Canadian Guidelines for Controlled Pediatric Donation after Circulatory Determination of Death

Report and Recommendations
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Canadian Guidelines for Controlled Pediatric Donation after Circulatory Determination of Death

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LIST OF ACRONYMS

Acronym	Extension, Explanation
CACCN	Canadian Association of Critical Care Nurses
CBS	Canadian Blood Services
CCCS	Canadian Critical Care Society
cDCD	Controlled Donation after Circulatory Determination of Death
CPS	Canadian Paediatric Society
CST	Canadian Society of Transplantation
DCD	Donation after Circulatory Determination of Death
DDR	Dead Donor Rule
DGF	Delayed graft function
EC-DCD	Extracorporeal support - Donation after Circulatory Determination of Death
ECMO	Extracorporeal membrane oxygenation
EOL	End of Life
GCS	Glasgow coma scale
GDC	Guideline Development Committee
HCP	Health Care Professional
ICU	Intensive Care Unit (including neonatal and pediatric intensive care units)
NICU	Neonatal Intensive Care Unit
NDD	Neurologic Determination of Death
ODO	Organ Donation Organization. Used throughout document to refer to organizations or programs that coordinate organ donation and transplantation in a designated jurisdiction
OTD	Organ and Tissue Donation
OTDT	Organ and Tissue Donation and Transplantation
PAD	Physician Assisted Death
pDCD	Pediatric Donation After Circulatory Determination of Death
PICO	Population, Intervention, Comparator, Outcome
PICU	Pediatric Intensive Care Unit

RR-DCD	Rapid recovery - Donation after Circulatory Determination of Death
uDCD	Uncontrolled Donation after Circulatory Determination of Death
WG	Working Group
WHO	World Health Organization
WIT	Warm Ischemic Time
WLST	Withdrawal of Life Sustaining Therapy

INTRODUCTION

Since the publication of the 2006 consensus national recommendations(1) , donation after circulatory determination of death (DCD) has become an increasingly frequent pathway to deceased organ donation for adults in Canada (2). The implementation of DCD in children (pDCD), however, has lagged behind. According to 2014 data from Canadian Blood Services, DCD represented 21% (123/592) of national deceased donation, but pDCD made up only 8% (3/37) of pediatric deceased donation. This practice remains concentrated in a limited number of centres with active pDCD protocols and programs. In an effort to enhance the uptake and implementation of pDCD in Canada, the purpose of this document is to provide rigorously developed, evidence-based guidelines that centres can adapt to their own practices.

While the gap between transplanted organ need and supply is well documented (3), the implementation of pDCD practices has potential benefits that extend beyond this important issue. Incorporating the option of deceased donation into end-of-life (EOL) care has been reported to be beneficial for families dealing with the death of a loved one (3-7). Also, the legal requirement to identify patients who are potential donors and notify provincial organ donation organizations (ODOs) has also been incorporated into provincial organ donation gift acts in many provinces (see Appendix 1). Finally, the neurological determination of death (NDD) is a rare event that is becoming rarer in adults (8) and children (9), leading to a decrease in potential NDD donors. For patients undergoing withdrawal of life sustaining therapy (WLST) during EOL care, DCD is the only pathway available to respect the family and loved one's desire to pursue organ donation (10).

Ethical concerns regarding DCD, in general, and pDCD, specifically, represented the most common theme found in our recent review of the literature that informed these guidelines (11). The concerns are wide-ranging but principally focused on respect for the dead donor rule, perceived or actual conflicts of interest in regards to the medical team, defining what constitutes valid informed consent, and concerns that pDCD could negatively impact EOL care. Similar ethical concerns have been cited, addressed, and managed in adult DCD (1, 12-14).

As summarized in our related scoping review (11), most retrospective estimates report that potential pDCD donors will likely represent 5–10% of ventilated deaths in an intensive care unit (ICU) setting. There are only two published reports from active programs, both from the same centre in Salt Lake City, Utah (15, 16). The first, from a pediatric intensive care unit (PICU) environment, reported that, while successful pDCD recovery occurred in only 6% of ventilated patient deaths, this resulted in a 58% increase in the number of deceased pediatric organ donors compared to historic controls (15). The second report analyzed pDCD activity in their neonatal intensive care (NICU), which found 2.9% of eligible donors became pDCD donors (16). Of particular significance from this NICU report, retrospective analysis determined that only 10% of potential pDCD donors in the NICU were appropriately referred for evaluation, likely substantially decreasing their overall donation rate. These reports confirm that pDCD, while uncommon even in high volume centres, can increase overall donation rates, particularly in ICUs where NDD rates are low and WLST is a common pathway to death.

Post-transplantation organ outcome reports also suggest that pDCD is a viable pathway to increasing the available organ pool. While outcomes vary by organ and inclusion criteria, the few existing reports of long-term transplant outcomes suggest that kidneys and livers retrieved through pDCD have graft outcomes similar to those retrieved through NDD. The impact of cardiac and lung pDCD is in evolution, but these practices have been shown to be feasible (17, 18). Detailed organ-based outcomes were summarized in our scoping review (11).

As a low frequency, high impact event pDCD would benefit from standardization of best practices, but surveys of current practice shows significant practice variation across jurisdictions and centres (19, 20). Although pediatric-specific concerns are mentioned in several guidelines, to our knowledge, there are no current national or international guidelines that specifically address potential pediatric donors in DCD.

Thus, we sought to provide recommendations for pDCD practices in a Canadian context, based on a rigorous guideline development methodology, including extensive literature reviews and multi-disciplinary consultation, as detailed below.

SCOPE AND DEFINITIONS

Scope

As part of a national pDCD workshop with Working Group members, held in Toronto, Ontario on October 28, 2014, participants worked together to determine the scope of the guidelines (Table 2).

Table 2 Scope of Guidelines

In scope	• Canadian centres caring for critically ill children • Potential pDCD donors (neonatal, pediatric, infant) • Canadian organ / tissue donation programs • Controlled pDCD in a hospital setting • Review of literature, including national or regional policies and protocols related to the practice of pDCD • Rigorous review of published pDCD guidelines using AGREE II criteria, where applicable • Recommendations for physicians and administrators developing pDCD hospital policies • Surveillance of graft and patient outcomes after pDCD • Solicitation of provider perspective of barriers and facilitators to pDCD • Implementation tools (e.g., checklist, guidelines for implementation)
Out of scope	• While the appropriateness of certain practices of elements within the practice of DCD may be discussed, deliberation on the overall ethical appropriateness of pDCD is out of scope

	• Uncontrolled pDCD • Adult DCD • Clinical practice recommendations from individual centres or ODOs • pDCD in the context of physician-assisted death

Definitions

Definitions relevant to the discussion of deceased donation and used in these guidelines are given in Table 3. Considering the importance of the definition of death and the dead donor rule to the development of these guidelines, expanded explanations are included in the Determination of Death section.

Table 3 Glossary of terms for pediatric donation after circulatory death

Activity	Physiologic properties of cells and groups of cells that can be measured by laboratory means
Accepted Medical Practice	Standards of medical practice that are based on credible scientific evidence published in peer-reviewed, medical literature generally recognized by the relevant medical community. Could include, but is not limited to, physician specialty society recommendations or guidelines, the views of physicians practicing in the relevant clinical area, and other relevant factors
Allocation	The process of selecting a patient on the waitlist to receive a donated organ according to a pre-defined set of rules
Ante mortem	From Latin, meaning before death is determined
Asystole - electrical	A condition characterized by the absence of electrical, and hence mechanical, activity of the heart, resulting in the absence of contractions of the myocardium and cardiac output/anterograde blood flow
Asystole - mechanical	The absence of effective contractions of the myocardium and no cardiac output/anterograde blood flow. May occur in the presence of an organized or disorganized electrocardiac rhythm, e.g. pulseless electrical activity
Autoresuscitation	The spontaneous unassisted resumption of heart contractions causing anterograde circulation that is not induced by cardiopulmonary resuscitation or other external assistance
Brain death	Traditional and not-preferred terminology generally referring to death determined by neurologic criteria, defined below
Cardiac arrest	The abrupt cessation of circulation of blood due to failure of the heart to contract effectively. Also known as cardiorespiratory arrest, cardiopulmonary arrest or

	circulatory arrest
Cessation	Stoppage, termination
Circulation	Anterograde flow of blood through the aorta and arterial system
Cold Ischemia Time (CIT)	The amount of time an organ spends preserved in a cold perfusion solution after organ recovery and before transplantation
Consent to Deceased Organ and Tissue Donation	A process where legally valid permission for organ or tissue donation is obtained either from the donor (also called first person consent) or from the donor's legally appropriate surrogate decision maker, following the donor's death. Sometimes referred to as authorization to donate
Dead Donor Rule	A principle governing deceased donation practices stating that vital organs should only be taken from dead patients and that living patients must not be killed by organ recovery
Death	The permanent loss of capacity for consciousness and all brainstem functions, as a consequence of permanent cessation of circulation. Permanence is defined as loss of function that will not resume spontaneously and will not be restored through intervention. See discussion in Definitions section of text
Death Determined by Neurologic Criteria	Diagnosis and confirmation of death based on the irreversible cessation of all clinical functions of the brain
Delayed Graft Function (DGF)	Refers to the condition in which the transplanted tissue or organ does not function properly immediately after the transplant but takes time before it begins to function adequately
Donation after Circulatory Determination of Death (DCD)	The recovery of organs for transplantation from individuals who are determined dead by circulatory criteria
Donor	A person (either living or deceased) who provides cells, tissues or organs for transplantation
Donor Management	The process of medically caring for deceased donors in order to keep their organs viable until organ recovery can occur
Effective referral	A referral for medical services that is made in good faith with a view to supporting, not frustrating or impeding, access to care
Extracorporeal membrane oxygenation (ECMO)	Technology allowing extracorporeal (outside of the body) oxygenation and circulation of blood that is deployed for life-threatening lung, heart, or heart–lung failure
***Ex vivo* perfusion**	Various technologies used to provide mechanical perfusion (typically oxygenated) to organs after recovery
Function	In the context of organs, the primary and fundamental purpose of that organ that can be assessed by observation

	and examination and is necessary for sustained life
Graft	A transplanted organ or tissue
Graft Survival	The length of time an organ functions successfully after being transplanted
Hands off Time	A period of observation to confirm cessation of circulation, during which no interventions are permitted and continuous monitoring of circulation is required
Informed Consent	A person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, required prior to diagnostic or medical procedures or participation in research for all living patients
Irreversible	Pertaining to a situation or condition that will not or cannot return or resume. In the context of death determination, there are variable definitions including: 1. Loss of function or a condition that cannot be restored by anyone under any circumstances at a time now or in the future 2. Loss of function or a condition that cannot be restored by those present at the time 3. Loss of function or a condition that will not resume and will not be restored; also referred to as permanent
Minimal Risk	The probability and magnitude of harm or discomfort anticipated are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests
Minimum Criteria	Refers to the lowest acceptable standard. The standards recommended by this committee should be considered to represent minimum acceptable clinical practice
Neonate	An infant less than or equal to 28 days of age, and includes the entire population of infants less than 44 weeks corrected gestational age
Neurological Determination of Death (NDD)	The process for determining death of an individual based on neurological or brain-based criteria
Organ	A part of the body made up of tissues and cells that enable it to perform a particular function. Transplantable organs include the heart, liver, lungs, kidneys, pancreas and intestines
Organ Donation	A donation of an organ or a part of an organ for transplantation
Organ Donation Organization (ODO)	Regional or provincial organizations responsible for facilitating and coordinating the donation, procurement, and distribution of organs from deceased donors. Used

	throughout this document to refer to organizations or programs that coordinate organ donation and transplantation in a particular jurisdiction
Oxygenated circulation	Blood-based fluid that carries sufficient oxygen to maintain cellular metabolism
Perfusion	The passage of blood or other fluid through the vessels of organs or tissues. Deceased donor organs are perfused to sustain the ability to function for transplantation
Permanent	Pertaining to a situation or condition that will not return to its previous state. In the context of death determination, refers to loss of function that will not resume spontaneously and will not be restored through intervention
Post Mortem	From Latin, meaning after death is determined
Preservation	The use of chemicals or other methods to prevent or slow biological or physical deterioration of tissues, in order to be able to use them at a later time
Presumed or Opt-Out Consent Model	Model of organ donation consent where, unless otherwise specified, a person is presumed to have consented to donation in the case of their accidental death. No Canadian jurisdiction currently employs presumed consent
Recipient	A patient that has received a cell, tissue or organ transplant
Regional Oxygenated Perfusion	Various techniques used to provide oxygenated perfusion to transplantable organs *in situ, post mortem* and prior to organ recovery with exclusion of brain perfusion
Research Ethics Board (REB)	Committee formally designated to approve, monitor, and review biomedical and behavioral research involving humans
Recovery	The surgical procedure of removing cells, tissues or organs from a donor. Also referred to as recovery or procurement
Substitute decision maker	A person who is legally authorized to make decisions on behalf of the patient. In the case of pDCD, this person is often, but not always the biologic parents
Tissue	An aggregation of specialized cells, which together perform specific functions. Examples of tissues that can be transplanted are skin, bones, cornea, heart valves, ligaments, muscles and tendons
Transplant / Transplantation	The surgical transfer of cells, tissue, or organs from a donor into a recipient with the aim of restoring functions in the body
Transplant Centre / Transplant Program	A hospital that performs transplants and provides related services, including qualifying patients for transplant, registering patients on wait lists, and providing care before and after transplant. A transplant centre may have many organ-specific programs for the transplantation of hearts,

	lungs, liver, kidneys, pancreas, and/or intestines
Withdrawal of life sustaining therapy (WLST)	The discontinuation of any treatment that serves to prolong life without reversing the underlying medical condition. In the setting of DCD, the therapies most frequently withdrawn are mechanical ventilation, inotropic support of hemodynamic function and mechanical circulatory support. WLST does not imply cessation of comfort care
Warm Ischemic Time (WIT) - functional	The time interval between the first act of withdrawal of life-sustaining treatment (e.g. extubation) and the determination of death. Distinct from the total WIT, which is measured by recovery teams and ends at the initiation of cold perfusion

METHODS

General Procedure

Our purpose was to create a well-developed, evidence-based, and properly disseminated national guideline for pDCD with a high probability of broad implementation. We adhered to a rigorous process of guideline development based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methods and as delineated by handbooks for this process created by the World Health Organization (WHO) (21), the Canadian Medical Association (CMA) (22, 23), and the GIN-McMaster Guideline Development Checklist (24). In addition, we followed the principles delineated by the Appraisal of Guidelines, Research and Evaluation (AGREE II) (25) instrument for guideline assessment. Concepts of the AGREE II instrument were incorporated into the development protocols, procedural documents, and reporting templates and AGREE II provided a framework for reaching consensus on methodological principles and reporting requirements for national cooperation. Supporting evidence was systematically reviewed and summarized in a process consistent with the GRADE method (26).

