RESEARCH PROGRAM IN ORGAN DONOR CARE

FOUNDATIONAL WORK FOR A NATIONAL RESEARCH PROGRAM IN ORGAN DONOR CARE

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Lay Abstract

Organ donation saves lives and it is the most effective therapy available to treat end stage organ failure of a number of organs. Unfortunately, there is a growing gap between the number of donors and the number of patients waiting for transplantation. This thesis summarizes the foundational work of a national research program in deceased donor management. It describes the study design of a 4 centre prospective observational study in deceased donor management with outcome assessment on corresponding organ-recipients. This thesis also contains a justification for waiving the procurement of consent to research on organ donor management. Finally, it will inform investigators of future national multicentre observational studies on design and implementation issues related to donor management, in order to improve care provided to donors and outcomes of recipients while reducing the gap between transplant needs and organ supply.

Abstract

This thesis is divided in three chapters: (i) introduction to organ donation, (ii) rationale, implementation and design of a pilot observational study currently underway and (iii) justification for use of a waived consent model for observational research studies on organ donor care.

Organ donation is a complex event that remains a mystery to most health care providers. The first chapter reports knowledge gaps in clinical management of deceased organ donors across Canada and summarizes ongoing trials in organ donor care. The persistent deficit in transplantable organs along with the limited scientific evidence to guide the clinical management of the organ donor justify the need for a national research program in organ donor care.

There are logistical and methodological challenges unique to the design and conduct of research on deceased donors. To identify potential stakeholders involved in the process of organ donation and to provide an accurate description of usual management of deceased donor and assess its variability, we developed and initiated a prospective observational study called DONATE. The second chapter of this thesis described the pilot phase of this study. It contains the following sections: i) objectives of the study ii) the screening process, iii) data collection, iv) clinical outcomes, v) methods of measurement, vi) analysis plan and vii) strategies used to minimize the biases inherent to observational studies.

The normative goal of obtaining informed consent from participants may not be appropriate for an observational study in organ donor care. The third

chapter summarizes the justification for use of a waived consent model for observational studies of organ donation medicine. In this chapter, I discuss regulatory, ethical and logistical issues relevant to use of a waived consent model in organ donation research.

Aknowledgements

Today is the day. Writing this note of "remerciement" is the last touch of my thesis, which summarizes my work over the last three years. It has been a period of intense learning, not only in the scientific arena but also on a personal level. This experience has had a profound impact on me. I would like to reflect on the people who have helped and supported me greatly throughout this period.

To Veronick, to whom this thesis is dedicated. Your unconditional love, patience and support throughout these years have made this life experience possible. To Thomas and Camille, who have been a constant source of motivation for me.

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Declaration of Academic Achievement

This thesis is submitted in partial fulfillment of the requirements for the Master of Science program in Health Research Methodology. The work takes the form of a traditional thesis, consisting of three related chapters on the foundation of a national research program in donor management.

Frederick D'Aragon is the first author of these chapters and the co-principle investigator of the pilot study. He developed the pilot study protocol under the supervision of Maureen O. Meade. Frederick D'Aragon created the third chapter of this thesis with the support of two of his thesis committee members, Maureen O. Meade and Francois Lamontagne. Appendices were created by Frederick D'Aragon with the close collaboration of Erika Arseneau, Lori Hand and Maureen O. Meade.

List of Abbreviations and Symbols

1. CBS: Canadian Blood Services

2. CCCS: Canadian Critical Care Society

3. CCCTG: Canadian Critical Care Trials Group

4. CHUS: Centre Hospitalier Universitaire de Sherbrooke

5. CI: Confidence Interval

6. CIHR: Canadian Institute of Health Research

7. CNTRP: Canadian National Transplant Research Program

8. CRC: Central Research Coordinator

9. CVP: Central Venous Pressure

10. DCD: Donation after Circulatory Determination of Death

11. DDAVP: Desmopressin

12. DFNet: DataFax System

13. DND: Donation after Neurological Determination of Death

14. DPM: Donor Per Million of Population

15. HHS: Hamilton Health Sciences

16. ICU: Intensive Care Unit

17. ICTRP: International Clinical Trials Registry Platform

18. IR: Infirmiere Ressource

19. ISRCTN: International Standard Randomized Controlled Trial

20. KT: Knowledge Translation

21. MC: Methods Centre

22. NS: Not Significant

23. NSERC: Natural Sciences and Engineering Research Council

24. ODTC: Organ Donation and Transplant Coordinator

25. OPO: Organ Procurement Organization

26. OR: Odds Ratio

27. PEEP: Positive End Expiratory Pressure

28. PICU: Pediatric Intensive Care Unit

29. PRA: Panel Reactive Antigen

30. QI: Quality Improvement

31. RC: Research Coordinator

32. RCT: Randomized Controlled Trial

33. REB: Research Ethics Board

34. RR: Relative Risk

35. SD: Standard deviation

36. SSHRC: Social Sciences and Humanities Research Council

37. TCPS: Tri Council Policy Statement

38. TGLN: Trillium Gift of Life Network

39. TQ: Transplant Quebec

40. US: United States

41. WHO: World Health Organization

Preface

Transplantation has become the definitive treatment for many people suffering from end-stage organ failure. However, the demand for transplantable organs far exceeds their supply. For many years, donation after neurological determination of death has been the principal source of organs for transplantation. In the last decade, prevention measures, improvements in neurocritical care and new surgical approaches have led to a significant decrease in the number of organs from neurologically deceased donors in Canada.[1, 2]

Optimizing the care of organ donors will increase transplant rates, thereby prolonging and improving allograft function and the quality of life of transplant recipients.[3-5] A number of organizations including, the World Health Organization, international and national organ procurement organizations, medical experts and the lay media have all called for the intensification of clinical research on organ donor care.[6-8]

This thesis presents key aspects of a pilot observational study on organ donor care, which is the foundation of a national research program on organ donor medicine. Specifically, this document is divided into three chapters. The first chapter provides the reader an overview of the current organ donation process in Canada and a summary of research data on organ donor care. The first chapter demonstrates that there is a weak evidence base pertaining to clinical care of organ donors lack of evidence based on clinical care for organ donation and identifies challenges for the future conduct of clinical trials. The

second chapter reports on the pilot phase of a national prospective observational study of clinical practices in organ donor care. Methods to address anticipated challenges in study design and implementation will be developed and piloted during this study. The third chapter of this thesis discusses how the normative informed consent model is misadapted to organ donation research. An alternate approach is proposed along with its justification.

In summary, research is lacking for advancing medical knowledge and donor care. This thesis presents the key aspects of a pilot observational study on organ donor care.

