit. Bicarbonate is often added to the priming solution since DCD donors may be profoundly acidotic, though there is conflicting evidence supporting a beneficial nature for this practice [53–55]. In countries that do not permit antemortem heparin administration, heparin must be added to the priming solution. Table S5 gives an overview of the composition of NRP perfusates, as reported in literature. Red blood cells are added to maintain perfusate haemoglobin levels >8–10 g/dl, and heparin is supplemented to maintain activated clotting time within or above therapeutic range.

We cannot make recommendations regarding antemortem interventions, as they are dictated by prevailing legislation (not graded).

Antemortem interventions, which include guidewire placement, cannulation and heparinization, are performed according to local legislation. Antemortem heparin administration is performed in Belgium, France, Norway, Spain and Italy (in the latter case, only after the onset of functional WIT, defined as systolic blood pressure <50 mmHg, and in the absence of risk to cause further harm to the patient, based on the clinical judgement of treating physician). Antemortem cannulation is allowed only in Spain, though antemortem vessel localization with guidewires or small catheters may be performed in Belgium, France, Italy and Norway. No antemortem interventions are allowed in the Netherlands or UK.

Concerning WLST in cDCD with intention to start NRP after declaration of death, we state

- WLST may take place in either the intensive care unit or the operating room (not graded);
- WLST and verification of death should be performed by a physician or group of physicians entirely separate from NRP and organ recovery teams (not graded);
- During WLST, the potential cDCD donor is ideally continuously monitored for arterial pressure using an indwelling catheter, pulse oximetry and the electrocardiographic waveform (not graded);
- Further research is needed to establish a universal definition for the start of functional warm ischaemia that correlates with the onset of end-organ ischaemia (not graded);
- National legislation dictates criteria for declaring death (not graded).

In all countries, WLST is performed by a physician or group of physicians entirely separate from the NRP and organ recovery team(s), either in the operating room or the intensive care unit. All countries perform continuous arterial pressure monitoring using an indwelling catheter during WLST. Additionally, it is common to monitor electrocardiographic and pulse oximetric waveforms. The onset of significant hypoperfusion is assessed based on evolution of blood pressure, with or without oxygen saturation. There is no consensus regarding which specific blood pressure threshold (systolic or mean) should be used. Oxygen saturations with pulse oximeters may give a false impression of onset of ischaemia and is not recommended. A 5-minute no-touch period of absent circulation and absence of spontaneous respiration is most often used to declare death (Table S6). In some countries, 20 minutes of electrical asystole are required to declare death.[1]

Concerning post-mortem surgical cannulation required for NRP, we can state this may be performed in the open abdomen or in the common femoral vessels (not graded).

Post-mortem cannulation for NRP may be performed either in the open abdomen or in the common femoral vessels (Table S7). The latter can be easier to perform and is helped by antemortem vessel localization using guidewires or catheters. When an occlusion balloon is used to prevent restoration of cerebral flow by occluding the descending thoracic aorta, correct positioning needs to be confirmed using either X-ray or ultrasound before initiating NRP (Table S7). Placing an open cannula in the ascending aorta allows confirmation of absence of brain perfusion by monitoring pressure and flow in the aorta during A-NRP [48].

When NRP has been established, we recommend

- NRP to be maintained between 1 and 4 hours (not graded);
- Continuous monitoring of temperature (not graded);
- Monitoring flow and serially assessing blood gases and other analytical/biochemical parameters at least once every hour (not graded).

In general, a minimum of one and maximum of four hours of NRP are stipulated (Table S5). During NRP, circuit temperature and flow are monitored continuously, while blood gases and other parameters, including perfusate transaminases and lactate, are evaluated at least once every hour. No validated viability criteria are available and protocols for viability assessment vary. Based upon reported practice and expert opinion, we can state that liver viability in cDCD during NRP is best based on the evolution of hepatic transaminases (ideally <4x upper limit of normal and stable) and lactate (ideally declining) in the perfusate, bile production and pH, macroscopic aspect and occasionally microscopic findings (<30% macrosteatosis) (Table S8). Given the limited experience with uDCD liver transplantation and considerable PNF rates after NRP, further research is needed to recommend any viability criteria but it would make sense these are also based on similar biochemical measurements. For kidneys, published reports mention macroscopic aspect, occasionally microscopic findings and urine production, although in our experience, the absence of urine output *per se* should not lead to organ discard (Table S9). Centres using *ex situ* hypothermic perfusion report using renal resistance, though studies outside the NRP field have shown kidneys should not be discarded based upon renal resistance criteria only (Table S9) [56–58]. The pancreas is commonly assessed

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based on its macroscopic appearance, also taking into account the viability assessment of other organs [59–61]. For heart, acceptance is based on left ventricular ejection fraction, cardiac index, flow-volume curves and the ability of the heart to support thoraco-abdominal circulation after weaning from NRP (Table S10). For lung, one study mentions acceptance based on PaO_2 >300 mmHg [62].