Committee Composition (See Appendix 2 for full details of committee membership)

The development of this guideline was led by a steering committee of 5 members (A.A., L.H., B.R., S.D.S., M.W) who were also part of the multidisciplinary guideline development committee (GDC) that consisted of a Chair (M.W.), co-Chair (S.D.S), an information specialist (W.W.), a health research methodologist (B.R.), policy makers (A.A., L.H.), and the leads of 7 Working Groups (WGs): Neonatal (M.vM.; other members: K.B., K.C., D.M., C.T.); Cardiac (V.B.S.; other members: K.B., A.D., D.F.); Eligibility, Potential and Outcomes (A.G.; other members: A.B., A.D. V.L.); Withdrawal of Life Supporting Therapies (C.F.; other members: J.B., M.M., M.vM.); Ante and Post Mortem Interventions (M.B., R.S.; other members: A.C., D.M., K. D-P., S.Z.); Death Determination (S.D.; other members: A.B., L.H., M.M.); and Ethics and Legal (R.G.; other members D.B., K.C., C.C., R.D., A.G., C.M., G.M).

Within the GDC and WGs there were 5 neonatal and 18 pediatric critical care physicians, 2 critical care nurses, a pediatric nephrologist, a pediatric cardiologist, a cardiac surgeon, 2 bioethicists, and a lawyer with expertise in donation and transplantation. The health research methodologist (BR), is a member of the MacGRADE Centre at McMaster University, has expertise in evidence synthesis and the guideline development process, and is also an adult critical care physician. The GDC members represented the Canadian Pediatric Society (CPS, C.F., M.W., K.C.), the Canadian Association of Critical Care Nurses (CACCN, K.D-P), the Canadian Society of Transplantation (CST, A.G.), and the Canadian Critical Care Society (CCCS, CF).

Once drafted, the guideline was reviewed by two patient partners (E.T., J.W.), selected by the steering committee based on their experience as family members of deceased donors, and an external reviewer. These reviewers completed a standardized questionnaire based on AGREE II (25) for rating the guideline and assessing their agreement with each recommendation. Comments by external reviewers were discussed by teleconference and recommendations were incorporated. CPS, CACCN, CST, and CCCS reviewed the final guideline for endorsement, with CPS providing a publication outlet for a peer-reviewed summary of the guidelines.

Confidentiality Agreement and Conflict-of-Interest Management

All committee members completed disclosure statements for any potential conflicts of interest at the beginning of the guideline development process and again prior to finalization of recommendations. The chair and co-chair (M.W., S.D.S.) reviewed all the disclosure statements with Canadian Blood Services staff. None of the committee members were found to have any major financial or intellectual conflicts of interest.

Funding Disclosure

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Canadian Blood Services is not responsible for the management or funding of any Canadian ODOs or Transplant Programs. Canadian Blood Services receives its funding from the provincial and territorial Ministries of Health. The federal government, through Health Canada, also contributes to the Canadian Blood Services OTDT mandate.

Canadian Blood Services provided meeting facilities and logistical and financial support for expenses resulting from the meeting and conference calls. The views and interests of Canadian Blood Services, CPS, CACCN, CCCS, as well as of any commercial entity that provided external funding for professional societies, had no influence on the topics discussed and recommendations made.

Meetings

In May 2014, a Steering Committee (M.W, L.H., S. C-M., S.D.S., S.T.) was formed to explore the necessity of developing a national guideline for pDCD. The initial steps in the guideline development process were completed over a six-month period (May – November, 2014) and included preparation for a national pDCD workshop with WG members, held in Toronto, Ontario in conjunction with the Canadian Critical Care Forum on October 28, 2014. As part of this initial phase, a scoping review of literature for pDCD was completed (11) and the preliminary findings presented as part of the pDCD workshop, where they were used to guide consensus determination of the scope of the guideline (see Scope and Definitions section).

Participants at the conference attended presentations from content experts and worked together to define the following:

1) The area of practice and policy to which the guideline applies;
2) Those whom the recommendations are intended to affect;
3) The actions and interventions of interest;
4) The outcomes that may result – both positive and negative.

Over the following 15 months (December 2014-March 2016), additional meetings of the steering committee were held in person and over the phone. Conference calls and email correspondence were used to solicit topic-specific input from each of the WGs. Each WG participated in a training webinar on GRADE methodology led by the health research methodologist (B.R.), followed by 2-3 conference calls to review and revise the Good Practice Statements as well as the actionable PICO (Population, Intervention, Comparator, Outcome) questions that were formulated by the steering group (please see following section for further details). An additional conference call was required to review the generated evidence summaries associated with each PICO question and to apply the evidence to decision (EtD) framework to formulate recommendations (27). The entire GDC met in Toronto on March 22 2016, at which time each of the Good Practice Statements and recommendations was reviewed and approved by all members. Final revisions based on these recommendations were carried out by the steering committee and all GDC members approved of the final document.

Formulating Clinical Questions

Using the results from the scoping review on pDCD (11), participant input from the 2014 workshop, and the existing 2006 Canadian DCD recommendations (1), the steering committee developed the initial clinical questions for consideration by each of the WGs. All outcomes were identified *a priori*. Questions were divided into those that would be best addressed by Good Practice Statements (28) and those that were amenable to formal evaluation of the evidence by the GRADE approach (26).

Literature Searches and Screening of Citations

The initial search strategy involved a broad-based scoping review (11), which resulted in retention of 91/7,597 discovered references. For this scoping review, only references that specifically addressed potential pediatric donors in DCD were retained. The references from this scoping review informed our Good Practice Statements and were used to identify potential

PICO Questions

Once the PICO questions were finalized, an extended search was performed around each question in order to ensure that any potentially informative indirect evidence (e.g. from adult DCD or NDD) was captured. An information scientist (W.W.) designed search strategies for each actionable PICO question using medical subject heading keywords and text words (see Appendix 4) limited to human studies (adult or pediatric) or non-indexed citations and articles in English or in any language with English abstracts. The Ovid platform was used to search MEDLINE, EMBASE, and Cochrane Registry of Controlled Trials from inception to November 2015. Two reviewers from the GDC (L.H., M.W.) screened titles and abstracts according to pre-specified criteria to identify articles for full review and evaluated the full text of articles deemed potentially relevant. One reviewer screened the results for each PICO question and then reviewed the retrieved citations with the steering committee and appropriate WG members to ensure all relevant literature had been captured.

Evidence Review and Development of Clinical Recommendations and Good Practice Statements

Clinical Recommendations

Evidence summaries for each of the actionable questions were prepared by two members of the GDC (L.H., M.W.) with guidance from the health research methodologist (B.R.), following the GRADE approach (26), and using the GRADEpro Guideline Development Tool online software (29) (see Appendix 5). The members of each WG reviewed the summaries of evidence pertaining to their clinical questions and corrections were made when appropriate. WG members were also queried for any additional studies not identified by the search. If adequate outcome data were not available from RCTs, observational studies were also used to support recommendations. For each study, risk of bias was assessed by the reviewers using the Cochrane Risk of Bias tool (30) for RCTs and the Ottawa-Newcastle tool (31) for observational studies.

Given the heterogeneity in the selected studies and overall lack of high quality data, pooling of study data was not feasible and meta-analysis was not possible for any of our recommendations. The overall certainty in effect estimates (also known as confidence in effect estimate) for each outcome of interest was assessed following the GRADE approach (32), based on the following criteria: risk of bias, precision, consistency, directness of the evidence, risk for publication bias, presence of dose-effect relationship, magnitude of effect, and assessment of the effect of plausible residual confounding or bias. The confidence in effect estimates for each outcome was categorized into one of four levels: high, moderate, low, or very low.

The GDC and WGs developed recommendations based on the GRADE evidence profiles for each recommendation. We employed the GRADE EtD frameworks in the guideline development tool to help organize discussion around each recommendation and ensure each of the following factors was considered in recommendation development: the quality of the evidence, the balance of desirable and undesirable consequences of compared management options, the assumptions about the values and preferences associated with the decision, the implications

for resource use and health equity, the acceptability of intervention to stakeholders, and the feasibility of implementation (see Appendix 5). Recommendations and their strength were decided by consensus at the March 22, 2016 face-to-face meeting. Points of conflict were resolved through discussion and review of the summarized literature. All GDC members agreed on the final wording of each of the final Good Practice Statements and Actionable Recommendations, sometimes with qualifications found in the discussion of each recommendation (e.g., subgroup considerations, justification, and implementation considerations).

The recommendations were classified as either "strong" or "conditional," according to the GRADE approach (33). As suggested by GRADE, we used the phrasing "we recommend" for strong recommendations and "we suggest" for conditional recommendations. Table 4 provides suggested interpretation of these recommendations by intended stakeholders, including patients, clinicians, and health policy makers (34). For four PICO questions, the panel decided to not offer a recommendation because it was determined that there was insufficient evidence to suggest clear benefit or harm.

Table 4 Strength of recommendations

Implication for…	Level 1 "We recommend…"	Level 2 "We suggest…"
Patients	Most people in this situation will want the recommended course of action and only a few will not	The majority of people in the situation would want the recommended course of action, but a substantial minority would not
Clinicians	Most patients should receive the recommended course of action	Different choices will be appropriate for different patients. Patients will need help to arrive at a management decision consistent with their values and preferences
Policy	The recommendation could be adopted as policy	There is a need for substantial debate and involvement of stakeholders

Good Practice Statements

According to recommendations from the GRADE group, when the GDC members are confident that the benefits of a recommendation are clear despite a lack of comparison trials, a Good Practice Statement can be employed (28). As outlined in a 2015 editorial, Good Practice Statements are best used in cases where there is a large body of indirect evidence that strongly supports the net benefit of the recommended action (28). For the purposes of the pDCD guidelines, most of the recommendations were based on these principles. There was full consensus by all members of the GDC on all Good Practice Statements.

Manuscript/Report Preparation

The writing committee (B.R., L.H., S.D.S., M.W.) drafted the full guideline report document as well as an abbreviated manuscript version for publication, which was then reviewed by the entire GDC. Feedback was provided primarily by electronic communication, and, to a lesser extent, during teleconferences.

The entire GDC had the opportunity to correct factual errors, clarify the presentation of background information or evidence summaries, and suggest changes to the Recommendations and Justification sections if they improperly captured the discussion from the face-to-face meetings. The wording of recommendations (including strength and direction) was done during the face-to-face meeting and teleconferences. The final approved version was submitted to each cosponsoring professional society for endorsement and/or peer review.

RECOMMENDATIONS

1. Ethics and Withdrawal of Life Sustaining Therapy

Good Practice Statements

1.1 pDCD is a medically and ethically viable pathway to provide access to deceased organ donation.

1.2 The option of deceased donation, including pDCD, should be routinely incorporated into end-of-life care.

1.3 Health care systems should establish processes to ensure pDCD access.

1.4 Throughout the WLST and donation process, health care professionals must respect the dignity of the dying process.

a. WLST processes should be guided primarily by the interests, needs, and desires of the patient who is a potential donor and his or her surrogate decisions makers.

1.5 The discussions and process of deceased donation should respect the beliefs and values of the surrogate decision makers and other loved ones involved.

1.6 In recognition of diversity of perspectives on pDCD, health care professionals should be allowed to conscientiously object to participation in pDCD.

a. In the case of health care professional objection, institutions should work to honour the surrogate decision makers' wishes to donate.
b. These efforts could include effective referral efforts (see glossary) such as contacting the ODO, transfer of care to another colleague, or an offer of transfer to another centre.

Justification

The option to offer DCD as part of EOL care is universally supported by professional societies and organ donation organizations that have examined the issue, including: Canadian Blood Services (1); the CCCS (35); the American Thoracic Society, the Society for Heart and Lung Transplantation, the Society of Critical Care Medicine, the Association of Organ Procurement Organizations, and the United Network of Organ Sharing (12); the British Transplant Society and the British Intensive Care Society (36); the Australia and New Zealand Intensive Care Society (13); and, of most relevance to the current work, two pediatric specific recommendations from the American Academy of Pediatrics (37, 38).