CHAPTER 1: Thesis Introduction

1. Introduction

Organ donation is a complex event that remains a mystery to most health care providers. This chapter presents an overview of the process leading to organ donation process in Canada and elaborates on the: (i) epidemiology of organ donation, (ii) eligibility criteria for organ donation, (iii) organizations involved in the management of organ donors, (iv) current knowledge on clinical management of deceased organ donors across Canada and (v) ongoing trials in deceased donors management.

2. Epidemiology of Organ Donation in Canada

2.1 Patients Waiting on the Transplant List

Organ donation save lives, but in Canada as in other countries around the world, the discrepancy between organ supply and demand is increasing. In 2013, there were 4433 patients registered on Canadian transplant lists (Figure 1).[9, 10] During the same period, 553 deceased donors gave 1779 organs were recovered. More than 75% of patients on the transplant list were waiting for a kidney transplantation and 23% for liver, lungs and heart transplants (Figure 2).[9, 10] The number of pediatric cases represented 6% of all deceased donors.[11] In that same year, 246 patients died awaiting an organ transplant. Compared to other countries, Canada ranks twenty fourth with 15.4 donors per million (dpm) of population. This is significantly less than donation rate in Spain (36 dpm), Croatia

(35 dpm) and the United States (30dpm).[12]

2.2 The Changing Profile of Deceased Donors in Canada

In 2013, Canada had 553 deceased donors. More than 72% were from Ontario and Quebec.[9, 10] This proportion remained the same over the last five years (Figure 3).

The implementation of effective car accident prevention campaigns, improved neuroresuscitation protocols and the use of decompressive craniectomy have all contributed to a decrease in the number of patients eligible for DND in Alberta[2] and limited the increasing rate in Ontario[13] and Quebec.[10] In addition, the incidence of severe cerebral vascular injuries affecting older and sicker patients (e.g., stroke) has not decreased. Accordingly, the profile of potential donors is changing. As severe cerebral vascular injuries are increasingly becoming a dominant cause of catastrophic neurological injury for DND (GCS ≤ 5 with brain injury) the clinical management of the organ donor is becoming more complex[11] and is associated with reduced graft function.[14, 15]

2.3 Organ Procurement Organizations

Each provincial government, with the exception of Prince Edward Island and the territories, delegates the overall process of organ donation to organizations called Organ Procurement Organizations (OPOs). They have the mandate to promote, coordinate and support organ donation and transplantation across their provinces. To accomplish their mandates, The OPO staff are usually multidisciplinary and include nurses, physicians, managers and communication

experts working either at the headquarters or in local hospitals. In 2015, for the two largest OPOs in Canada, the Trillium Gift of Life Network (TGLN) had 269 deceased donors and transplanted 960 organs and the Transplant Quebec (TQ) had 172 deceased donors and transplanted 627 organs.[10, 16] Their operating budgets were $33 899 086[13] and $8 225 081[17] respectively. By comparison, all the other provinces combined had 1/3 of all deceased donors in Canada (Table 3).

3. Eligibility Criteria For Deceased Organ Donation

Organ donation is possible in three circumstances: (i) living donation, (ii) donation after declaration of death by neurological criteria (DND) and (iii) donation after declaration of death by cardiocirculatory criteria (DCD).

(i) Living donation: Living donors may donate a single kidney, a part of the lung (lobe) or part of a liver.[18] In Ontario, roughly half of organ donors are living donors. However, because deceased organ donors provide on average 3.6 organs each,[16] deceased donors provide more than 75% of all organs for transplantation in Ontario. Quebec, British-Columbia, Alberta, Manitoba, Nova Scotia and Saskatchewan have also living donor programs. However, they provide a smaller number of organs. The **exclusive focus** of this research program is on deceased organ donors (either DND or DCD) management.

(ii) Organ donation after neurological determination of death: After a catastrophic

injury to the brain such as trauma, stroke, anoxia or hemorrhage, patients are rushed to hospital and provided life sustaining therapy, including artificial respiration. Some will suffer complete and irreversible loss of all brain function. Organ donation in this setting requires that two physicians undertake a detailed clinical examination to legally confirm a death by neurological criteria.[19] With artificial respiration still in place after the determination of death, other vital organs continue to be perfused and function. One organ donor can improve survival in up to eight patients through the organ donation process.

(iii) Organ donation after circulatory determination of death: ICUs provide life support to patients with catastrophic injury to brain that are not progressing to DND but for whom the chance of recovery is dismal. In these circumstances, families may choose to compassionately withdraw life support, knowing that "circulatory death" (the absence of a heart beat, blood pressure, and breathing) will follow. If a patient is likely to die within a few short hours after withdrawal of life support, there may be an opportunity for organ donation after circulatory determination of death. In this situation, two physicians undertake a clinical examination to legally confirm a death by circulatory criteria[20][20,19] and then surgery for organ recovery proceeds immediately.[20] Organ donation in this circumstance is possible in Ontario, Quebec, Nova Scotia, Alberta and British Columbia. Organ donation after circulatory determination of death (DCD) can improve survival in up to five patients.

4. Organ Donation System in Canada

4.1 Category of Donors

In 2011, a group of international experts in organ donation and transplantation developed a systematic approach for the process of organ donation called the "critical pathway".[21] This provides a tool for evaluating organ donation system performance and acts as a mechanism by which the prospective identification and referral of a possible organ donor could be undertaken. Although the critical pathway was designed for clinical care it may serve research interests by providing standardized definitions.

A critically ill patient going through the process of organ donation is categorized by clinical status:

(i) Possible deceased donor: A patient with a catastrophic brain injury, or circulatory failure, and apparently medically suitable for organ donation.

(ii) Potential donor: A possible deceased donor whose clinical condition is suspected to fulfill the criteria for DND or DCD. If family does not consent, the patient is considered a potential donor.

(iii) Consented organ donor: A potential donor from whom consent for organ donation was obtained. If no organs are recovered, the patient is considered a consented organ donor.

(iv) Actual organ donor: In Canada, a consented organ donor whose family has consented to organ donation and from whom at least one organ was transplanted. United States and Europe considers an actual organ donor when at

least one organ was recovered even if not transplanted.

4.2 Organizations Involved

In Canada, there are three different levels of organization involved in the care of potential donors.

Community hospitals and tertiary care donation centres are responsible for the identification and referral of potential donors to the OPO. These organizations are responsible for the organ donation process in their province. Specifically, they support bedside physicians caring for potential donors, assess organ viability for transplantation, allocate organs to recipients, and centrally coordinate all aspects of organ recovery. Each province has its own OPO except Prince Edward Island and the territories. Follow-up of recipients is under the jurisdiction of the transplant programs. There are 72 transplant program in Canada (Table 1). At the national level, since 2007, Canada Blood Services (CBS) has had an interprovincial role for Canada's organ and tissue donation and transplantation system.[22] This role was previously under the auspices of the Canadian Council for Donation and Transplantation. CBS focuses on practice guidelines related to death declaration, medical management of donors as well as professional and public education.