In addition, many countries adhere to strict donor criteria, and especially to limitation of (f)WIT before the start of NRP. In uDCD, maximal accepted time between cardiac arrest and start of basic life support varies between 15 and 90 min, reflected by reported values (Table S11). Reported maximal accepted time between start of basic life support and NRP start varies between 30 and 150 min, reflected by reported values (Table S11). Reported maximal accepted time from cardiac arrest to start of NRP is 150 min for liver and kidneys (Table S12). Based on reported NRP cDCD literature, it is difficult to provide guidance on (f)WIT at which point donation should be abandoned as no single definitions for WIT and fWIT are used (Table S6, Table S12). Apart from WIT limitations, some protocols, especially in uDCD, take strict donor and procedural inclusion and exclusion criteria into account (Table S13). These are mostly age limits, a witnessed cardiac arrest in uDCD and low anticipated risk of cancer or transmissible disease.

When NRP is discontinued, and organ procurement is commenced, we recommend that abdominal organs be removed as quickly as possible following the onset of cold preservation (not graded).

Similar to DBD and ISP DCD procedures, colloid-containing solutions are preferred in most countries for abdominal organ (UW and IGL-1) and lung preservation (Perfadex). Abdominal organs are removed as quickly as possible, either sequentially or *en bloc*, following the onset of cold preservation [63].

We recommend special consideration for thoracic organ recovery in DCD donors with NRP (not graded).

During A-NRP, haemostasis in the thorax should be meticulous while A-NRP is running. Special care should be taken to control caval tributaries in the chest, with meticulous haemostasis. Continuous communication among all involved (abdominal, thoracic and perfusionist) is critical to ensuring favourable outcomes. There is not enough experience in TA-NRP to make any recommendations.

Authorship

This article has been developed by a team of European experts within Workstream (WS) 04 of the European Society for Organ Transplantation (ESOT) through series of email and virtual discussions and ESOT teleconferences together with related presentations at the ESOT TLJ2.0 online congress in November 2020. All WS04 members have considerable expertise and interest in the study and application of normothermic regional perfusion in transplantation. IJ, AJH, DP and AN drafted the manuscript. The fully written and referenced article was circulated to all WS members and collaborators for review by email and teleconference. The document was finalized by IJ and circulated to all co-authors and collaborators for approval before submission for publication.

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Conflicts of interest

IJ reports speaker fees from XVIVO Perfusion paid to her institution. AJH reports research funds from Instituto de Salud Carlos III paid to her institution and research funds and consultancy fees from Guanguong Shunde Innovative Design Institute paid to her institution. DPZ reports speaker fees from Novartis, and Sandoz as well as support for congress registration. JD reports research support to Institution from XVIVO Perfusion. CJEW reports consultancy fees from Nefro Health and Jazz Pharma paid to his institution as well as speaker fees from OrganOx Ltd. All other authors report no potential conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. ESOT Workstream 04 of the Transplant Learning Journey (TLJ) project.

Appendix S2. Key questions to be addressed in the consensus statement.

Appendix S3. Limited set of variables essential to be collected in any transplantation registry.

Table S1. Summary of findings table of evidence NRP compared to ISP in uDCD.

Table S2. Summary of findings table of evidence NRP compared to ISP in cDCD.

Table S3. Topics addressed by the Workstreams Logistics Team.

Table S4. Statements of the Workstreams Technical Team.

Table S5. Composition of prime solution and regional perfusion targets.

Table S6. Definitions of warm ischaemia and duration of the no-touch period for each study, by country.

Table S7. Technical details of NRP protocols per donor type.

Table S8. Reported liver acceptance criteria during and after NRP.

Table S9. Reported kidney acceptance criteria during and after NRP.

Table S10. Reported heart acceptance criteria during and after NRP.

Table S11. Maximal accepted intervals between cardiac arrest and NRP, reported time to basic life support and cannulation for NRP in uDCD donors.