Despite this broad consensus, some authors have expressed concerns around ethical aspects of DCD, in general, and pDCD, specifically (39, 40). The most frequently mentioned objections are over how death is determined, whether valid consent is possible in pDCD, and if pDCD could influence decisions to pursue WLST. We also recognize that based on societal, cultural, religious, and other personal beliefs, some individuals within the health care team may have differing views on the meaning and permissibility of deceased organ and tissue donation (41). These concerns justify the above recommendation to allow conscientious objection by HCPs to not participate in pDCD, consistent with other policy and position statements (12, 38, 42, 43). However, considering the importance that donation can play for individuals and families during the EOL care process, these objections should not prohibit substitute decision makers and families from participating in pDCD if they so desire, which is why we emphasize that institutions should work to accommodate these requests using the principles of effective referral.

2. Decision-Making Process for Withdrawal of Life Sustaining Therapy

Good Practice Statements

2.1 The decision to pursue WLST must not be influenced by donation potential and should proceed according to accepted medical practices.

2.2 The ODO, organ recovery, and transplant team must not be involved in the decision to pursue WLST or have direct contact with surrogate decision makers before WLST decisions are finalized.

a. Treating teams may contact ODOs to assess eligibility prior to the decision to pursue WLST, as long as there is no direct contact between the ODO and surrogate decision makers.

2.3 The decision to pursue WLST should be made before any discussion of organ and tissue donation that is initiated by health care professionals.

a. If a substitute decision maker or family initiate organ donation discussions prior to the decision to pursue WLST, information may be provided, but consent

discussions should be deferred until WLST decisions have been finalized.

b. Mention of donation potential by the substitute decision maker must not alter the goals of treatment, which must remain continued care of the patient in his or her best interest regardless of donation potential.

2.4 Safeguards should be in place to ensure mitigation of conflict of interest for the case where a patient who is a potential donor and a patient who is a potential recipient are being cared for in the same care unit, such as a mandatory second opinion or ethics consult.

a. While intensive care physicians do not have a role in allocation decisions, it is strongly preferable that the attending hospital physicians who are involved with pDCD consent or procedures be different from those who are actively caring for potential recipients. Complete separation of physician roles may be impossible due to small teams or physician non-availability.

b. Similar to physicians, within locally feasible constraints, other health care professionals should abstain from actively caring for potential donors and potential recipients during the WLST and donation decision process.

Justification

The medical practices and ethical considerations pertinent to WLST, including the decision to pursue WLST and the act of WLST, remain within the domain of EOL care. It is the responsibility of the critical care and neuroscience communities to ensure optimal practice in this field.

In order to avoid real or perceived conflicts of interest, decisions pertaining to organ and tissue donation (OTD) must be kept as separate as possible from decisions regarding WLST. This concept was universally supported in our review of the literature, and among guideline development members (12, 13, 36-38, 44-48). The above recommendations support that WLST decision making follow established, best practices regardless of pDCD potential.

It is recognized that the role of donation-focused ICU physicians is evolving in Canada. These ICU physicians may be involved in the administration of deceased donation programs, quality assurance, professional education, research, and/or clinical practice related deceased donation. None of these physicians have any involvement in allocation decisions or transplant procedures. These roles may be funded through provincial health care plans or organ donation organizations. The Canadian Medical Association has endorsed an ethics guide for this role, which should guide the conduct and role disclosure for donation-focused ICU physicians who may also be involved in pDCD care ("Ethics Guide for Donation Physicians in Canada" available upon request c/o Sylvia Torrance, Canadian Blood Services).

One area we thought merits particular attention is when a potential donor and recipient are simultaneously cared for in the same unit. This possibility is more likely in pediatric than adult practice given the smaller number of recovery and transplant hospitals. We acknowledge this as a potential conflict and encourage health care professionals to pursue ethical safeguards if the substitute decision maker is motivated to pursue donation in this setting. Measures to mitigate

this potential conflict will depend on local context but could include ethics consultation or a second opinion from an uninvolved health care professional. As noted above, it is universal practice across Canada that the physician caring for a potential donor has no involvement in graft allocation decisions. Therefore, while a professional caring for a potential donor and recipient might have a perceived conflict of interest, he or she will not have actual influence in regard to where retrieved organs are allocated.

Another situation of possible concern is if the substitute decision maker or family addresses the possibility of organ donation before the decision to pursue WLST has been made. This situation requires that the health care professional acknowledge and respond to the posed question, while not entering into a consent-for-donation discussion. In these circumstances, it is recommended that the health care professional inform the requestor that a pathway for organ donation exists after WLST, but that until a WLST decision is finalized, the focus will remain on providing optimal medical care. Only after that decision has been formalized and documented, may detailed consent discussions proceed.

3. Eligibility

Good Practice Statements

3.1 Individual transplant programs, in collaboration with pediatric and neonatal health care professionals and ODOs should determine criteria for donor eligibility, and limits of warm and cold ischemic time. Special consideration should be given for neonatal patients who are potential donors.

a. Treating teams who have reached a consensual decision to pursue WLST should routinely assess donor eligibility with ODOs to ensure that potential donation opportunities are not missed due to incorrectly assumed ineligibility.
b. For certain organs (e.g. heart, liver), it may be anticipated that organ recipients will need to be in the same hospital centre in order to improve graft outcomes. This may pose limitations to potential pDCD recipients. This consideration may change with further experience and *ex-vivo* organ support.

3.2 Coroners must be notified prior to donation proceedings according to provincial laws. If coroner evaluation and approval to pursue pDCD is required, this should be done prior to consent discussions with the surrogate decision makers.

Justification
We chose to limit our recommendations related to pDCD eligibility. Further national recommendations will require input from a multi-disciplinary group, including transplant surgeons and physicians caring for recipients of pDCD organs, in order to form organ-specific recommendations. These criteria will be subject to change based on centre experience, further research, and recommendations from organ-specific transplantation groups. Current recommendations from groups such as the Canadian Society of Transplantation (CST) should inform these discussions, including their recommendations on high-risk donors (49).

Considering the evolution of inclusion and exclusion criteria, treating teams who have reached a consensual decision to pursue WLST should routinely assess eligibility with ODOs to ensure that potential donation opportunities are not missed due to incorrectly assumed ineligibility. This is particularly true early in the implementation of a pDCD program.

Coroner reporting requirements vary throughout Canada. In some jurisdictions, all child deaths are reportable and in others, child deaths are not specifically referenced but are reportable under other provisions relating to sudden, unexpected, or unnatural deaths (Stewart, Kent; personal communication, 21 April 2016.). Coroners will also likely have various levels of comfort and experience with DCD particularly in the case of children. For these reasons, we recommend that protocols regarding when to contact local coroners be established during the implementation of pDCD programs and that these protocols include contacting the coroner to ensure eligibility prior to consent discussions. This would avoid the possibility that a family consents to pDCD, only to have the donor determined ineligible by the coroner.

4. General Consent for pDCD

Good Practice Statements

4.1 Consent for organ donation discussions should be initiated only after the consensual decision to pursue WLST but prior to initiation of WLST. Distinct from common practice after NDD, in pDCD it is necessary to present the option of donation before the potential donor's death.

a. As noted in Good Practice Statement 2.3, when a substitute decision maker or family member approaches the health care team regarding donation prior to a decision to pursue WLST, preliminary discussions can be had, but consent discussions should be deferred.

4.2 ODOs should not be involved for consent discussions or donor care until after the consensual decision between substitute decision makers and the treating team to pursue WLST.

a. The exact moment of involving the ODO in consent discussions should be determined according to provincial legislation, ODO protocols, and local hospital practice.

4.3 The health care professional discussing consent for the pDCD process must ensure that the substitute decision maker has appropriate (legal) authority to provide such consent.

a. This determination should be done considering consent to treatment legislation, tissue and organ donation legislation, and case law.
b. When appropriate, consideration should be given to previously expressed desires from patients. While in most jurisdictions it will not represent legal consent for patients under 18-years-old, health care professionals should seek

out if developmentally capable patients had expressed assent or dissent to donation prior to illness or injury.

4.4 The consent discussions for the pDCD process could include members of the care team, representatives of the ODO, or a collaborative team of both groups.

a. The person or team discussing consent should have extensive knowledge of the local process.
b. People discussing consent should also clearly identify their institutional affiliations to the substitute decision maker and care team.
c. Actionable Recommendation #1 refers to the level of recommended training for health care professionals that discuss consent.

4.5 Consent conversations with surrogate decision makers should include the opportunity to discuss beliefs and values around all aspects of pDCD, including death and death determination.

4.6 At minimum, the following information should be provided to substitute decision makers regarding the pDCD process:

a. Logistics of the process, including that WLST may be delayed due to pDCD logistics, and where WLST will occur,
b. Which specific organs are potentially eligible for recovery,
c. The procedures and methods of determining death, including that these practices conform to accepted medical and legal standards,
d. That consenting for pDCD does not guarantee that organ recovery or transplantation,
e. If organ recovery is not possible, tissue donation may remain an option,
f. How end-of-life care would proceed if they decline organ donation or if recovery does not occur after attempted donation,
g. That the treating team has no influence over allocation, which may include allocation to adult or pediatric recipients,
h. A description of how WLST would proceed should they decline organ donation,
i. That surrogate decision makers will be supported if they consent to or decline pDCD,
j. That consent can be withdrawn at any time, including after the determination of death.

4.7 If the substitute decision makers decline the opportunity to donate, their decision should be fully supported, and end-of-life care should proceed according to standard practices.

4.8 Consent to deceased donation provided by the substitute decision makers authorizes the recovery team to proceed with interventions *after death* required for organ recovery and transplantation.

5. Consent for *Ante-Mortem* Interventions

Good Practice Statements

5.1 Tests and interventions *prior* to death to facilitate donation in pDCD require the specific and informed consent of the substitute decision maker for each intervention.

a. *Ante mortem* interventions should only be undertaken with disclosure and consideration of risks and benefits to the patient who is a potential donor.
b. The benefit of any such intervention should be understood in terms of how they might improve successful donation after death.
c. Interventions should not be intended to hasten death.
d. *Ante mortem* interventions should pose no more risk to the patient than routine intensive care practices.
e. While the risks and benefits of each *ante mortem* intervention require individual discussion, these discussions can be documented on a single consent form or note for the medical record.

5.2 Ante mortem interventions should be recognized as providing non-medical benefit to the patient who is a potential donor by allowing realization of interest and intent to donate, despite the fact that these interventions provide no medical benefit to the patient who is a potential donor. This justifies surrogate decision maker's authority to consent to interventions that pose no increased risk beyond routine intensive care practices despite no medical benefit to the patient who is a potential donor.

5.3 Attempts should be made to accommodate families and substitute decision makers who provide consent to pDCD but do not provide consent to a specific *ante mortem* intervention (e.g. heparin).

a. Discussions with the local ODO and/or receiving transplant team in these cases should confirm whether modifications to the existing protocol could result in acceptable conditions for organ recovery.

Justification

Analysis of consent and authorization issues arising in pDCD requires an understanding of the legal framework governing consent in the context of deceased organ donation. It is outside the scope of these guidelines to extensively review the legal framework governing pDCD in all jurisdictions; however, a brief review illustrates important tenets of how consent is defined in the context of deceased organ donation. In Canadian provinces and territories, deceased donation is governed by provincial tissue gift legislation. As a gift after death, deceased donation has different legal requirements than nearly all other medical acts (50). Legally, providing a gift requires a voluntary expression of donative intent wherein the donor has 'formed an affirmative objective to donate' (50). This requirement is different and legally less demanding, than the typical requirement of informed consent as it applies to medical treatments before death. Consideration of benefit or harm posed to the patient, which forms

the basis of informed consent to treatment, should not be applied in the context of organ recovery from a deceased person any more than it should applied to the processes of cremation or embalming (50). While in the United States, the term 'authorization' has been well accepted, Canada variously uses language such as consent, consent to proceed, direction, or authorization, when discussing aspects of the donation process that occur after death has been determined, all of which simply require a voluntary expression of a desire to gift tissues or organs after death.

In contrast to donation after NDD where consent and donor management is conducted after the legal determination of death, aspects of the pDCD process occur before the determination of death. These include organ preservation treatments that could theoretically pose a risk to the patient (e.g. heparin administration) and alterations to the process of WLST that might affect EOL care. As these procedures and treatments occur before death is determined, they are subject to the same standard of informed consent as any medical treatment, including consideration of risk and benefit for the patient with a fiduciary relationship between patient and physician. While we recognize this distinction between consent and authorization, since practitioners typically obtain consent for the pDCD process and authorization for organ recovery at the same time, for the remainder of these guidelines we will refer to the entirety of that process as obtaining consent for DCD.