5. Current State of Knowledge

The overall body of scientific evidence on organ donor care is relatively small. This fact has been highlighted in the publication of a recent consensus on

deceased donor management in the US.[23] However, some interventions are well supported by clinical trials. The following paragraphs will give a summary of the current body of evidence on intervention done before the organs are recovered. Most studies focus on patient care and do not include interventions at the system level.

5.1 Therapies to Support Vital Organ Function

5.1.1 Lung Protective Ventilation

In a multicentre randomized controlled trial (RCT), Mascia et al. assigned 118 adult DND donors, from 18 centres over 6 years, to either a protective ventilation strategy (tidal volume 6-8 ml/kg body weight, with positive end-expiratory pressures [PEEP] of 8-10 cm H_20) or a conventional strategy (tidal volume 10-12 ml/kg, with PEEP of 3-5 cm H_20) from the time of the neurological determination of death until surgery.[24] Both groups were similar at baseline and there was no difference in the primary outcome: pre-surgery criteria for lung donation suitability. However, lung-protective ventilation was associated with more donors eligible to donate any organ (95% vs 54%; $p<0.001$), and more patients meeting intraoperative criteria for lung donation suitability (54% vs 27%; $p=0.004$). The six-month survival among the lung recipients was also higher in patients receiving organs from donors treated with lung protective strategy (75% vs 69%; p=NS).

5.1.2 Fluid Repletion

The infusion of large volume of intravenous fluids (to achieve a central

venous pressure [CVP] of 8-12 mmHg) is perceived to be ideal for the kidneys transplantation, and for most organs in general.[25] For lung donors, however, it may be preferable to administer less intravenous fluid (to achieve a lower CVP of 4-6 mmHg). Observational studies suggest that restricting fluid administration may improve lung transplantation rates, possibly at the expense of other organs.[25, 26] In a recent multicentre RCT, the MOnIToR study, investigators randomized 556 DND adults from 8 OPO in the US to protocolized or usual fluid therapy.[27] In the protocolized arm, a non-invasive monitor (LiDCO) was connected to the patient's arterial cannula, and pulse pressure variation was measured to guide fluid therapy based on an algorithm. Both groups were similar at baseline and the protocolized care group received significantly more fluid compared to the usual care group (1229.10 vs 986.18 p = 0.037). The authors found no difference in the primary outcome: the mean number of organs transplanted per donor with protocolized care 3.39 [95%CI 3.14-3.63] vs 3.29 [95%CI 3.04-3.54] with usual care. Twelve-month recipient survival was similar between groups (Hazard Ratio [HR]=0.97 [95%CI 0.66-1.42], p = 0.86). The projected sample size was 960 DND donors. The trial, launched in 2009, was terminated three years later, with only 59% of the enrolment completed, due to a lack of funding.

5.1.3 Vasopressor Therapy

Vasopressin is currently recommended as the first line vasopressor agent for hemodynamic stability, with norepinephrine, phenylephrine or epinephrine

reserved for refractory hypotension.[28] Evidence to support this recommendation is extremely limited and the only vasopressors studied to date are vasopressin and epinephrine.[29] In 1 centre, 25 DND donors were randomized to epinephrine vs vasopressin plus epinephrine, and these agents were titrated to achieve a mean arterial pressure (MAP) >100 mmHg.[30] The authors found significantly more cardiac arrests in the epinephrine group compared to the epinephrine/vasopressin group (Relative Risk [RR]=5 [95%CI 1.45-17.27], p<0.005). However, the sample size was small, randomization was not concealed, the groups were not comparable at baseline and were managed for more than four days after death. This is a longer period of management than what we usually do in Canada. Moreover, achieving a MAP of 100 mmHg in our deceased donors does not represent usual care in Canada. Taken together, these factors limit the strength of inferences that can be drawn from this trial and bring into question the relevance to practice in Canada.

5.1.4 Enteral Nutrition

Maintaining enteral nutrition in organ donors may, in theory, improve the quality of organs. After cerebral herniation, the increase in catecholamine levels can deplete glycogen reserves, thus impairing the capacity of organs to tolerate an ischemic episode following withdrawal of life support in the DCD setting.[31] This can result in a higher incidence of ischemia-reperfusion injury, the principal mechanism of graft dysfunction or failure.[32] Enteral nutrition, through immunomodulating properties, may alter the cascade of inflammation.[31] Despite

this theory, current trial evidence from randomized trials is inadequate to support enteral nutrition. One RCT allocated 36 DND donors to either enteral nutrition (containing omega-3, glutamine, plus antioxidant) or fasting. The authors found no difference between groups with regard to energy expenditure, the number of organs recovered and graft function at six months.

5.2 Organ Donation Specific Therapies

5.2.1 Hormone Replacement Therapy

One of the most widely researched topics in donor management is hormone replacement therapy, including corticosteroids (11 RCTs; ~1000 donors; no clear benefit)[33], thyroid hormone (8 RCTs; 366 donors; no clear benefit)[34, 35], and vasopressin (2 RCTs; 200 donors; no clear benefit).[35] Combination therapy with all three hormones is currently recommended for hemodynamically unstable potential organ donors or for patients with a cardiac ejection fraction less than 40%.[28] Moreover, corticosteroids are specifically recommended for potential lung donors.[28] This recommendation based on retrospectives studies (2 studies; ~251+118) studies, demonstrated an association between corticosteroid and lung recovery (Odds Ratio [OR]=3.0, 95%CI [1.9-4.9], $p<0.001$[36], OR=5.3, 95%CI [1.49-18.9], $p<0.01$[37]) These therapies are routinely administered to potential organ donors at most Canadian centres despite a lack of supporting data. However, the RCTs are generally limited by small sample sizes, lack of concealment, lack of blinding, and important imbalances baseline characteristics between groups. Moreover, there is variability in the perceived indications, timing

of initiation, dosage and the mode of administration [bolus vs infusion].

5.2.2 Therapeutic Hypothermia

Targeted temperature hypothermia is a recognized intervention to protect neurologic function in patients following cardiac arrest.[38, 39] Until recently, hypothermia in a context of organ donation was limited to organ preservation strategies.[40] Proposed mechanisms are numerous and include reduction in cell metabolism and reduction of free-radical production.[41]

In a recent published RCT, Niemann et al. randomized 394 adult donors to undergo either hypothermia (34-35ºC) or normothermia (36.5-37.5ºC) after determination of death by neurological criteria and up to the time of organ recovery.[42] Baseline characteristics were similar between groups. The administration of mild hypothermia resulted in a significant reduction in the rate of delayed graft function in the kidney recipients (OR=0.62, [95%CI 0.43-0.92], p=0.02). The effect was greatest among recipients of expanded-criteria donors (donors aged ≥ 60 years old or > 50 years old with at least two of the following conditions: hypertension, serum creatinine > 1.5 mg/dl or cause of death from cerebrovascular accident) (adjusted OR=0.31, [95%CI 0.15-0.68], p=0.003). It is important to note that this trial was stopped early after the interim analysis demonstrated the efficacy of hypothermia, and the primary outcome was analysed in a modified intention to treat (per-protocol analysis). Irrespectively, these results raise important future research questions related to the field of organ donor management.