Table S12. Maximal accepted and reported WIT per organ, categorized by donor type.

Table S13. Donor and procedural acceptance criteria, by donor type and country.

REFERENCES

1. Lomero M, Gardiner D, Coll E, *et al*. Donation after circulatory death today: an updated overview of the European landscape. *Transpl Int* 2020; **33**: 76.
2. De Beule J, Vandendriessche K, Pengel LH, *et al*. A systematic review and meta-analyses of regional perfusion in donation after circulatory death solid organ transplantation. *submitted*. 2021. TRI-MA-21-0480 (in revision).
3. Domínguez-Gil B, Ascher N, Capron AM, *et al*. Expanding controlled donation after the circulatory determination of death: statement from an international collaborative. *Intensive Care Med* 2021; **47**: 265–281.
4. Hessheimer AJ, García-Valdecasas JC, Fondevila C. Abdominal regional in-situ perfusion in donation after circulatory determination of death donors. *Curr Opin Organ Transplant* 2016; **21**: 322.
5. Guyatt GH, Oxman AD, Vist GE, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; **336**: 924.
6. Summers DM, Pettigrew GJ. Kidney transplantation following uncontrolled donation after circulatory death. *Curr Opin Organ Transplant* 2020; **25**: 144.
7. Lazzeri C, Bonizzoli M, Marra F, *et al*. Uncontrolled donation after circulatory death and liver transplantation: evidence and unresolved issues. *Minerva Anestesiol* 2020; **86**: 196.
8. Savier E, Lim C, Rayar M, *et al*. Favorable outcomes of liver transplantation from controlled circulatory death donors using normothermic regional perfusion compared to brain death donors. *Transplantation* 2020; **104**: 1943.
9. Padilla M, Coll E, Fernández-Pérez C, *et al*. Improved short-term outcomes of kidney transplants in controlled donation after the circulatory determination of death with the use of normothermic regional perfusion. *Am J Transplant* 2021. https://doi.org/10.1111/ajt.16622.
10. Vandendriessche K, Tchana-Sato V, Ledoux D, *et al*. Transplantation of donor hearts after circulatory death using normothermic regional perfusion and cold storage preservation. *Eur J Cardiothorac Surg* 2021. https://doi.org/10.1093/ejcts/ezab139.
11. Mergental H, Laing RW, Kirkham AJ, *et al*. Transplantation of discarded livers following viability testing with normothermic machine perfusion. *Nat Commun* 2020; **11**: 2939.
12. Nasralla D, Coussios CC, Mergental H, *et al*. A randomized trial of normothermic preservation in liver transplantation. *Nature* 2018; **557**: 50.
13. Jochmans I, Brat A, Davies L, *et al*. Oxygenated versus standard cold perfusion preservation in kidney transplantation (COMPARE): a randomised, doubleblind, paired, phase 3 trial. *Lancet* 2020; **396**: 1653.
14. van Rijn R, Schurink IJ, de Vries Y, *et al*. Hypothermic machine perfusion in liver transplantation - a randomized trial. *N Engl J Med* 2021; **384**: 1391.
15. Watson CJE, Jochmans I. From, "Gut Feeling" to objectivity: machine preservation of the liver as a tool to assess organ viability. *Curr Transplant Rep* 2018; **5**: 72.
16. De Beule J, Jochmans I. Kidney perfusion as an organ quality assessment tool-are we counting our chickens before they have hatched? *J Clin Med* 2020; **9**: 879.
17. Antoine C, Savoye E, Gaudez F, *et al*. Kidney transplant from uncontrolled donation after circulatory death: contribution of normothermic regional perfusion. *Transplantation* 2020; **104**: 130.
18. De Carlis R, Schlegel A, Frassoni S, *et al*. How to preserve liver grafts from circulatory death with long warm ischemia? a retrospective italian cohort study with normothermic regional perfusion and hypothermic oxygenated perfusion. *Transplantation* 2021;. https://doi.org/10.1097/tp.0000000000003595.
19. Orman ES, Barritt AY, Wheeler SB, Hayashi PH. Declining liver utilization