With that understanding, one of the most important consent questions in pDCD, particularly regarding *ante mortem* interventions, is whether substitute decision makers or families can give valid consent for a procedure that might cause harm or discomfort to the donor while providing medical benefit only to the organ recipient. Several authors (44, 51, 52), including the 2013 American shared position statement from the American Thoracic Society, the Society for Heart and Lung Transplantation, the Society of Critical Care Medicine, the Association of Organ Procurement Organizations, and the United Network of Organ Sharing (12) answer in the affirmative. Their rationale is that if the process presents minimal potential harm to the donor and the procedure is in line with parental values, an assumption of altruism is legitimate (44, 51). The benefit to the patient who is a potential donor is therefore allowing donation to proceed in order to fulfill family or surrogate desire to donate and it is this benefit that justifies assumption of risk without direct medical benefit. This is consistent with the ethical reasoning supporting children's participation in medical research where there is no hope for direct benefit to them. Furthermore, some have argued that disallowing patients' substitute decision makers or families to act altruistically would limit their autonomy (42). These arguments, however, are not universally accepted and others claim that altruism on the part of an incompetent child cannot be assumed based on parental values (39). We conclude that divergent opinions regarding the ethicality of such *ante mortem* interventions would be a justifiable reason for health care professionals to excuse themselves from pDCD proceedings through conscientious objection.

The logistics of consent discussions were also considered for this document. There is significant practice variability concerning which health care professionals should be present during consent discussions and at what stage an ODO should be notified of a patient who is a potential

donor. Some centres encourage or require that a representative from the local ODO be present during consent discussions (53). Regardless of whether an ODO representative is present during the consent request, we recommend the requesting health care professionals have detailed knowledge of the local processes and procedures. Further discussion of training requirements for people requesting consent can be found under Actionable Recommendation 1. Furthermore, the stage in the EOL pathway at which ODOs are to be notified varies across jurisdictions, where some have automatic triggers, such as Glasgow coma scale (GCS) on admission, that lead to mandatory contact of the local ODO. The laws and local practices of patients who are potential donors reporting should be carefully considered when establishing a pDCD protocol.

The content of the consent discussion will and should vary based on individual circumstances, and the above recommendations should not be considered exhaustive. Instead, these were the points thought by the GDC and WG members to be the most important for substitute decision makers or families to understand about the pDCD process. Other points could include that allocation decisions in Canada are determined by regional ODOs and that organs cannot be directed to certain groups, including children. The option to discuss the relationship between the biological determination of death and the religious or philosophical perspectives on death may be appropriate for some substitute decision makers or families. These discussions could be carried out by ICU health care professionals or by pastoral care professionals. Further exploration on the attitudes of world religions on death and organ donation was recently summarized by Setta and Shemie (41). For further information regarding general best practices in organ donation consent, please consult the Leading Practices for End-of-Life Discussions with Families of Potential Donors from Canadian Blood Services (54).

Actionable Question #1: Training of requestors

Should trained professionals vs. professionals without specific training be used for approaching families for consent in the setting of pediatric donation after circulatory death?

Actionable Recommendation #1

The panel did not make a recommendation regarding specific training of professionals for approaching families for consent in the setting of pediatric donation after circulatory death.

GRADE Profile 1: Training of requestors

Quality assessment							Impact	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Family Satisfaction with Consent Process									
1(55)	observational study	serious [1]	not serious	very serious [2,3]	not serious	none	Family response to follow up survey regarding satisfaction with communication around EOL and donation issues was identical with or without trained requester.	⊕◯◯◯ VERY LOW	CRITICAL
Consent Rates									
13(55-67)	Randomized and observational trials	serious [4]	serious [4,5]	very serious [4,6,7,8]	not serious	none	The literature is mixed and indirect. The most methodologically rigorous study showed no effect in consent rates with a model involving ODO staff present at the time of consent. Observational studies of various other training methods and models seem to support requestor training as a method to raise consent rates. None of these studies were exclusive to pediatrics or DCD.	⊕◯◯◯ VERY LOW	CRITICAL

1. Single observational study
2. Few if any children
3. Unclear if all NDD or NDD and DCD
4. Only one RCT which had results that are contrary to the majority of the observational studies
5. Most data from observational studies
6. Only NDD donors in the UK
7. Only 13/201 pediatric donors
8. Intervention was involvement of ODO staff, not training for health care professionals

Background

Some centres or jurisdictions require that the health care professional discussing consent from the patient who is a potential donor's substitute decision makers have specific training. This practice varies across Canada with consent requests performed by health care professionals with a variety of clinical backgrounds (e.g. physicians, ODO representatives) and training. Our literature review investigated evidence in support of requiring training for consent requestors.

Summary of Evidence

While several publications have examined the question of whether the person seeking consent for deceased organ donation should have specific training in consent requesting, we found no references that directly addressed this question in a pDCD setting. There was one randomized controlled trial in adult, mostly NDD cases in the United Kingdom (The ACRE Trial), which was considered as indirect evidence (56). This trial found no significant difference in organ donation

consent rates with ODO staff present (collaborative approach) or not present (control) with treating clinical staff at time of initial request and a non-significant trend to lower conversion rates with the collaborative approach.

The findings of the ACRE study generally contrast with those of a systematic review published by Simpkin et al. in 2009 (68) of observational and pre/post studies, as well as an observational study published after the 2009 review (58), that suggest consent rates were generally higher when trained personnel requested consent. The reasons for the discordant findings between the one, high quality randomized trial and the several observational reports are not immediately apparent.

Two other references were considered as indirect evidence. The first was a finding from Australia (57) that demonstrated a 22% increase in Australian organ donors two years after a national training program for donation physicians was implemented. Caution should be taken in generalizing these findings because the rate was already increasing prior to the training initiative, which was part of a broader national program for promotion of donation. The second (55) was a prospective cohort study of hospitals with or without a system of non-clinical support nurses who provided long-term contact with substitute decision makers or families from the time of diagnosis of significant neurologic injury, and were trained in consent requesting. A higher consent rate was found with these nurses as trained requesters. This study came from the Netherlands, which has a presumed consent model for deceased donation.

Justification
While several observational reports suggest that trained requesting is effective at increasing consent rates, the most methodologically rigorous study showed no effect of a model involving trained ODO staff present at the time of consent. None of these studies were exclusive to pediatrics or to DCD. Only one of 13 references included in our summary of findings examined the outcome of family satisfaction after the consent process. As donation recommendations, this outcome is ultimately at least as important as consent rates, since the fiduciary responsibility of the patient's care team is to ensure that their best interests are respected throughout the process.

Considering the lack of conclusive evidence supporting benefit, and the substantial system investment in personnel and training that would be required to have trained requesters present at every consent conversation, we chose to not recommend for or against this intervention. For further information on general effective requesting techniques in deceased donation, please refer to the recently published report from Canadian Blood Services (54).

6. WLST Procedures in the Context of pDCD

Good Practice Statements

6.1 WLST practice should be based on established ICU or hospital practices, policies, and guidelines. The practices should:

a. Apply to all patients where WLST is considered regardless of donation status;
b. Be locally determined and informed by best practice in the field.

6.2 The critical care team must be responsible for patient management between the decision to WLST and the determination of death.

6.3 As it applies to EOL care in other settings, the principle of double effect supports the administration of treatments with the intent to support patient comfort and alleviate suffering, even if there is a risk (foreseen but not intended) of hastening death.

6.4 The ODO, organ recovery, and transplant team must not be involved in any aspect of management of the dying process.

6.5 WLST may occur in the critical care unit, near the operating room, or in the operating room, as determined by surrogate decision makers' preferences, institutional logistics, resources, and facilities.

6.6 Psychosocial, spiritual, and bereavement support should be provided to surrogate decision makers regardless of WLST location.

6.7 Wherever WLST occurs, surrogate decision makers and other loved ones should be given the option to be physically present with the patient who is a potential donor until the determination of death is complete.

6.8 The organ recovery team should not be physically present in the room until the determination of death has been completed and the surrogate decision makers are escorted from the bedside.

6.9 If a patient who is a potential donor is hospitalized where pDCD is not available, and the surrogate decision makers are motivated to donate, consideration should be given for patient transfer to a hospital that performs pDCD.

a. Transfer should only after obtaining informed consent by the substitute decision makers regarding potential risks of transfer and after consultation with, and acceptance by, the receiving hospital.
b. Logistics and funding to support this activity should be provided by individual jurisdictions and costs associated with transfers should not impose an economic burden on the substitute decision makers or family.
a. The substitute decision maker and family should be aware that transfer would not guarantee organ recovery or transplantation will occur.

Justification

Consistent with practice outside of donation settings, the fiduciary responsibilities of ICU health care professionals are first and foremost to act in the best interest of his or her patient (12, 13,

37). This responsibility remains regardless of the patient's donation potential. We strongly support that in the event of a conflict in management goals between organ donation and optimal EOL care; care for the dying child should always take precedence.

WLST practices, including EOL care, should be provided with minimal deviations from standard practice. This concept is universally supported in the published literature (12, 13, 36-38, 42, 44, 45, 47, 48, 69), and should include administration of narcotics or other comfort medications. As in EOL care outside the pDCD setting, and consistent with the principle of double effect, the medications given to comfort the patient might hasten death, even though this is not the intended effect. Physicians should take care to neither deny patients who are potential donors symptom relief for fear of being perceived to hasten death, nor to administer more medications than other EOL care settings in an attempt to limit warm ischemic time (WIT). When these medicines are given, physicians should carefully document the indication. For a further information regarding WLST procedures and practices, including a more detailed explanation of the principle of double effect, please refer to the guidelines from the Canadian Critical Care Society (CCCS) (35).

The logistics around pDCD are complex, and local flexibility should be maintained regarding factors such as where WLST occurs (e.g. proximity to the OR). Decisions should be determined by local factors to permit effective recovery while sustaining family support (13, 36, 47). Thus, implementing local WLST protocols that take into account pDCD practice may assist consistency of practice.

While at this time our recommendation is that no medication can be given with the intent to hasten death in pDCD, we emphasize that physician assisted dying (PAD) is out of scope of the current recommendations.

7. Time from WLST to Determination of Death

Good Practice Statements

7.1 A maximum time limit from the start of WLST to death, beyond which organs will not be recovered, should be established in collaboration with ODOs and local transplant teams.
   a. This time period should be referred to as Warm Ischemic Time (WIT).
   b. These time limits should be guided by organ specific transplant programs, ODO practices, and individual donor factors.
   c. In addition to warm ischemia effects on organ function, time limits may also be influenced by ICU or operating room logistics.

7.2 If the patient who is a potential donor does not die within predetermined time limits for organ recovery, the patient should be returned to the ICU for ongoing care.
   a. In this case, tissue donation may remain an option.

Justification

The duration of acceptable WIT should be locally informed and based on organ specific concerns. Current practice in most pDCD centres recommends WIT of 30-90 minutes, depending on the organ to be retrieved. Adult practices may vary from 1-4 hours depending on multiple factors. The GDC anticipates that these thresholds will likely change as new techniques and technologies (e.g. *ex vivo* support) are introduced into pDCD practice. Also our GDC did not consist of transplant surgeons or post-transplantation physicians who could provide meaningful expertise into the effects of various WIT thresholds on specific organs. We therefore specifically chose not to make recommendations regarding the length of acceptable WIT prior to recovery of specific organs.

Some adult DCD programs and guidelines recommend making a distinction between *overall* WIT, which is the time that elapses from treatment withdrawal to cold perfusion, and *functional* WIT (sometimes referred to as the agonal period) which is defined as the time from a drop in systolic blood pressure below specified thresholds (e.g. systolic blood pressure less than 40-50mmHg) for a sustained period. This definition attempts to adjust for the temporal influence of hypotension and hypoxemia on organ injury during the dying process after WLST. Some groups have suggested functional WIT may be a better measure of ischemic injury (13, 14, 70) and predictor of graft outcome. These thresholds have not been explored in pediatric patients undergoing WLST and would require age specific adjustments. Considering that these thresholds have not been defined in children, physiologic-based criteria to define the start of WIT were not considered to be a reasonable comparator and this recommendation was considered as a Good Practice Statement.

ODOs and transplant programs also record when preservation solution is perfused, but since that involves transplantation procedures, it is outside of the scope of these guidelines to recommend how that should be defined and documented. We have limited our definition of WIT to when the determination of death is complete.

Careful documentation of physiologic data (onset of hypotension and hypoxemia) during the dying process could facilitate future research or quality improvement efforts in pDCD.

Actionable Question #2: Prediction tool for time-to-death after WLST

Should formal predictive tools vs. no formal tool (clinical judgment) be used for predicting time of death within 30 or 60 minutes of WLST?

Actionable Recommendation #2

The panel did not make a recommendation regarding use of prediction tools to predict the time from WLST to death.

GRADE Profile 2: Prediction tool for time-to-death after WLST

Quality assessment							Impact	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
False positive rates (predicted to die within time, but did not)									
2(71, 72)	observational studies	not serious	not serious	not serious	serious [1]	none	30 min model - Shore 111 of 145 (76.6%); Das 12 of 25 (48%) 60 min model - Shore 61 of 66 (92.4%); Das 2 of 10 (20%)	⨁◯◯◯ VERY LOW	CRITICAL
False negative rates (missed donation opportunity)									
2(71, 72)	observational studies	not serious	not serious	not serious	serious [1]	none	30 min model - Shore 21of 373 (5.6%); Das 9 of 37 (24%) 60 min model - Shore 5 of 452 (1.1%); Das 13 of 52 (25%)	⨁◯◯◯ VERY LOW	IMPORTANT
True positive rates (correctly predicts death within time)									
2(71, 72)	observational studies	not serious	not serious	not serious	serious [1]	none	30 min model - Shore total n=518, 352 of 373 (94.4%); Das, total n=62, 28 of 37 (76%) 60 min model - Shore 447 of 452 (98.9%); Das 39 of 52 (75%)	⨁◯◯◯ VERY LOW	CRITICAL
True negative rates (correctly predicts patient will not die within time)									
2(71, 72)	observational studies	not serious	not serious	not serious	serious [1]	none	30 min model - Shore total n=518, 34 of 145 (23.4%); Das total n=62, 13 of 25 (52%) 60 min model - Shore 5 of 66 (7.6%); Das 8 of 10 (80%)	⨁◯◯◯ VERY LOW	IMPORTANT
The available tool from Shore (2012) was done using a large "DCD-like" sample size. For both the 30 min and 60 min time periods, the tool was sensitive for predicting death within the allotted time, but poorly specific. The publication by Das et al. (2016) was an external validation study of the Shore tool, using a relatively small sample size. It demonstrated good sensitivity for both the 30 min and 60 min times. Specificity of the tool for the 60 min time was good but poor for the 30 min time.									