5.2.3 Heparin

Current North American guidelines recommend administering the pharmacologic anticoagulant heparin prior to withdrawing life support to, purportedly, improve graft function within transplant recipients.[43, 44] Anecdotally, many Canadian transplant surgeons decline organs unless the donor has received a large dose (30,000-40,000 units) of intravenous heparin prior to withdrawing life support. Clinical research on this topic is limited to 9 retrospective cohort studies (~2000 kidney donors) with no comparator groups.[45-53] While ethical concerns exist pertaining to heparin administration in patients who have suffered a neurologic event neither increased size of cerebral hemorrhage nor other bleeding complications have been reported in these studies. Meanwhile, countries that lead the world in organ donation after circulatory death (i.e., Spain, Netherlands) do not administer heparin therapy until death.[54] In Canada, ICU physicians encounter a real or perceived ethical conflict in administering heparin to a live patient who cannot benefit from its administration and may sustain a death-hastening bleed, facilitating organ donation, as a result of its administration There are no published data about how these decisions impact organ procurement rates.

5.2.4 Pharmacologic Preconditioning

Preconditioning refers to the initiation, by pharmacological or technical intervention, of ischemia and reperfusion for a short period of time before exposure to prolonged ischemia and reperfusion).[55] Studies measuring the

effect of pharmacological and ischemic preconditioning are numerous.[34] However, most are observational or monocentric RCT. In a multicentre RCT conducted in 60 European centres (N=264), Schnuelle and colleagues studied the effect of dopamine on kidney transplants.[56] Two hundred and sixty-four DND donors were randomly allocated to receive a low dose infusion of dopamine (4 ug/kg/min) or a placebo immediately after a neurological determination of death and up to organ recovery. Groups were similar at baseline with the exception of a statistically significant but not clinically significant higher urine output in the 24 hours preceding surgery in the dopamine group. Dialysis was significantly reduced in kidney recipients from donors allocated in the dopamine group compared to the placebo group (RR=0.86, [95%CI 0.76-0.96], p=0.01). This study showed the benefit of pharmacological intervention administered to donors with an impact on organ function in recipients.

5.3 Donor Management Goals

Compliance with clinical guidelines is an important determinant of the number of organs donated. This fact is supported by a single retrospective cohort study involving 40 patients[57] and three prospective cohort studies including 1453 patients[58-60] suggesting that optimization of oxygenation, cardiac function, volume status and glycemic control according to pre-specified "donor management goals" is associated with an increase in the number of organs recovered and transplanted. These studies consistently showed a significant increase in the number of organs recovered per patient (OR=4.39, [95%CI 2.49-

7.73], p<0.001;[57] OR=1.90, [95%CI 1.35-2.68], p<0.01;[59] OR=2.34, [95%CI 1.43-3.84], p=0.02[60]), and a significant decrease in kidney graft dysfunction (OR=0.49, [95%CI 0.28-0.85], p=0.012).[60]

6. Ongoing Research

There is little ongoing research on organ donor management. We provide a summary of the current research registered at Clinicaltrial.gov, the ISRCTN registry or the WHO ICTRP (Table 2). In combination with section 5, this demonstrates numerous knowledge gaps in organ donor care that must be addressed.

7. Summary

In summary, this first chapter has highlighted the clinical importance of organ donation in Canada. Moreover, it has described the organizational structure of organ donation in Canada. The paucity of research on organ donor care in various areas has been demonstrated. There are also several controversial topics such as optimal fluid therapy, combined hormonotherapy and heparin administration. Rigorous studies are needed to resolve these controversies, which will also enhance the donor pool. Therefore, there are scientific, economic and ethical reasons to answer research questions related to these areas.

Overall, this first chapter supports the foundation of a national research program on critical care of potential organ donors.

CHAPTER 2: Study Design DONATE-Pilot

1. Introduction

After summarizing the current state of knowledge on organ donor care and highlighting the limitations of current clinical research to inform practice, we are left with many important, unresolved clinical research questions related to strategies to optimize organ donor management and recipient outcome. Before addressing these research questions, we must better understand our current clinical practices in organ donor care. Accordingly, a national prospective cohort study is an appropriate next step. This chapter describes the rationale for a prospective cohort study and reports the design of the pilot phase for a national prospective study called DONATE, launched on September 1st, 2015.

2. Study Rationale

This section justifies the scientific need and the design, as well as highlights the timeliness of a pilot study followed by a national prospective observational study on deceased donor management.

2.1 Limitations of Clinical Research to Inform Best Practices

The previous chapter (Section 5, Current State of Knowledge) summarized the clinical research that has informed current clinical practice guidelines for organ donation.[6, 43] The key finding of evidence base, is the paucity of research conducted in this field to inform the clinical care of donors and outcomes of recipients. Limitations in the number of studies, the scope, and the quality of this body of evidence warrant a concerted national effort to advance knowledge on

the medical management of organ donors. To this end, international health organizations,[6] federal government publications,[61] medical editorialists,[7, 62] and national newspapers[8] have all called for more clinical research in this field. Even the WHO has highlighted the need for research to advance the management of deceased organ donors to improve organ supply.[6] In 2012, the WHO joined forces with CBS, to establish a research agenda addressing the shortfall in organ supply. The DONATE study is a direct answer to this call for additional research.

2.2 Justifying a Prospective Observational Study Design

While RCTs are ideal for such comparative studies, their expense cannot be justified before developing a research framework including: recruiting hospitals to participate, developing adequate research infrastructure, collating first-hand knowledge of current clinical practices at these hospitals, and establishing feasible methods for measuring clinically important outcomes among transplant recipients. These steps will be completed in the context of a prospective observational study, thus laying the foundation for subsequent RCTs.

Although retrospective studies are less costly than prospective studies, data collected currently at the provincial level are insufficient (in breadth) and of questionable accuracy to address the research question posed. While these data are satisfactory for reporting trends in donation and transplantation activity across the province, OPO data do not capture specific information needed to address the current objective. For example, this includes data pertaining to the timing,

frequency and dose of commonly used medications; data characterizing the frequency and duration of periodic episodes of hemodynamic instability and hypoxemia; data on consented donors who did not become actual organ donors; and data pertaining to organ function in transplant recipients. Moreover, the suitability of existing provincial data to support clinical research is also unclear – relying at times upon information collected by non-clinical personnel, remote in both time and place.