for transplantation in the United States and the impact of donation after cardiac death. *Liver Transpl* 2013; **19**: 59.
20. Berney T, Boffa C, Augustine T, *et al*. Utilization of organs from donors after circulatory death for vascularized pancreas and islet of Langerhans transplantation: recommendations from an expert group. *Transpl Int* 2016; **29**: 798.
21. Jochmans I, van Rosmalen M, Pirenne J, Samuel U. Adult liver allocation in eurotransplant. *Transplantation* 2017; **101**: 1542.
22. van de Leemkolk FEM, Schurink IJ, Dekkers OM, *et al*. Abdominal normothermic regional perfusion in donation after circulatory death: a systematic review and critical appraisal. *Transplantation* 2020; **104**: 1776.
23. Oniscu GC, Randle LV, Muiesan P, *et al*. In situ normothermic regional perfusion for controlled donation after circulatory death–the United Kingdom experience. *Am J Transplant* 2014; **14**: 2846.
24. Domínguez-Gil B, Delmonico FL, Shaheen FA, *et al*. The critical pathway for deceased donation: reportable uniformity in the approach to deceased donation. *Transpl Int* 2011; **24**: 373.
25. Abt PL, Marsh CL, Dunn TB, *et al*. Challenges to research and innovation to optimize deceased donor organ quality and quantity. *Am J Transplant* 2013; **13**: 1400.
26. Cooper J, Harvey D, Gardiner D. Examining consent for interventional research in potential deceased organ donors: a narrative review. *Anaesthesia* 2020; **75**: 1229.
27. Krishnamoorthy V, McLean D, Ohnuma T, *et al*. Causal inference in perioperative medicine observational research: part 2, advanced methods. *Br J Anaesth* 2020; **125**: 398.
28. Martins PN, Rizzari MD, Ghinolfi D, *et al*. Design, analysis, and pitfalls of clinical trials using ex situ liver machine perfusion: the international liver transplantation society consensus guidelines. *Transplantation* 2021; **105**: 796.
29. Bos MA. Ethical and legal issues in non-heart-beating organ donation. *Transplant Proc* 2005; **37**: 574.
30. Dominguez-Gil B, Ascher N, Capron AM, *et al*. Expanding controlled donation after the circulatory determination of death: statement from an international collaborative. *Intensive Care Med* 2021; **47**: 265.
31. Haase B, Bos M, Boffa C, *et al*. Ethical, legal, and societal issues and recommendations for controlled and uncontrolled DCD. *Transpl Int* 2016; **29**: 771.
32. Saemann L, Karck M, Korkmaz-Icoz S, Wenzel F, Szabo G. Ethical decision diagrams on donation after cardiocirculatory death heart transplantation considering organ preservation techniques. *Transplant Direct* 2020; **6**: e617.
33. Jericho BG. Organ donation after circulatory death: ethical issues and international practices. *Anesth Analg* 2019; **128**: 280.
34. Kompanje EJO, Epker JL. Controlled Donation after circulatory determination of death: ethical issues in withdrawing life-sustaining therapy. *J Intensive Care Med* 2018; **33**: 270.
35. Pana R, Hornby L, Shemie SD, Dhanani S, Teitelbaum J. Time to loss of brain function and activity during circulatory arrest. *J Crit Care* 2016; **34**: 77.
36. Veatch RM. Transplanting hearts after death measured by cardiac criteria: the challenge to the dead donor rule. *J Med Philos* 2010; **35**: 313.
37. den Hartogh G. When are you dead enough to be a donor? Can any feasible protocol for the determination of death on circulatory criteria respect the dead donor rule? *Theor Med Bioeth* 2019; **40**: 299.
38. Ave ALD, Sulmasy DP, Bernat JL. The ethical obligation of the dead donor rule. *Med Health Care Philos* 2020; **23**: 43.
39. Dhanani S, Hornby L, Ward R, Shemie S. Variability in the determination of death after cardiac arrest: a review of guidelines and statements. *J Intensive Care Med* 2012; **27**: 238.
40. Othman MH, Dutta A, Kondziella D. Public opinion and legislations related to brain death, circulatory death and organ donation. *J Neurol Sci* 2020; **413**: 116800.
41. Shemie SD. Clarifying the paradigm for the ethics of donation and transplantation: was 'dead' really so clear before organ donation? *Philos Ethics Humanit Med* 2007; **2**: 18.
42. McGee A, Gardiner D. Permanence can be defended. *Bioethics* 2017; **31**: 220–230.
43. White FJ. Controversy in the determination of death: the definition and moment of death. *Linacre Quarterly* 2019; **86**: 366.
44. Bernat JL. Conceptual Issues in DCDD Donor Death Determination. *Hastings Cent Rep* 2018; **48**(Suppl 4): S26.
45. Dhanani S, Hornby L, van Beinum A, *et al*. Resumption of cardiac activity after withdrawal of life-sustaining measures. *N Engl J Med* 2021; **384**: 345.
46. Gardiner D, Shemie S, Manara A, Opdam H. International perspective on the diagnosis of death. *Br J Anaesth* 2012; **108**: I14–I28.
47. Dalle Ave AL, Gardiner D, Shaw DM. Cardio-pulmonary resuscitation of brain-dead organ donors: a literature review and suggestions for practice. *Transpl Int* 2016; **29**: 12.
48. Manara A, Shemie SD, Large S, *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. *Am J Transplant* 2020; **20**: 2017.
49. Shapey IM, Summers A, Augustine T, van Dellen D. Systematic review to assess the possibility of return of cerebral and cardiac activity after normothermic regional perfusion for donors after circulatory death. *Br J Surg* 2019; **106**: 174.
50. Bernat JL, Capron AM, Bleck TP, *et al*. The circulatory-respiratory determination of death in organ donation. *Crit Care Med* 2010; **38**: 963.
51. Perez-Villares JM, Rubio JJ, Del Rio F, Minambres E. Validation of a new proposal to avoid donor resuscitation in controlled donation after circulatory death with normothermic regional perfusion. *Resuscitation* 2017; **117**: 46. https://doi.org/10.1016/j.resuscitation.2017.05.030
52. Figini MA, Paredes-Zapata D, Juan EO, Chiumello DA. Mobile extracorporeal membrane oxygenation teams for organ donation after circulatory death. *Transplant Proc* 2020; **52**: 1528.
53. Follette D, Fey K, Livesay J, Maloney JV Jr, Buckberg GD. Studies on myocardial reperfusion injury. I. Favorable modification by adjusting reperfusate pH. *Surgery* 1977; **82**: 149.
54. Follette D, Fey K, Mulder D, Maloney JV Jr, Buckberg GD. Prolonged safe aortic clamping by combining membrane stabilization, multidose cardioplegia, and appropriate pH reperfusion. *J Thorac Cardiovasc Surg* 1977; **74**: 682.
55. Trummer G, Benk C, Beyersdorf F. Controlled automated reperfusion of the whole body after cardiac arrest. *J Thorac Dis* 2019; **11**: S1464–S1470.
56. Parikh CR, Hall IE, Bhangoo RS, *et al*. Associations of perfusate biomarkers and pump parameters with delayed graft function and deceased donor kidney allograft function. *Am J Transplant* 2016; **16**: 1526.
57. Jochmans I, Moers C, Smits JM, *et al*. Renal resistance during machine perfusion is a risk factor for delayed graft function and poorer graft survival. *Am*