1. Small sample size (62) for external validation by Das et al. 2016 (72) To externally validate a multivariable prediction model a minimum of 100 events (die in time) and 100 non-events (do not die in time) are recommended within the validation cohort (Vergouwe et al. 2005 (73); Collins et al. 2015 (74)).

Background

As mentioned above, in most centres pDCD will only occur if the time to death after WLST does not exceed 30-90 minutes, due to warm ischemic effects on organs and recovery logistics. The uncertainty of the time to death can also be difficult for families who consent for their child to be an organ donor. For the healthcare team, beyond the emotional component of this uncertainty, utilisation of significant resources are required for the complex, logistical process of potential pDCD including the operating theatre, standby availability of a specialised surgical recovery team at the patient's hospital, and mobilizing transplant teams in potential recipient centres. Some tools exist to predict mortality within certain windows of WIT but no recommendations exist on their applicability to pediatric patients.

Summary of Evidence

In 2012, Shore et al. (71) published a report on the only known pediatric-specific tool to predict time to death after WLST based on a retrospective study of 518 children who underwent WLST. The median time to death was 17 minutes (range, 0 min–73 hours). 72% of patients died within 30 minutes of WLST, 87% died within 60 minutes, and 13% died after more than 60 minutes. When risk factors were combined into a clinical score, cut off values were found with a predicted probability of death with 85% and 98% accuracy at 30 and 60 minutes respectively. A retrospective validation study of the same tool by Das et al. (72) on 70 children after WLST reported a 69% and 79% classification accuracy at 30 and 60 minutes respectively.

We excluded reports on other scoring tools to predict death after WLST that were validated only in adult populations.

Justification

Though a prediction tool developed by Shore et al. has shown reasonable predictive value, it remains to be tested against clinical judgment or prospectively validated. Prediction tools cause no direct harm to a patient, may provide important information to the clinical team and SDMs, and are low cost. The risk, however, is if clinicians choose whether or not to pursue donation proceedings based solely on such a tool, without understanding its strengths and limitations. While future iterations may result in improved sensitivity and specificity, we currently do not recommend for or against the use of death prediction tools.

8. Minimum Standards Required for Death Determination in pDCD

There is currently no Canadian federal, provincial, or territorial statute mandating how clinicians determine when a patient is dead. Most provincial statutes reference “standard” or “accepted” medical practice (Appendix 1). As there is also no widely accepted medical standard from Canadian professional societies, we have chosen, for the purposes of this guideline, to use the following definition taken from recently proposed guidelines at the World Health Organization (WHO) (43):

<u>The definition of death by circulatory determination</u>:

> The permanent loss of capacity for consciousness and all brainstem functions, as a consequence of permanent cessation of circulation. Permanence is defined as loss of function that will not resume spontaneously and will not be restored through intervention.
>
> Function refers to the primary and fundamental purpose of the brain that can be assessed by observation and examination and is necessary for sustained life. Function should be distinguished from activities as defined by physiologic properties of cells or groups of cells that can be measured by laboratory means (43).

While similar death definitions have formed the ethical basis for the widespread acceptance of DCD, we acknowledge the widely published ethical discourse regarding whether circulatory

death should be defined as permanent or irreversible. This issue largely stems from differing interpretations of the 1981 U.S. Uniform Determination of Death Act (UDDA), which defines death as the irreversible cessation of circulatory and respiratory functions or of the entire brain (75). Since its original publication, one of the original co-authors of the UDDA has stated that the intended definition of irreversible was in the context of attempted resuscitation and is therefore not relevant in a DCD context where resuscitation is by definition not attempted (76). Several authors and policy statements support *permanence* as an ethically valid definition for *irreversible* in the context of DCD (12, 37, 44, 45, 76, 77), where *permanence* is defined as the point when the absence of circulation is sufficient to preclude spontaneous return. The currently accepted practice of declaring death by cardiorespiratory criteria in non-donation settings is also consistent with this concept of *permanence*. In this setting, physicians determine death without formal tests of brain irreversibility nor a waiting period to preclude autoresuscitation (44, 76, 77).

While all references from professional societies accept permanence as a replacement for irreversible, a number of authors reject the premise that irreversible means anything other than an univocal, ontological state of biological irreversibility of brain or circulatory function regardless of context or circumstance (39, 47, 78-82). Some argue that the limited data surrounding autoresuscitation prohibits certainty regarding when arrest of circulation becomes permanent (39, 78).

Having carefully considered these issues, we have chosen the definition published in the WHO conference report as the definition of death for these pDCD guidelines (43). We also advocate to formally replace irreversible with permanent in definitions of death, and that death determination, regardless of the context, is primarily clinical. See the Death Determination Recommendations and justifications for further information.

The Dead Donor Rule (DDR) refers to the standard of practice wherein an individual must be determined dead before donation occurs and the act of donation cannot cause the death of the individual. This is considered to be a foundational principle of deceased organ donation (12, 13, 37-40, 42, 44-46, 48, 51, 76-79, 83, 84). While there are some advocates for abandonment of the DDR in the setting of pDCD (80, 85), this represents the minority viewpoint in the published literature, and, to our knowledge, no professional society supports abandonment of the DDR. More importantly for these guidelines, respect for the DDR is the law in Canada where donation of vital organs cannot occur prior to determination of death.

Good Practice Statements

Please note, the following recommendations include a summary of current Canadian laws and practices governing deceased donation. These laws and recommendations should be understood to represent the minimum standards necessary to determine death. They do not preclude additional standards, as long as those standards are accepted prior to implementation by all stakeholders (health care professionals, ODOs, transplantation programs, etc.).

8.1 The dead donor rule must be respected within the context of pDCD.

8.2 In the context of pDCD, death must be determined by two physicians in accordance with accepted medical practice.

a. The two physicians must confirm their determinations concurrently at the end of a hands-off period of observation during circulatory arrest.

8.3 No physician who has active involvement in transplant procedures or allocation of donated organs shall take any part in donor death determination.

8.4 The minimum level of physician qualification required to determine death in pDCD is:

a. They possess the requisite skills and training. A particular level of specialty certification is not required, but skills and training should include ability to interpret monitoring used.
b. At least one of these physicians must be an attending physician staff in the intensive care unit of the patient, and possess full and current licensure for independent medical practice in the relevant Canadian jurisdiction.
c. The second physician could be on an educational register (e.g. residents, fellows), as long as they have the requisite skills and training.

8.5 The following criteria must be met before organ recovery:

a. Circulatory arrest, defined as the absence of anterograde arterial circulation. See Actionable Recommendation #3 for the panel's recommended method for determining absence of anterograde arterial circulation.
b. A hands off period of continuous observation of circulatory arrest during which no interventions are undertaken to facilitate donation. See Actionable Recommendation #4 for duration of hands off period.
    i. There must be no interventions undertaken to facilitate donation during this period of observation.

8.6 Recovery d transplantation of the heart in pDCD is consistent with the dead donor rule, as death is based on the permanent cessation of circulation.

8.7 The same criteria should apply to all potential pDCD donors including those undergoing withdrawal of mechanical circulatory support, such as ECMO.

Justification

In a donation context, two physicians are legally required to determine death according to accepted medical standards. As discussed in the Definitions section, the definition of death used for these guidelines represents both current accepted Canadian practice and is consistent

with evolving international consensus (43). The details of how cessation of circulation is determined and for how long are detailed below in Actionable Recommendations #3 and #4.

The guideline authors have chosen to recommend that while the first physician determining death in pDCD must have a full, unrestricted license to practice, the second may be a trainee on an educational register. This recommendation considers that the death determination in pDCD requires skills or training that would be readily available to a resident or fellow undergoing training in a PICU or NICU. If the second physician is on an educational register, he or she should be reminded that they are not obligated to participate and that a decision to participate or no will not affect their evaluation. Also, the second physician need not be from a certain specialty, as long as he or she possesses the capacity to determine death in this setting, specifically the ability to interpret an arterial line wave form tracing.

Regarding Good Practice Statement 8.6 and 8.7, some authors, publishing at a time when DCD was often referred to as donation after cardiac death, contended that transplantation of a functional heart would negate the irreversible loss of donor cardiac function prior to determining death (82, 84). Others countered that the accepted definition of death is permanent cessation of circulation and brain perfusion beyond the period of autoresuscitation (45, 76). Using this definition, whether the heart remains un-resuscitated in the donor or is removed and resuscitated in another patient does not alter donor outcome: body and brain circulation remains permanently ceased in the dead donor. Since this is the definition that we have used in these guidelines, we also support the concept that cardiac pDCD respects the dead donor rule.

Actionable Question #3: Method for confirming absence of anterograde circulation
Should arterial line vs. palpable pulses and auscultation be used for confirmation of lack of anterograde circulation?

Actionable Recommendation #3
We recommend that a well-functioning arterial line be used to confirm arrest of anterograde arterial circulation for the determination of death. (Strong recommendation, low certainty in evidence)

GRADE Profile 3: Method for confirming absence of anterograde circulation

Quality assessment							Impact	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Incorrect assessment of pulse									
3(86-88)	observational studies	not serious	not serious	serious [1,2]	not serious	strong association	No studies were found directly addressing this PICO question. However, the question of detectable pulses in low flow states (but not donation) has been studied in the context of mechanical circulatory support. While not specific to a pDCD setting, findings from studies examining the ability of healthcare professionals to detect pulses from low and or non-pulsatile bypass states suggest that even experienced physicians commit frequent errors when distinguishing between the absence or presence of pulse in pediatric patients.	⊕⊕◯◯ LOW	CRITICAL
Adverse events associated with installation or maintenance of arterial catheter – not reported									
-	-	-	-	-	-	-	No reports were discovered that examined the risk of arterial line placement or maintenance in the setting of deceased donation.	-	IMPORTANT

1. Not a donation setting
2. Participants encouraged to assess pulse status rapidly

Background

As summarized in the pDCD scoping review, different jurisdictions have proposed variable methods for determining death (11). Whatever methods are used, there is broad agreement that the determination of death in pDCD requires a high degree of precision and accuracy (39, 76, 77, 80, 81, 89) and that tests should be sensitive, objective, and standardized (37, 43, 44, 75, 76, 90). Despite these calls for standardization, significant variability remains with respect to which techniques are recommended (11). Specifically, clinicians are often unsure as to what methods are acceptable to confirm loss of anterograde circulation, which formed the basis for this question.

Summary of Evidence

There have been no published reports that directly addressed the use of arterial line versus palpable pulse to confirm circulatory arrest in the setting of adult or pediatric DCD. However, the question of detectable pulses in low flow states has been reported in three observational studies and used in the context of informing resuscitation guidelines (91). A 2009 report from Tibballs et al. asked pediatric health care professionals to assess pulses in patients undergoing mechanical circulatory support with variable levels of native heart function (86). This included some with no pulse pressure (no palpable pulse) to near normal pulse pressures (pulse present), and investigators pre-determined the presence or absence of pulse (by arterial wave form) prior to evaluation by participants. Correct responses were given by 78% of participants

with sensitivity of 0.86 and specificity of 0.64. A 2010 follow-up study using similar methods by the same group (87) demonstrated total accuracy for experienced physicians was 85%. An earlier study of adults undergoing cardiopulmonary bypass had lay people and ambulance personnel at varying stages of their training assess palpable pulses (88). In this setting, 6/59 (10%) did not correctly identify pulselessness and 66/147 (45%) did not detect a carotid pulse when one was present (as monitored by an arterial line).

Despite an extensive literature search, no evidence was discovered evaluating other methods of death determination. We therefore chose not to consider other related PICO questions evaluating the use of echocardiography or Doppler ultrasound in this setting.

Justification

While not specific to a pDCD setting, data from studies designed to test clinicians' ability to determine between low and or non-pulsatile bypass states suggest that even experienced physicians commit errors when assessing the absence or presence of pulse in pediatric patients. Given the high consequence setting of pDCD (i.e. inappropriately determining a pediatric patient as having died), the panel strongly felt that palpation of pulse was an inadequate method to confirm lack of circulation, despite low overall certainty in the evidence. Meanwhile, arterial line monitoring is commonly used, easily interpreted, and objective. The recommendation to rely on arterial line monitoring assumes a functioning and verified arterial line. The scale of the display should be adjusted to monitor for the small pulse pressures observed in a low flow state. While auscultation or palpation should not be used to confirm lack of circulation, they could be applied to verify that an observed flat waveform corresponds with the clinical state. We make no recommendation as to the required site of the arterial line (e.g. peripheral vs. central) as long as it is confirmed to be well functioning.