While a few OPOs have implemented new standards for data quality, their new database has not been used for clinical research purposes, nor has it been evaluated for this purpose. This observational study will evaluate the robustness of OPO data for supporting future clinical research. To the extent that we can capitalize upon and improve upon the quality and quantity of provincial data currently being collected, we will the efficiency of future research and contribute to the goals of OPOs.

2.3 Need for a Pilot Observational Study

Background work has revealed various challenges in carrying out prospective observational studies in this field, including the need for the recruitment of multiple study sites (e.g., low number of organ donors annually); variable practices across centres; independant databases used by OPOs; the lack of an existing databases to describe donor management; the limited ability to link organ donor data to recipient outcomes; and various ethical considerations related to study design and implementation. Thus, prior to embarking on a large,

multicentre observational study at a provincial or national level, we need to (i) better understand Hospital practice patterns, (ii) acquire an in-depth knowledge of the content of the various available databases, and (iii) foster regional and national collaborative networks.

3. Study Objectives

3.1 Pilot Study Feasibility Objectives

Specific objectives for this pilot study include:

(i) Refining data collection procedures for adult intensive care units (ICU) and estimating the time required for data collection on donors;

(ii) Developing efficient links to post-transplantation data;

(iii) Sharing data as it accrues with clinicians and clinical researchers at major organ donation centres and transplant programs in an effort to develop national collaboration.

3.2 Main Study Objectives

The overarching objective of the DONATE study is to observe the medical management of deceased organ donors across Canada. There are four general objectives:

(i) Knowledge translation- To describe the medical management of organ donors in Canada. A report of current practices (including consistent practices as well as variability) will help clinicians (by providing a benchmark for care and offering practice alternatives), educators (by revealing knowledge gaps) and policy

makers (by providing accurate provincial data).

(ii) Quality assurance- To assess the accuracy and completeness of organ donor data collected by the TGLN, Ontario's organ procurement organization. The TGLN recently revised their data program to include more data and to enhance accuracy and completeness. However, data are collected inconsistently and retrospectively by non-clinical staff.

(iii) Advancing research- Follow-up of organ function in transplant recipients provides the most clinically important outcome for studies on organ donor management. Current OPO databases do not link donor and recipient data in this manner, which limits the potential for multicentre research.

(iv) Evaluation of medical interventions- Follow-up on management strategies for organ donors that have been validated in RCTs (e.g., lung protective ventilation, therapeutic hypothermia) or that are perceived to improve transplant rates (e.g., heparin administration, steroid administration) provides information on the effectiveness and safety of these interventions. This study objective is in line with what we consider a post-marketing surveillance study (phase IV) in drug development. Some interventions are specific to DND. Others are specific to donor management that precedes imminent death by circulatory criteria (i.e., after the withdrawal of life support; DCD).

4. Research Question

4.1 DONATE-Pilot

4.1.1 Research Question DONATE-Pilot

"Is it feasible to perform a national observational study of deceased donors in approximately 25 organ donation centres in Canada to investigate current practices for medically managing organ donors and determining organ suitability?"

4.1.2 PICOT Question DONATE-Pilot

Population: Deceased organ donors (DND and DCD)

Intervention: Detailed data collection

Control: None

Outcome: For the pilot study, the main outcomes are feasibility (used of a waived research consent model, refining of study procedures linking organ donor data collection with transplant recipient data, collecting data on transplant recipient)

Type of study: Prospective observational study

4.2 DONATE-Main Study

4.2.1 Research Question DONATE-Main Study

"For approximately 25 organ donation centres in Canada, what are the current practices for medically managing organ donors and determining organ suitability?"

4.2.2 PICOT Question DONATE-Main Study

Population: Deceased organ donors (DND and DCD)

Intervention: Detailed data collection

Control: None

Outcome: Number of organs recovered per donor, transplant graft function within one week and three months post-transplantation.

Type of study: Prospective observational study

5. Methods

5.1 Study Design

This is a one-year, prospective observational cohort study evaluating the management of potential organ donors in four ICUs in Canada. Consented organ donors are being identified prospectively and data collection is being conducted, both prospectively and retrospectively, as described below.

5.2 Pilot Study Setting

This pilot study is to be conducted in the adult medical-surgical ICUs in Hamilton (Juravinski, Hamilton General, St-Joseph's Healthcare), London (University Hospital, Victoria Hospital), Montreal (Hopital Sacre Cœur) and Sherbrooke (Centre Hospitalier Universitaire de Sherbrooke [CHUS]- Fleurimont and Hotel Dieu). These four centres will provide information on the feasibility of the main study because (i) they all have our population of interest, (ii) they have different rates of organ donors, (iii) they are part of the two largest OPOs, (iv)

they have different type of research infrastructure and (v) they will adequately address the study's feasibility outcomes.

5.3 Eligibility Criteria

Adults for whom TGLN or TQ have consent for deceased organ donation from a legal substitute decision maker are eligible for this study. This includes adults, in settings of DND and DCD. We limited the study to adult patients recognizing that many aspects of the medical management of pediatric organ donors are very unique to this group and donation rates are extremely small.

5.4 Screening

One of four screening approaches (A-D), described below, are being used to minimize selection bias, ensure a representative sample of the larger population of deceased donors in Canada, obtain sufficient statistical power and to ensure that all consented organ donors are enrolled in these four centres.

5.4.1 Approach A: OPO → Methods Centre → Research Coordinator

This approach is the most common method for Ontario sites. The provincial OPO, TGLN, has set up an automatic notification system whereby a study coordinator at the DONATE methods centre (MC) at McMaster University receives an e-mail notification once consent for organ donation has been obtained for a potential donor. Once received, the MC sends the notification to the corresponding site's research coordinator (RC) who will begin data collection. It is possible that the local RC may become aware of potential donors prior to this automatic notification (Approaches B-D).

5.4.2 Approach B: OPO → Research Coordinator → Methods Centre

This approach is the most common method for Quebec sites. The provincial OPO, TQ, has personnel called "infirmieres ressources" (IR) very similar to the role of the OPO coordinator at TGLN. The IR notify local RCs of any newly consented organ donors at participating sites. In Ontario, OPO coordinators may notify RC of potential donors before consent has been obtained and before the automatic notification is sent. Additionally, it is possible that the RC or ICU staff become aware of potential donors before the OPO coordinators or the MC, while working day-to-day in critical care areas (Approaches C&D).