J Transplant 2010; **10**: 107. https://doi.org/10.1111/j.1600-6143.2011.03685.x
58. Matillon X, Danjou F, Petruzzo P, *et al*. Hypothermic pulsatile preservation of kidneys from uncontrolled deceased donors after cardiac arrest - a retrospective study. *Transpl Int* 2017; **30**: 1284.
59. Butler AJ, Randle LV, Watson CJ. Normothermic regional perfusion for donation after circulatory death without prior heparinization. *Transplantation* 2014; **97**: 1272.
60. Rojas-Peña A, Sall LE, Gravel MT, *et al*. Donation after circulatory determination of death: the university of michigan experience with extracorporeal support. *Transplantation* 2014; **98**: 328.
61. L'Agence de la Biomédicine. Conditions for recovery of organs by donation after circulatory death (Maastricht category 3) in health care facility authorized to recover organs. 2018. Available at https://www.agence-biomedecine.fr/IMG/pdf/v7_guide_ddac_miii_novembre_2019_eng.pdf. Accessed 24/05/2021
62. Fernández E, Calatayud J, Jarabo JR, *et al*. Profitability of our lung retrieval program from non heart beating donors. *Eur J Cardiothorac Surg* 2009; **35**: 287.
63. Heylen L, Pirenne J, Naesens M, Sprangers B, Jochmans I. "Time is tissue"-A minireview on the importance of donor nephrectomy, donor hepatectomy, and implantation times in kidney and liver transplantation. *Am J Transplant* 2021.

APPENDIX 1

TLJ 2.0 WS04 – Collaborators

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