Some rare settings, such as refusal of arterial line insertion by substitute decision makers or technical impossibility, might preclude an arterial line at the time of death determination. In such cases, if the substitute decision makers wish to pursue pDCD, other methods to confirm arrest of circulation (such as echocardiography, Doppler ultrasound) in the context of pDCD may be used, but only after careful consideration.

In the absence of cardiac electrical activity, it is impossible for the heart to generate a contraction capable of producing anterograde blood flow. This would be equivalent to a confirmation of arrest of circulation, and, assuming an appropriate hands-off observation time, would satisfy criteria for determination of death. For these purposes, only isoelectric ECG would be considered adequate, not other presumably non-perfusing rhythms (e.g. low amplitude fibrillation). Routinely waiting for isoelectric ECG however, is not recommended given it has been well documented that cardiac electrical activity may persist well after the arrest of circulation (89). Since the definition of death used in these guidelines requires absent circulation, not absent electrical activity, this prolonged waiting could unnecessarily prolong the warm ischemic time, placing the desire to donate at risk with potential grafts becoming ineligible for transplantation.

Echocardiography could also provide an adequate assessment of circulatory arrest; if the aortic valve does not open and anterograde flow is not demonstrated during the period of hands off observation, the patient can be confirmed to have an arrest of circulation. While this test could theoretically fulfill the requirements for death determination, in the absence of published reports we cannot formally comment on its proven effectiveness compared to the current gold standard of arterial line monitoring. The use of echocardiography during death determination would also pose several logistic challenges. The presence of a machine and operator might interfere with the family's ability to stay close to the patient who is a potential donor during his or her EOL care. The use of echocardiography also might interfere with sterile preparation of the patient and would require the availability of experienced echocardiographers at all times where pDCD might proceed.

Although Doppler ultrasonography could also theoretically be used to determine an arrest of arterial circulation, there is currently no evidence assessing the use of Doppler ultrasound of large arteries (e.g. femoral) to confirm cessation of circulation. Our literature searches found no reports of the sensitivity or specificity of Doppler to confirm lack of circulation in a low flow state and no data on the effect of operator experience.

Finally, while absent circulation by functioning arterial waveform is considered standard of practice to determine death; clinical markers can be used to confirm that the clinical state corresponds to the arterial trace. Observation of apnea, pulse palpation, and cardiac auscultation are reasonable to perform and document to rule out a malfunctioning arterial line monitor, but should not be considered to be required confirmatory procedures for death determination.

Actionable Question #4: Hands off period

Should 10 min hands off time vs. 5 min hands off time be used for death determination in pDCD donors?

Actionable Recommendation #4:

We suggest 5 minutes of hands off observation of arrest of circulation prior to determination of death. (Conditional recommendation, very low certainty in evidence)

GRADE Profile 4: Hands off period

Quality assessment							Impact	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Kidney Outcomes									
1(92)	observational studies	serious [1]	not serious	very serious [2]	not serious	none	No studies of donors with 10 min wait time. Wait time of 5 mins, comparison of outcomes to NDD: n=91 patients from retrospective database review (1981-2006).Twelve percent of the DCD kidneys were from uDCD. After correction for confounding variables, the risk of graft failure was higher in the DCD group [hazard ratio 2.440 (95% CI 1.280– 4.650; p = 0.007]. Patient survival, however, was similar between groups [hazard ratio 1.559 (95% CI 0.848– 2.867; p = 0.153)].	⊕◯◯◯ VERY LOW	CRITICAL
Liver Outcomes									
1(93)	observational studies	not serious	not serious	very serious [2]	serious [3]	none	No studies with donors with 10 min wait time. Wait time was 5 mins, comparison to NDD: n=7 DCD donors over 20 years in case-control matched 1:3 for NDD donors over 12 months. No difference in liver function short and long term. 10-year patient and graft survival was 100%.	⊕◯◯◯ VERY LOW	CRITICAL
Lung Outcome									
1(18)	observational studies	serious [1]	not serious	very serious [4]	serious [3]	none	No studies with donors who had 10 min wait times. Wait time was 5 mins for 3 donors. Recipients were 1 pediatric and 2 adults (16,62,58yrs). Two patients were alive and well at 15, 4 months; 1 patient died at 34 months with bronchiolitis obliterans syndrome, in part attributable to medication non-compliance.	⊕◯◯◯ VERY LOW	CRITICAL
Cardiac Outcome									
1(17)	observational studies	not serious	not serious	serious [2]	serious [3]	none	No studies with donors with 10 min wait time One donor had 3 min wait time, 2 donors had 75 sec wait time. Comparison was to NDD donors. 3 recipients of pDCD donors had no late deaths (within 3.5 years), and they have had functional and immunologic outcomes similar to those of recipients of pNDD.	⊕◯◯◯ VERY LOW	CRITICAL
Autoresuscitation									
2(89, 94)	observational studies	not serious	not serious	not serious	serious [3]	none	Two studies designed to look for autoresuscitation: 1 prospective study in 73 DCD donors, 8 of whom were < 18yrs, found no cases of autoresuscitation during 5 min waiting/observation period for death determination. 1 prospective feasibility study in 41 patients monitored during dying process after WLST. 4 patients were pediatric, no cases of autoresuscitation in 30 min period after death determination.	⊕◯◯◯ VERY LOW	CRITICAL

1. retrospective
2. comparison was to NDD not 10 min wait

3. No explanation was provided
4. small number
5. no comparison to donors with 10 min wait time

Background

The hands off period of observation is critical to pDCD in order to ensure that the patient is beyond the time period where autoresuscitation could occur while not subjecting potential donated organs to prolonged ischemic time. Our scoping review of pDCD revealed that guidelines for death determination in the setting of DCD all require a waiting period after circulatory arrest, most commonly 5 minutes (range 2-10 min), after which death is determined. For the remainder of this document, this period will be referred to as the hands off time, defined as a period of observation during which no interventions are permitted and continuous monitoring of circulation is required. Though no consensus definition exists, we consider the start of this wait period to be when there is no discernible waveform on an appropriately calibrated arterial line.

No international consensus has been reached concerning how long the hands off period should be (12, 13, 36, 37, 43). The American Academy of Pediatrics Committee on Bioethics is the only organization to give recommendations specific to pediatrics, and recommends a wait period of 2-5 minutes without specifying diagnostic tests (37).

Summary of Evidence

There have been no published studies that have directly addressed our clinical question by comparing 10-minute vs. 5-minute hands off period with outcomes of autoresuscitation and graft and/or recipient survival in adults or pediatrics. We therefore included studies that investigated at least one of these outcomes, downgraded for indirectness for our question. With respect to graft and/or recipient outcomes for pDCD the only studies that documented the duration of hands off time used 5 minutes (18, 92, 93) or less (17). Some studies did not explicitly report the duration of their hands off time, and none reported a 10-minute hands off period. For the outcome of autoresuscitation, a 2010 systematic review of published autoresuscitation reports (95) concluded that autoresuscitation has been reported only after failed CPR and did not occur beyond 7 minutes in studies with continuous observation and exact times. There were no reported cases of autoresuscitation after WLST in children. Subsequent to this review, there have been 4 reported cases of autoresuscitation in children. All occurred in the context of failed CPR (96-98) and are, thus, not applicable to controlled DCD where CPR is not provided. Within the context of a controlled DCD, we found only two studies that were designed to look for autoresuscitation. One was a prospective study in 73 DCD donors, 8 of whom were < 18yrs, that reported no cases of autoresuscitation during the 5 minute waiting/observation period for death determination (94). The other was a prospective feasibility study that included 4 children who were monitored after WLST (89). In this study there were no reported cases of autoresuscitation in the 30-minute period after determination of death.

Justification

In the development of this clinical question, we considered a 2-minute hands off period, but rejected it as a comparator based on perceived lack of acceptability by Canadian clinicians (39). Currently, all Canadian adult and pediatric centres performing DCD use a 5-minute hands off period and, based on existing evidence, this period is long enough to avoid risk of autoresuscitation and provide transplantable organs with acceptable outcomes. However, based on the low quality of the reviewed autoresuscitation evidence and the fact that no reports directly compared organ outcomes using 5 vs 10-minute hands off times, we chose to make a conditional as opposed to strong recommendation.

9. *Ante* and *Post Mortem* Interventions

Good Practice Statements

Ante Mortem

9.1 Any intervention or test that may pose discomfort to the patient who is a potential donor should be managed with analgesia and/or sedation as per standard ICU practices.

9.2 Consideration should be given to the timing of administration of any *ante mortem* pharmacologic intervention in order to minimize any potential risks.

9.3 Protocols for the administration of *ante mortem* donation-based interventions should be established in concert with local ODOs and surgical recovery teams.

9.4 The short-term maintenance of life sustaining treatment (prior to WLST), including inter-hospital transfer, is permissible in order to arrange pDCD logistics.

a. The risks and benefits of such maintenance of therapy or transfer must be explained and consent obtained as for any *ante mortem* therapy.

9.5 For the purposes of death determination, maintenance of an existing arterial line or insertion of a new arterial line (with appropriate sedation and/or analgesia) is permissible.

Post Mortem

9.6 Interventions that do or may re-institute oxygenated brain blood flow after death must not be performed, including cyclic ventilation after re-intubation for lung donation.

9.7 Only the organ recovery team may carry out *post mortem* surgical interventions.

Justification

The above recommendations emphasize that any *ante mortem* intervention, including transfer of a patient who is a potential donor, carries the same requirements for informed consent,

minimization of risk, and respect for the comfort of the patient as given in routine care of ICU patients. Refer to the *Consent for Ante-Mortem Interventions* section above for additional discussion of this topic.

Regarding *post mortem* interventions, our primary concern was the need to avoid interventions that might re-establish oxygenated brain blood flow. Absence of oxygenated brain blood flow is the key component of the determination of death, so procedures that potentially re-establish that flow at the time of organ recovery could violate the dead donor rule. Understanding that risk, we recommend that tracheal re-intubation is permissible as long as cyclic ventilation is not provided. Through cardiopulmonary interactions, cyclic ventilation has the theoretical risk of restoring oxygenation and brain circulation, and its avoidance has also been recommended by other groups (12, 36).

Actionable Question #5: Ante mortem interventions: heparin
Should Heparin vs. no anticoagulation be used for pDCD as an *ante mortem* intervention?

Actionable Recommendation #5:
The panel did not make a recommendation regarding the universal administration of heparin in the setting of pDCD.

GRADE Profile 5: *Ante mortem* interventions: heparin

Quality assessment							Impact	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Graft outcome (specific to each type of graft)									
2(99, 100)	observational studies	very serious [1]	not serious	very serious [2,3]	serious [4]	none	Very little is known regarding the use of heparin in DCD with no published data in pDCD. The two included references are both retrospective cohort studies that are organ specific, one for kidney DCD and one for lung DCD. No other human data has been published for other organs. Furthermore, one of the included studies (Cypel et al.) compares DCD lungs to NDD lungs, not DCD with or without heparin. There were no significant outcome differences between DCD and NDD lung outcomes in the Cypel et al. study. The other included reference (Kamal et al.) examined DCD kidney outcomes with or without *ante mortem* heparin and found no difference in early or late graft function.	⨁◯◯◯ VERY LOW	CRITICAL
Hemorrhagic risk to the patient who is a potential donor (cerebral or uncontrolled bleeding) - not reported									
-	-	-	-	-	-	-	No studies reported the incidence of any hemorrhagic complications with *ante mortem* heparin administration	-	CRITICAL

1. Kamal - no indication as to why heparin was or wasn't given

2. No pediatric patients
3. One study was comparison of DCD to NDD
4. Very few patients

Background

Concerns over thrombus formation during the low perfusion period of WIT have lead many programs to administer anti-coagulants either before or during WLST (11). The most frequently cited potential risk of anti-coagulation would be the creation or worsening of life-threatening bleeding (11). Heparin is the agent used in all references reviewed in our pDCD scoping review. Protocols in some centres, including all pDCD programs in Canada (101, 102) routinely use *ante mortem* heparin administration in their DCD patients. In some international centres, heparin is not administered consistent with national recommendations against its use (12, 13).

Summary of Evidence

A review of the available pediatric and adult literature was undertaken to identify any positive or negative effects of *ante mortem* administration of heparin in DCD for all age groups. Only 2 papers met the criteria for inclusion; these were organ-specific retrospective cohort studies for kidneys (99) and lung (100), respectively. Neither reference provided clinical reasoning for administration or non-administration of heparin. Both references were downgraded for indirectness, since neither directly compared heparin use to no heparin use in a pediatric population. Kamal et al. (99) compared early and late survival in DCD kidneys with and without *ante mortem* heparin administration. Fifty-two patients were evaluated, of whom 44% received heparin, and there was no difference in recipient outcomes. Cypel et al. (100) reported outcomes of lung transplantation from 224 DCD patients, of whom 48% received heparin, compared to 2,744 NDD patients. Early and intermediate graft survival was comparable. No studies identifying harm or complications from *ante mortem* heparin administration were found. No other human data was found, and animal data were excluded.

Justification

Given the lack of available evidence in pediatric patients, and concerns regarding any *ante mortem* interventions in this patient population that could cause harm, we make no recommendation regarding routine *ante mortem* heparin administration for pDCD. General and case-specific practices, including dose and timing of administration, should be determined through discussions between intensive care teams, ODOs, and transplant programs. If administered, heparin should be given in a manner that minimizes potential hastening of donor death (e.g. consider giving during agonal phase of WLST as opposed to during the first act of WLST).