5.4.3 Approach C: Research Coordinator → Methods Centre/OPO

When in the ICU, RCs are screening daily for any potential donors at their site. Thus, it is possible that RCs become aware of a potential organ donor before MC or OPO staff. If this happens, the OPOs will also be contacted according to standard hospital and provincial regulations.

5.4.4 Approach D: ICU Staff → Research Coordinator → Methods Centre/OPO

In some cases, it is possible that ICU staff inform local RCs and/or local OPO coordinators of potential organ donors that arrive in the ICU. If the OPO coordinator has not already been notified of this patient, local RCs should notify the correct personnel. It is thus important to inform local personnel of DONATE,

as mentioned previously, to aid in this method of screening.

5.5 Enrolment

The central research coordinator (CRC) records the OPO referral number and assigns each participant a study identification number, and registers the patient into the clinical research database.

5.6 Data Sources

Clinical data relevant to this study are very similar to data collected by OPOs; however, the study data being collected is more detailed and includes more frequent measurements. For instance, while the OPO records administration of a drug, the research team also records the time, dose, and frequency. Whereas an OPO may record a single blood creatinine level, the research team records twice-daily creatinine levels to capture physiologic trends. RCs at participating centres collate study data from multiples sources including direct observation, hospital charts, hospital and regional electronic records, Organ Donor (OD) Coordinators and the OPO database. However, none of these data require interaction with families.

OPO procedures to obtain organ recipient data from transplant programs do not currently exist and are under development by our research team.

5.7 Time Frame for Data Collection

Since patients are enrolled following consent for organ donation, some data in the pilot study are being collected prospectively, while data preceding enrolment are being collected retrospectively (Figure 4). Retrospective data

includes: past medical history and chronic illnesses, details related to the illness necessitating hospital admission, data related to cardiorespiratory stability, and key aspects of care in the ICU up to the time of consent. To the extent that it is possible to collect the following data prospectively, RCs do so up to and including the time of surgery for organ recovery: cardiopulmonary monitoring, organ donor interventions and assessments of organ suitability. For those who are ultimately unable to donate, RCs collect data up to the time this determination is made and document the reason for this outcome. Finally, methods centre staff collect data on organ function among transplant recipients from transplant clinics within the first week and at three months post-transplantation.

5.8 Data Types

5.8.1 Organ Donation After Determination of Death by Neurological Criteria

For DND donors, we record the following data: time of death by neurological criteria, the use of ancillary tests, and any complications (e.g., low blood pressure, oxygen desaturation) that occur during the declaration.

5.8.2 Organ Donation After Determination of Death by Circulatory Criteria

For DCD donors, the following data are recorded: the unit (emergency room, ICU, operating room, etc.) where life-sustaining therapy is withdrawn, the use of lung recruitment maneuvers prior to transfer to this area and all medication administration.

5.8.3 Study Subject Baseline Characteristics

For all study participants, we collect the following are collected:

demographic data (age, sex, race), *administrative data* (date of injury, hospital and admission, and initiation of mechanical ventilation)*, diagnostic data* (type of neurological injury), and *premorbid clinical data* (past medical history, chronic and acute comorbidities).

5.8.4 Clinical Management of the Organ Donor.

Moreover, we record information regarding daily care during the ICU stay, including *cardiopulmonary monitoring technologies* (arterial line, central line, pulmonary artery catheter, echocardiography), *general advanced and basic life sustaining therapies* (mechanical ventilation, vasopressor and/or inotrope administration, cardiopulmonary resuscitation, renal replacement therapy, fluid resuscitation volume, enteral nutrition) and *general prophylactic interventions* (gastroprophylaxis, thromboprophylaxis, pneumonia prophylaxis, glycemic control).

Importantly, data collection will include *organ-donation specific therapies* (corticosteroids, thyroxine, vasopressin infusions, DDAVP doses, transfusions, therapeutic heparin, antimicrobial therapy).

All aspects of the *organ suitability assessments* performed before organ recovery surgery are recorded: bloodwork, chest x-ray, bronchoscopy, body imaging, echocardiography, coronary angiography, microbiological cultures, as well as reasons underlying any decision to reject organs prior to or during surgery.

5.8.5 Clinical Outcomes in ICU

Any event considered a *clinical complication* while in ICU must be reported, such as oxygen desaturation, hemodynamic instability (hypotension or hypertension), arrhythmias (requiring chemical or electrical cardioversion), diabetes insipidus (urine output > 4 ml/kg with serum Na >145mmol/L and serum osmolarity >300 mosM), unexpected cardiocirculatory arrest, active bleeding (requiring blood transfusion), hypothermia or hyperthermia (T<36 or T>38.5 degree Celsius) and the corresponding interventions.

5.8.6 Outcomes Following Organ Recovery

Data related to *organ viability* including warm ischemic time, cold ischemic time, method of organ preservation are being collected. Finally, information will be sought on the *functional status of the transplanted organs* within the first month or at the time of a recipient's death (normal function, delayed graft function, graft failure).

5.9 Development of Case Report Forms (CRFs) and a Data Operations Manual

For the pilot study, case report forms (CRFs) (Appendix 1) and an operations manual (Appendix 2) for the study that include explicit definitions and procedures for each data element were developed. For data similar to those recorded by OPOs, uniform definitions were used where possible.

An expert panel assessed the CRFs for face validity and content validity, and included a donation physician specialist, an organ donation coordinator, an

ICU clinical research coordinator and two coinvestigators trained in the methodology. Then, the database manager and the data analyst reviewed the CRFs and provided input prior to finalizing the CRFs.

During the ongoing pilot study, these CRF and operation manual will be refined based on feedback from our participating sites.

5.10 Data Management and Validation

The study database was programmed prior to launching the pilot study. Clinical research staff record data on paper or electronic CRFs. Encrypted transmission to the Methods Centre is enabled by fax or internet using the DataFax System (DFNet). Automated data verification built into the DataFax system alerts local staff to the presence of potential errors (extreme, non-sensical or missing values). At the Methods Centre, administrative and clinical research staff validate all incoming data within seven days of receipt, for accuracy and completeness, generating data queries for research coordinators to resolve before a CRF is designated as "complete".

5.11 Study Outcome and Outcome Measurements

5.11.1 Primary Outcome

The primary outcome for the DONATE-pilot study is feasibility judged by four outcomes:

(i) Use of a waived consent model- A successful waived consent justification will be defined as getting a waived model of consent for research on donors and corresponding recipients for all participating sites in the pilot study.

(ii) Refine data collection procedures for adult intensive care units (ICU)- This outcome does not lead in itself to a formal assessment. However, reaching a consensus from our four participating sites regarding an acceptable time required to complete the CRF, ease of completing the CRF and the absence of redundancy.