Actionable Question #6: Regional oxygenated perfusion

Should regional oxygenated perfusion techniques vs. no such techniques be used for improving organ outcome in controlled pDCD?

Actionable Recommendation #6:
We recommend that regional perfusion not be used in the setting of pDCD. (strong recommendation, very low certainty in evidence)

GRADE Profile 6: Regional oxygenated perfusion

Quality assessment							Impact	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Organ outcome									
13(103-113)	observational studies	serious [1,2]	very serious [3]	serious [4,5]	serious [3]	none	The data regarding organ outcomes in NRP in a cDCD setting (see justification text for a detailed summary) suggest that it is feasible even in a setting where ante mortem interventions are prohibited. The available outcome data also suggest that graft function might be improved compared to standard DCD. These data must be interpreted cautiously for several reasons. They are exclusively retrospective, often with limited or no comparison even to a matched standard DCD cohort. They are indirect, with almost no pediatric representation. Finally, none of these reports included comparison of treatment with ex vivo machine perfusion after procurement. These treatments, either in isolation or after NRP in situ could substantially alter the impact of NRP and will require careful consideration in any future reports.	⨁◯◯◯ VERY LOW	CRITICAL
Risk of re-establishing oxygenated brain blood flow									
2(104, 112)	observational studies	very serious [6]	not serious	serious [4]	not serious	none	The only two papers to describe methods to ensure that brain blood flow was not re-established used primarily visual confirmation that the upper body was not perfused. Neither reported any cases where re-perfusion was thought to have occurred. No reference described a formal evaluation of brain blood flow.	⨁◯◯◯ VERY LOW	CRITICAL

1. Retrospective studies
2. Varied comparators (e.g. cDCD vs. uDCD vs. NDD)
3. Wide range of outcomes between reports
4. Almost exclusively adult patients
5. Many studies report only from uDCD donors
6. No systematic method described of eliminating possible brain blood flow

Background

To our knowledge, no adult or pediatric Canadian centre is currently employing regional perfusion techniques in the setting of DCD. Variously described in the literature, these techniques include methods that involve occlusion of the aorta and oxygenated perfusion (similar to extracorporeal membrane oxygenation (ECMO)) of abdominal organs after the determination of death and before organ recovery. Regional perfusion techniques can be applied for minutes to hours prior to recovery and are routinely used in uncontrolled DCD

settings in some jurisdictions (114). The theoretical advantages of these techniques include restoration of cellular energy stores, evaluation of organ function prior to recovery, and decreasing time pressure during surgical dissection and recovery after the determination of death (114). The potential disadvantages include ethical concerns regarding *ante mortem* cannulation, significant resource utilization, and the concern that such techniques might re-establish oxygenated brain blood flow, therefore violating the dead donor rule (114).

Summary of Evidence

A review of available pediatric and adult literature was conducted to evaluate whether regional perfusion techniques improve organ outcomes in the setting of controlled pDCD. No references were found that directly address this topic. Four references (103, 104, 112, 115), including a systematic review, were considered as indirect evidence. All studies, including those in the systematic review, were retrospective in nature and relatively small. Although the majority of study participants were adults, adolescents and children were included (total number < 18 yrs unspecified).

Three references (103, 104, 112) compared placing deceased donors on extracorporeal support (EC-DCD) and compared number of organs retrieved per donor to historical control, rapid recovery DCD (RR-DCD, the form of DCD most frequently practiced in Canada), or those where EC-DCD could not be performed for unspecified reasons. The results of these studies show no statistical difference in long-term survival or graft rejection; however, there was higher probability of abdominal organ recovery (3 to 2.6 organ/donor), a higher liver utilization rate (52% vs. 27%), and lower delayed graft function (DGF) in kidney recipients in the EC-DCD group.

In the systematic review by Shapey et al. (115), all patients who underwent controlled EC-DCD (4/11 studies) were heparinized and cannulated prior to death determination. Kidneys retrieved through EC-DCD generally demonstrated lower DGF rates (range 8-41%) than standard (Controlled Donation after Circulatory Determination of Death) cDCD kidneys (range 55-57%), with rates comparable to NDD kidneys (range 19-26%). 1-year graft and patient survival rates were similar between all groups. The one report of 11 patients with normothermic regional perfusion cDCD liver grafts (108) reported 1-year graft and patient survival to be similar when compared to historical outcomes of livers transplanted after NDD and better than historical standard DCD outcomes. In light of the ethical concerns of cannulation prior to death determination, Oniscu et al. (103) recently described the feasibility of EC-DCD applied in the ICU without any *ante mortem* interventions for 21 donors.

Among these reports, only two (both from the same centre) (104, 112) evaluated the risk of establishing brain blood flow, which was determined only through clinical assessment (e.g. upper body cyanosis). No study formally assessed this low probability but high-risk event.

Justification

For our guidelines, these data must be interpreted cautiously for several reasons. All studies were of low quality and downgraded for indirectness. None of these reports included comparison of treatment with *ex vivo* machine perfusion after recovery. *Ex vivo* treatments,

either in isolation or after regional perfusion *in situ,* could substantially alter the impact of regional perfusion and will require careful consideration in any future reports.

Given the low quality of the evidence reporting benefit, the risk of the significant consequence of re-establishing brain blood flow through inadequate aortic occlusion, and the cost/resources involved, we feel that EC-DCD should not be used for pDCD. For these reasons, we felt comfortable making a strong recommendation despite overall very low quality of evidence.

While we do not recommend its use in standard practice, regional perfusion techniques could be considered as part of a research protocol with research ethics board approval. If applied, techniques should be used to ensure the absence of brain blood flow during regional perfusion research.

Actionable Question #7: Ante mortem interventions: bronchoscopy
Should bronchoscopy vs. no bronchoscopy be used for ante mortem evaluation of lung function in potential pDCD donors?

Actionable Recommendation #7:
The panel did not make a recommendation for or against the routine use of *ante mortem* bronchoscopy in the setting of pDCD.

GRADE Profile 7: *Ante mortem* interventions: bronchoscopy

Quality assessment							Impact	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Graft lung function									
3(116-118)	observational studies	very serious [1,2]	serious [3]	very serious [4]	serious [3]	none	No trials were discovered that directly address this PICO question. The only discovered report to address bronchoscopy in DCD found no lungs were excluded based on bronchoscopy findings from 13 potential donors (Cypel et al. 2009). There was one adolescent of 17-years-old among the 9 donors. No correlation between bronchoscopy findings and graft or recipient outcomes. Bronchoscopy is frequently practiced in NDD and DCD organ donation, but it's association with graft or recipient outcome is currently unknown. The impact of continued *ex vivo* support and the possibility of *post mortem, ex vivo* bronchoscopy remains unreported in the current literature.	⨁◯◯◯ VERY LOW	CRITICAL
Risk to the patient who is a potential donor (e.g. desaturation, pneumothorax) – not reported									
-	-	-	-	-	-	-	None of the above trials report adverse effects associated with ante or post mortem bronchoscopy for lung eligibility evaluation.	-	CRITICAL

1. Retrospective reports
2. Bronchoscopy part of overall donation program
3. Significant variation between reported rates of lung refusal (0-38%)
4. Most data from adult NDD

Background

The practice of bronchoscopy for evaluation of donor lung eligibility has been considered standard since the published recommendations from Winton in 1992 (119). A subsequent report from 1994 in the setting of NDD (116) found abnormal bronchoscopy findings that precluded organ recovery in 10/26 (38%) of patients who were potential donors with normal chest X-rays and blood gases. These initial papers influenced the widespread adoption of bronchoscopy in the setting of both NDD and DCD. Since that time, pre-recovery bronchoscopy in child and adult patients who were potential donors to exclude the presence of visible oncologic lesions, assess for anatomical variation, or airway injury while removing secretions and evaluating for infection (118).

Summary of Evidence

We discovered no references that directly address the use of *ante mortem* bronchoscopy in pDCD. A 2010 retrospective report of 476 adult lung donors (presumed NDD, though not specified in report) found that 16% of their patients who were potential donors were excluded based on bronchoscopy findings (118). This group did not report a correlation between bronchoscopy findings and graft or recipient outcomes. The only report we identified that addressed bronchoscopy in DCD found no lungs were excluded based on bronchoscopy findings from 13 patients who were potential donors (including one 17-year old, no other children) (117). No correlation was reported between bronchoscopy findings and graft or recipient outcomes.

No references were found that reported harm to the patients who were potential donors as an outcome.

Justification

While bronchoscopy is frequently practiced in NDD and DCD organ donation, its association with graft or recipient outcome in pDCD is currently unknown. We acknowledge that *ante mortem* bronchoscopy prior to controlled pDCD is likely a low risk procedure, but there are no published reports evaluating adverse events in this setting. The possibility of *post mortem* bronchoscopy either *in situ* or *ex vivo* is unreported in the current literature, but would likely offer the potential benefit of *ante-mortem* bronchoscopic evaluation while eliminating risk conferred to the patient who is a potential donor. This balance of considerations led us to not recommend for or against *ante mortem* bronchoscopy.

10. Innovative Therapies, including Cardiac pDCD

Good Practice Statements

10.1 Considering the fact that pDCD remains an evolving field in medical practice, innovation within the field should be undertaken with appropriate oversight.

a. Research in pDCD should be encouraged, assuming appropriate REB oversight. See Table 5 for a list of identified pDCD knowledge gaps.

10.2 Considering the lack of published experience in cardiac pDCD:

a. Cardiac transplant programs should establish criteria for acceptance of heart donation, ex-vivo cardiac protocols, and heart allocation in pDCD;
b. Consideration should be given to initiate cardiac pDCD program as either research protocols with research ethics board oversight or through programs that oversee innovative therapies;
c. In the early phase of implementation of a cardiac pDCD program, the donor and recipient should be in the same centre to limit cold ischemic time. This practice should be revised based on clinical experience and research into *ex-vivo* applications.

Justification

The scientific evidence supporting pDCD remains limited and it is likely that many academic centres pursuing pDCD will develop research programs to address knowledge gaps. The guideline authors recommend that as centres develop new pDCD techniques and practices, innovative therapies should be undertaken with appropriate oversight. It is important to note that we do not see the general practice of pDCD, as recommended in this document, as requiring innovative therapy oversight.

We felt that cardiac pDCD required specific attention. The logistics of cardiac pDCD largely remain unexplored, since only 3 cases have been reported in the literature (17). This report involved hands off times that were less than 2 minutes and the recipient and donor were in the same hospital in order to limit cold ischemic time. While there is minimal published experience with cardiac pDCD, recent innovative reports of adult cardiac DCD using ex-vivo heart preservation suggests this option may evolve as a viable clinical pathway in the near future (120). We considered this lack of evidence when recommending that future Canadian cardiac pDCD should be undertaken under the supervision of a clinical trial or innovative therapy program.

11. Neonatal DCD

Good Practice Statements

11.1 Unless otherwise stated, the above GPSs and actionable recommendations that apply to infants and children should also apply to neonates, provided expertise in neonatal end-of-life care can be provided.

11.2 Diagnoses such as anencephaly or other similar severe, life limiting neurologic disorders, for whom NDD is impossible, do not preclude consideration as potential candidates for pDCD.

11.3 Establishment of neonatal eligibility criteria for pDCD, such as minimum weight and gestational age, is the responsibility of transplantation services in conjunction with neonatal critical care services with expertise in organ donation.

a. These processes should be under constant review to keep current with emerging pDCD criteria.
b. Communication between clinicians and ODOs should be encouraged for cases of WLST near the thresholds of eligibility.

11.4 Centres not providing pDCD should establish a clear process for transfer to hospitals with pDCD programs including: consideration of transfer of the mother of the patient who is a potential donor, ongoing provision of end-of-life care, limitation of economic burden on surrogate decision makers, and repatriation of the body.

Justification

NDD is an uncommon event in the neonatal population (127). Issues exist that limit the application of NDD criteria to the neonatal population, such as difficulty in establishing an exact cause of coma soon after birth, uncertainty regarding the validity of ancillary testing in severely encephalopathic neonates, and the open fontanels of newborns which limit brain herniation physiology. The modes of death are different in NICU relative to PICU (128, 129), and in many NICUs, WLST is the most common pathway to death (121), potentially creating a significant population that would be eligible for pDCD (16, 51). Despite this, neonatal pDCD remains extremely rare in Canada, with most centres not offering the service.

As with all potential DCD donors, optimal EOL care should remain the fundamental concern in a neonatal pDCD process. The particular relational and ethical aspects of neonatal death require the expertise of a clinician trained to deal with these EOL issues. Two recent reports variations of neonatal EOL practice in Canadian centres (121, 130).

Little has been published on neonatal DCD. Brierley has suggested neonatal pDCD as an ethical component of a multifactorial solution to the chronic organ shortage in the United Kingdom (51, 122, 123). In the United States, Stiers et al. (16) reported that of 136 deaths in their NICU,

60 (44.1%) met criteria for DCD; but less than 10% were referred appropriately to the regional organ procurement organization for evaluation. It is, thus, unknown how frequently neonatal pDCD might occur in Canadian NICUs if pDCD services were offered routinely as part of EOL care.