(iii) Develop efficient links to post-transplantation data- An efficient link to post transplantation data will be defined as the capacity to identify the transplant program and recipients of the organs from a donor enrolled in the study for at least 80% of the organs recovered.

(iv) Recipients data collection- Our capacity to obtain each item related to a recipient (year of birth, sex, Panel Reactive Antigen [PRA], date and time of transplantation, ordinal scale) will be measured. Obtaining at least 70% of the data for each item will be judged sufficient to proceed to the main study.

5.11.2 Secondary Outcome

The secondary outcome of the DONATE-pilot study is the primary outcome of the main study:

(i) Practice patterns - Description of various interventions and approaches in the management of deceased donors (e.g., use of an ancillary test to confirm brain death, lung protective ventilation, hormone therapy).

5.11.3 Tertiary Outcomes

The tertiary outcomes of the pilot study are the secondary outcomes of the main study. They are relevant to the four study objectives: knowledge translation,

quality assurance, research feasiblity and therapy evaluation.

Key outcomes relevant to the **knowledge translation** objectives include:

(i) Adherence to discrete recommendations of the Canadian Guidelines for donor management [28, 43] including, but not limited to, the administration of systemic corticosteroids, intravenous thyroid hormone, and glycemic control. The Steering Committee will pre-specify an explicit definition of "adherence" for each of the recommendations. For each patient, a measure of adherence as the proportion of criteria fulfilled divided by the total number of criteria evaluated will be recorded.

Key outcomes related to **data quality assurance** include measures of:

(ii) Accuracy for data points between research staff and OD coordinators.

(iii) Agreement on data points between research staff and OD Coordinators.

Accuracy and *agreement* will be tested for the following data types:

- Primary and secondary clinical outcomes related to therapy evaluation (including, but not limited to, those listed above, since these outcomes will apply to future research);
- Key determinants of clinical outcomes (to be prespecified by study investigators);
- Data at risk, i.e., data for which we expect important challenges in accuracy (e.g., use of lung protective ventilation; worst episodes of hypotension for each patient).

Key outcome measures related to **evaluating the feasibility of future RCTs**:

(iv) Ability to obtain data from the generic outcome scale. This tool is an ordinal scale for which transplant teams have to characterize graft function according to the following categories: normal graft function, abnormal graft function, graft failure (relisted for transplant), or death of the transplant recipient. An acceptable rate for moving forward with RCTs is to obtain an 80% response rate to this question (understanding that we would continue to work hard to achieve a 100% data capture).

Key outcomes relevant to the **therapy evaluation** objectives include:

(v) Number of organs recovered. Each kidney recovered will count as one organ, while each *pair* of lungs is counted as one organ (since kidneys are transplanted singly, and lungs are generally transplanted as a pair).

(vi) Number of organ transplanted (since not all organs recovered are ultimately transplanted, based on ABO or HLA mismatching, size, or idiosyncratic limits to the consent for organ donation).

(vii) Organ transplant function at one week and three months, defined on an ordinal scale as: normal graft function, abnormal graft function, graft failure (relisted for transplant), or death of transplant recipient. We recognized that different transplant programs define the organ function differently; we will record their classification and use program-specific definitions, to unify across programs where possible).

6. Analyses

Baseline patient data will be analyzed using descriptive statistics reporting means (and standard deviation), medians (and first quartile and third quartile) or proportions, as appropriate. Missing data will be addressed using the method described by Kenward.[63] All tests will be 2-sided with a nominal p value of 0.05. The statistical analysis plan will be finalized before commencing the analysis. We will follow the STROBE Statement in reporting our study findings.[64]

6.1 Primary Outcome Analysis

The analyses of the pilot study are descriptive and does not need further description.

6.2 Secondary Outcome Analyses

For the analyses related to knowledge translation, we will summarize all data using descriptive statistics including means, medians or proportions, as appropriate. The unadjusted proportion of all patients who receive specific interventions, such as ancillary testing, various components of a lung protective ventilation strategy, or hormone therapies will be analyzed. A hierarchical model (to account for clustering within centres, and deceased donors) to assess for determinants of specific interventions will be used (i.e; donor's age, DCD vs DND, volume of donors at a given centre, organs considered for recovery). The rate of adherence to other discrete components of the national guidelines will be analyzed similarly.

6.3 Tertiary Outcome Analyses

6.3.1 Quality Assurance Analyses

The accuracy for each prespecified variable will be analysed as the proportion with complete accuracy (with adjustment for clustering of measures within patients, or hospitals). A measure of agreement using the weighted kappa statistic test, where appropriate, will also be analyzed.

6.3.2 Feasibility Outcomes

The primary focus will be descriptive. The percentage of organs transplanted in Canada for which we are able to access recipient data will be reported. When these data are not available, the reasons for missing data, where available, will be reported.

6.3.3 Therapy Evaluation Analyses

The number of organs per donor recovered will be approached as "count" data. The impact of key variables (i.e., presence or absence of lung protective ventilation) will be assessed first with unadjusted comparisons. Then, we will adjust for other potential prognostic factors (e.g., age,[24] DCD vs DND,[60] lung protective ventilation,[65] corticosteroid and thyroid replacement therapy,[33, 34] donor physiologic goals,[59] and donor management time[66]). To conduct these analyses, a count regression model that can accommodate multi-level data (to account for clustering) – namely, a Poisson regression or a negative binomial regression, will be used, as required. Regression coefficients with 95% confidence intervals will be reported.

We will use the same approach to analyze the number of organs transplanted per donor. To analyze graft function at one week and at three months, an ordinal variable, a Cox regression model adjusted for prognostic factors (including the list above, with the addition of cold ischemic time,[43, 67] warm ischemic time[43, 67] and method of organ preservation[68, 69]) will be used.

7. Sample Size

This is a pilot observational study and does not lend itself to the usual sample size calculations. The goals to determine the sample size for this study are as follows: (i) to include as many organ donors as possible (for accuracy in descriptive analyses and regression models) from high and medium volume centres, and (ii) to collect current (one-year) data (for maximal relevance). Based on 5 year TGLN data, there were on average 64 consented organ donors per year, in total, at the two Ontario sites. In their first year (2013) of operation as a pilot organ recovery program in Montreal, Sacre-Coeur Hospital had 55 organ donors and the University of Sherbrooke Hospital Centre had 10 organs donors in the same year. Therefore, we expect that approximately 135 consented organ donors will be enrolled from four sites.

For the knowledge translation objectives, assuming that 70% of patients receive a particular intervention (i.e., corticosteroids), a sample of 135 donors will allow the investigators to measure this proportion with a margin of error of ~7% For regressions analyses assessing predictors of using different interventions, if

we follow a rule of thumb that requires at least 10 patients per predictor, we could include up to 10 variables in the regression models. Finally, 135 participants will afford a power of over 80% to detect a difference of 1 in the mean organ recovery rate observed between 2 interventions (e.g., lung protective ventilation vs conventional ventilation), assuming a baseline rate of 3.63 (sd 1.5) organs recovered per donor, and a nominal p-value of 0.05. In summary, this study will have sufficient power to achieve our various feasibility objectives and corresponding analyses.