One of the potential differences between neonatal and other populations is the relatively large numbers of regional, non-tertiary NICUs that do not offer pDCD (compared to relatively small number of PICU's) in which many potential neonatal pDCD donors may be initially hospitalized. If parents of children hospitalized in NICUs that do not offer pDCD wish to pursue pDCD, clear protocols for transfer would be necessary, including consideration that the mother might not yet be eligible for transfer or discharge (69, 124). These protocols could also consider applying policies to ensure that patients in a health care system have priority access to the few centres that perform pDCD.

We recommend that pDCD can be offered to patients born with anencephaly or other similar severe, life limiting neurologic disorders. On February 1, 2016, the Canadian Pediatric Society (CPS) reaffirmed its Position Statement (125) that recommends against allowing deceased organ donation in this population based on the impossibility to complete a NDD exam in the setting of a functional brain stem. This statement, however, was based solely on NDD. Since pDCD is unaffected by the fact that these patients do not fulfill NDD criteria, we recommend that pDCD can be offered to the substitute decision makers and family of patients born with this condition. The literature search done to inform these guidelines discovered no published references describing the application of pDCD to the anencephalic population (11).

12. pDCD Implementation and Oversight

Good Practice Statements

12.1 pDCD programs should seek out formal institutional approval within the existing hospital reporting structure.

12.2 There should be an integrated, collaborative approach to pDCD implementation with all hospital stakeholders, family and/or public partners, regional ODOs, and transplant programs.

a. Transplant programs and ODOs should create clear allocation strategies of organs recovered through pDCD to ensure optimal utilization.

12.3 Strong consideration should be given to incorporate family and/or public input into the design and implementation of pDCD programs.

12.4 Local coroners should be contacted early in the process of developing local pDCD procedures.

12.5 Communication and education of staff (e.g., ICU, operating room, risk management, pastoral care, and bioethics) should be considered a priority during the development and implementation of a pDCD protocol. This education should include:
   a. How to interact with substitute decision makers and family during pDCD;
   b. Preservation of the integrity of EOL decision making;
   c. Multidisciplinary simulation of clinical processes;
   d. Cognitive aids and checklists for the logistics of pDCD.

12.6 pDCD case management review and a periodic quality assurance process should occur.
   a. These processes could include joint procedures to assess donor identification and management as well as transplant outcomes in collaboration with transplant programs and the ODO.
   b. Quality assurance should also include measures of substitute decision makers and family experience, with outcomes informed by input from patient and family partners.
   c. This should also include periodic, planned auditing by an independent organization (analogous to a data safety monitoring board or research ethics board), an internal health region, or hospital based multidisciplinary group (such as a deceased donation committee).

12.7 There should be planned staff debriefing on a regular basis and after each case.

12.8 Support for health care professionals involved in pDCD should be provided.

12.9 Centres should conform to Accreditation Canada recommendations regarding DCD practice in children and adults.

Justification

The establishment of a pDCD program should involve multi-disciplinary collaboration with oversight from appropriate local authorities. The need for communication and education of all involved stakeholders has also been broadly emphasized in recent publications and was a frequently expressed sentiment during our pDCD symposium (47, 90). While ideally this would involve meaningful public consultation, we recognize that this type of input is difficult to organize and not feasible for all centres. If possible, broad public input should be sought, possibly through existing hospital patient partnership committees, organ donation committees, or in conjunction with the local ODO. This input should include particular concern for cultural minority groups served by the hospital and health system. Once a local protocol is established, multi-disciplinary simulation is an ideal method to test the complicated logistics related to pDCD. Consideration should be given to performing routine simulation, particularly in centres that perform pDCD infrequently. Debriefing after each case will also allow for improvement in local processes.

Consideration may given to initiate pDCD programs with lower risk organs, such as kidneys, and low risk patients who are potential donors. Regional expertise and experience in adult DCD will influence these decisions. Since organs retrieved through pDCD are considered by transplantation programs to be of higher risk for dysfunction, allocation strategies may have to be modified to accommodate pDCD (69). These decisions should be made early in the implementation process to ensure that when pDCD is offered, the substitute decision maker can be assured that any retrieved organs will be optimally utilized.

Quality control for this low frequency, high impact event is critical for pDCD programs. This process should involve medical and ethical oversight, ideally with linkage to measures of donor family experiences and transplant outcomes.

CONCLUSION

To our knowledge, this document represents the first pediatric-specific, national guideline governing pDCD practice. The recommendations within this guideline are in line with all other professional societies that have considered pDCD, including the American Academy of Pediatrics (38) and the Society of Critical Care Medicine (44), though tailored for a Canadian pediatric population.

The authors and our stakeholder partners strongly support that, when practiced according to these recommendations, pDCD is an ethical practice that can provide important meaning to families during EOL care and life saving organs to patients on transplantation wait lists. In an individual centre, pDCD will likely remain an uncommon event. The impact of these rare events, however, will likely increase as rates of NDD decline across Canada (8) and the need for organ grafts remains high. It will be important for centres to have well-structured systems capable of providing the complex logistics and family support necessary to ensure high quality pDCD services.

While these guidelines were generated according to a rigorous development process, they do have limitations. The evidence upon which they are based was generally of low or very low quality. Research in pDCD is a developing field, and few prospective and no randomized trials were discovered specific to pDCD. Furthermore, though we had input from patient partners late in the process, we did not have a structured method for soliciting patient input at the start of development. Our plan for future donation guidelines includes incorporation of patient partners in the earliest phases of the process. Finally, a lack of time and resources precluded the economic analysis recommended by the AGREE II process (25). An initial evaluation, however, revealed that such an analysis would have been difficult and likely of limited value considering the poor quality of the available data.

Despite these limitations, we feel that these guidelines are robust and should be widely adopted. In many recent cases of guideline development, a perceived lack of evidence often leads teams to use alternate methods of guideline development such as consensus statements. In our case, despite the lack of high quality evidence, we have chosen to adhere as much as

possible to the precepts of rigorous guideline development. The process used was transparent, potential sources of bias were minimized, the recommendations are based on a comprehensive and objective assessment of the available evidence, there was no funding from commercial sources, conflicts of interest were declared and reported, and the methods of developing the guideline are reported and are consistent with the AGREE II instrument. Evidence was systematically reviewed and summarized using the GRADE methodology. We employed good practice statements, a relatively recent addition to the GRADE process, for clinical questions with clear benefit, lack of harm, and large bodies of indirect evidence that were difficult to summarize. Stakeholder input was sought and incorporated into the guideline development process. There was national representation of multi-disciplinary experts on the GDC and WGs and the recommendations are appropriate for a Canadian audience. We have partnered with the professional societies whose members will be most directly involved in pDCD (CPS, CST, CCCS, CACCN). Their external review provided informative feedback and ensured distribution for knowledge translation among their members. This process permits us to assert that we have transparently created carefully considered recommendations linked to a reproducible evaluation of the available evidence.

Knowledge Gaps and Research Priorities

Given the limited evidence informing pDCD practice, there is substantial opportunity to advance knowledge in the field. Table 5 is adapted from the scoping review and highlights some potential questions and solutions. Broadly these can be considered under: 1) policy and legal changes to ensure clarity in death determination and pDCD practice; 2) studies examining the physiology of death after WLST in children and how this physiology might influence graft or recipient outcomes; 3) experience of families and health care professionals going through the pDCD process. Addressing these concerns will require coordinated, high quality research programs that serve to inform policy makers.

Table 5 Knowledge Gaps and Proposed Solutions

Lack of a definition of death that unambiguously allows or prohibits pDCD	- Professional societies and public health organizations should recommend a clear definition of how death is determined - Clinicians and professional societies should encourage legislative clarification of the definition of death
Lack of uniformity among pDCD practices and lack of knowledge of how to create local protocols	- Development of national and international guidelines governing pDCD based on the best available evidence and analysis
Uncertainty over organ outcomes in pDCD vs. pNDD	- Well designed, prospective surveillance of pDCD practice including standardization how organ outcomes are collected and reported in order to identify modifiable risk factors affecting pDCD organs specifically as compared to NDD
Uncertainty regarding tolerance of organs to	- Well designed animal and human studies to

cold ischemia following the WIT of pDCD	determine if pDCD organs have tolerance to cold ischemia similar to those retrieved through NDD - The impact of *ex vivo* techniques should be considered in these studies
Lack of knowledge regarding the physiology of the dying process after WLST, including the prediction of time to death and the uncertainly of the time period for the possibility of autoresuscitation	- Well-designed prospective studies examining the physiology of the dying process after WLST - Retrospective studies reporting organ outcomes for programs that use hands off times longer than 5 minutes - Basic physiology studies that examine the limits of monitoring devices in the low flow states common after WLST
Lack of clear guidelines regarding inclusion and exclusion criteria of potential pDCD donors	- Well-designed studies examining factors associated with short and long term outcomes of transplanted organs - Consensus recommendations between intensive care, surgical and transplantation experts regarding inclusion/exclusion criteria for the use of pDCD retrieved organs
Lack of validated tool to predict time of death following WLST	- Well-designed studies to validate existing or develop new prediction tools that accurately predict time of death after WLST
Lack of knowledge regarding the impact of physiologic instability during WIT on graft or recipient outcomes	- Well designed studies that link physiology during WIT to organ specific post-transplantation outcomes - These data could inform recommendations regarding if WIT should be defined by time or physiologic measures in this population
Lack of knowledge regarding the lived experience of pDCD donor families and substitute decision makers	- Well-designed qualitative studies examining how families and substitute decision makers perceive pDCD specific aspects of the process
Limited knowledge regarding the lived experience of health care professionals participating in pDCD	- Well-designed qualitative studies examining how health care professionals perceive pDCD specific aspects of the process
Lack of knowledge regarding the effect of effective requesting training on the consent discussion process in Canadian pDCD	- Well designed studies that analyze the effect of different training models for health care professionals discussing consent with families. Outcomes should focus on lived family experiences and consent rates
No reports of pDCD pathways other than controlled pDCD after planned WLST	- Protocols and guidelines that address the complex ethical and logistic issues regarding

(Maastricht category III)	uncontrolled pDCD or when cardiac arrest occurs after NDD but prior to organ recovery (Maastricht category IV) - Well-designed studies feasibility and efficacy of other pDCD pathways
Lack of knowledge regarding the safety and efficacy of *ante* and *post mortem* interventions, particularly heparin	- Well-designed studies that examine these intervention's effect on organ outcome and potential risk to donors - Feasibility study assessing the application of *post mortem* bronchoscopy
Tolerance of the heart to WIT and acirculatory time in cardiac pDCD	- Considering the dearth of data in cardiac pDCD, all aspects of this process should be prospectively monitored and reported in a research setting
Impact of ex-vivo cardiac resuscitation on pDCD heart donor potential	- Further human and animal studies investigating this technology
Potential impact of regional perfusion techniques on controlled pDCD	- Well designed studies evaluating the impact of such techniques on organ recovery and transplantation and potential for oxygenated brain blood flow
Limited knowledge of the pDCD process in the neonatal population	- Well-designed studies comparing actual numbers of organs retrieved to estimates based on chart reviews - Qualitative studies of health care professionals, families, and substitute decision makers who have gone through neonatal pDCD
No published references on the impact of applying pDCD protocols to the anencephalic patient population	- Well-designed studies including the use of pDCD protocols for patients with anencephaly undergoing WLST
No recommendations regarding the initiation of non-therapeutic resuscitation for possible organ donation in children born with severe congenital anomalies	- Ethical analysis - Qualitative studies of health care professionals attitudes

Competing Interests

The guidelines were developed by a group that declared no significant competing interests in this process. Several members of the committee are employed by or associated with Canadian Blood Services and Canadian Blood Services provided financial support for this process through a financial contribution from Health Canada and the provinces and territories. Canadian Blood Services is a federally, provincially, and territorially funded, non-profit organization mandated

to ensure that high quality donation services are provided across Canada. The views expressed herein do not necessarily represent those of the federal, provincial or territorial governments.

Knowledge Translation

Dissemination of these guidelines and knowledge translation efforts are planned by several means. First and foremost, the involvement of practitioners from across Canada has created a system of pDCD champions at centres throughout the country. These health care professionals will work to develop local protocols and practices and has already resulted in at least three successful case of pDCD, performed before finalization of these guidelines, in centres that did not previously have a program. In addition, these guidelines will be presented at conferences and professional meetings, and have been simultaneously published through the CPS. In support of its primary knowledge translation goals, Canadian Blood Services has plans to create a practice community around pediatric deceased donation that will continually audit the number of active pDCD programs and pDCD activity nationally. The guideline development committee also plans to interact with ODO leaders to ensure that barriers to implementation are addressed using system-specific solutions. The activity will allow members to focus efforts on areas where implementation may be problematic. This group also plans to interface with researchers in deceased donation to ensure that future recommendations will be based on evidence with fewer knowledge gaps.

The guidelines will be updated regularly at 4-year intervals. Currently, there is no plan to create a “living guideline” committee for continual updating of the guidelines as has been suggested (126), though the above mentioned pediatric deceased donation committee will actively survey the pDCD literature and may accelerate the timeline if enough impactful literature is published in the field.

It is our sincere hope that these guidelines provide clear, meaningful recommendations for those hoping to develop pDCD programs. Developing these programs has the potential to give families access to a desired service at a time of great personal loss. It also provides hope to the adults and children on organ wait lists that more transplantable organs will become available.

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