8. Efforts to Minimize Bias

To minimize selection bias and ensure a representative sample, we aim to enroll consecutive eligible patients at all centres. To this end, we propose to use a waived model of consent and a systematic notification process to enhance the likelihood of consecutive patient enrolment.

A detailed data operations manual was developed to standardize data abstraction. This manual will be updated continuously. To ensure data accuracy, trained research personnel will collect data using multiple data sources including direct observation, review of medical records, as well as OPO and transplant databases. This manual was developed specifically for RCs and will provide definitions for technical terms to standardize data collection procedures. To limit the potential for recall bias, the investigators created a list of time-sensitive data

that RCs need to observe. Also, we recommended to limit retrospective data collection to one day prior to admission to the ICU.

Confounders will be limited by analysis of our results with a regression model accounting for key prognostic factors influencing clinical outcomes. All analyses will follow pre-specified plans and will proceed with the oversight of a faculty biostatistician at the Methods Centre.

9. Ethics

The study will not begin without Research Ethics Board approval at participating centres. Patient confidentiality will be maintained through the use of anonymous study identification numbers. Given the observational nature of the study, minimal risk to participants and their families steps to ensure individual privacy and rapid de-identification of data, and the important biases that obtaining consent might introduce to the results, it is believed that a waiver of consent is necessary and appropriate, in accordance with the Second Tri-Council Policy Statement (TCPS2).

In the unlikely situation that families consent to organ donation but decline data use for research purposes, despite waived consent, their reasons will be clearly documented and honoured.

The third chapter of this thesis describes the rationale for a waived model of consent for donors and recipients across Canada.

10. Trial Administration

The Methods Centre (CLARITY; McMaster University) is responsible for the overall management of this study, as well as providing guidance and support to participating RCs and ICUs.

10.1 Steering Committee

Drs. F. D'Aragon and M. Meade are the study's Co-Principal Investigators. Both are intensive care consultants and Dr. Meade, recognized twice by the CIHR as a clinical research mentor, is supervising Dr. D'Aragon in his graduate training in Health Research Methodology at McMaster University.

Other Steering Committee members include S. Dhanani, S. Hanna, and F. Lamontagne. Among this group are experts in organ donation (SD is the Medical Officer of Donation at TGLN), critical care (FDA, FL, and MM, are adult intensive care consultants; SD is a pediatric intensive care consultant), research methodology (MM is a senior investigator and executive member of the CCCTG, which has led multiple CIHR-funded international trials; FL and SD are also CCCTG members with experience in leading multicentre trials; SH is Assistant Dean of the McMaster Health Research Methodology [HRM] Program and a biostatistician).

The Steering Committee will meet by conference call three times and as needed during the study. Performance reports summarizing the patients enrolled, data accuracy and completeness will be reviewed. The Steering Committee will also address the need for any protocol modifications, adherence to study

timelines, and any other necessary methodologic or practical decisions.

10.2 Observational Study Monitoring Board

The OSMB is an independent group monitoring the overall conduct of a study. In the United States, investigators of observational studies must consider having a study monitoring board They can make recommendations with respect to (i) the performance of individual centres, (ii) issues related to participant safety, (iii) adequacy of the study's progress, (iv) issues related to the participant burden, (v) impact of the proposed sub-study and (vi) overall scientific directions of the study.[70] In the DONATE-pilot study, there is no OSMB. This is a minimal risk study with few sites. The safety oversight is conducted by the principal investigators and research team in collaboration with local REB.

11. Knowledge Translation

We will use both "integrated KT" and "end-of-grant KT" strategies to dessiminate study results.

11.1 Integrated knowledge translation

The integrated KT, which has already started, involves working with provincial and national stakeholder groups. The TGLN and TQ are provincial organ procurement organizations that represent more than 65% of all organ donors in Canada. The CBS oversees all organ donations across Canada. All three organizations have been involved since the inception of this project.

Refined protocols were presented to the OPOs' executive (TGLN and TQ)

and OD Coordinators. Two months prior to launching the study, the protocol was shared with the local donation physician specialists, intensive care physicians and nursing staff of all participating sites.

During the recruitment period, handouts will be distributed to the OPOs' provincial resource centres. Each site will be updated with quarterly bulletins describing: (i) their current performance (e.g., number of donors, number of organs recovered, graft status), and (ii) the overall progress of the study. In addition, study progress will be reviewed during presentation at scientific meetings of the CCCTG and CNTRP.

11.2 End of Grant Knowledge Translation

Once the study has been completed, the research team will collaborate with local donation physician specialists to present the findings at each of the four sites, to (i) share the overall results, (ii) compare practices and outcomes across centres, (iii) share current recommendations on donor management, and (iv) reinforce the role of local hospital champions (donation physician specialists) and OPOs. In addition, each participating site will be provided with a written executive summary of their practices and outcomes of care, benchmarked against other institutions and national guidelines. Similar feedback will be provided to OPOs and transplant programs within the province. Study results will be presented at scientific meetings of the CCCTG and the CNTRP. Findings will also be presented at the Critical Care Canada Forum (Toronto) and published in peer-reviewed journals.

11.3 Patient and Family Engagement

Increasingly, patients and advocates can become research partners in different steps of a research project.[71, 72] Their engagement, although challenging, can enhance the quality and impact of studies. In the DONATE-pilot study, we have not planned to include deceased donor's relatives or recipients. However, including them as part of the research team for the main study could be helpful when we address the waived consent model for donors or recipients.

12. Relevance and Future Directions

This study will facilitate future funding applications to peer-reviewed funding bodies (CIHR, CNTRP, CBS) to conduct the same detailed observational study on a provincial and national level. Published, detailed descriptions of current practice patterns at participating sites will facilitate clinical care by enabling clinicians to compare their practices to others in Canada. Moreover, publishing this work will support future clinical research by informing investigator teams about research priorities, usual care protocols, and areas for knowledge translation initiatives.

In summary, the DONATE Pilot Study is the first step of a provincial or national prospective observational study on organ donation practices and will create the foundation for a national research program on organ donation.

CHAPTER 3: DONATE Research Consent Model-A Justification for a Waiver of Research Consent

1. Introduction

The persistent gap between the supply and demand for organs has led to growing interest in maximizing the number of organs recovered and their quality. Accordingly, there is a growing interest in conducting primary research in the field of organ donation. However, research on deceased organ donation is complicated by unusual aspects, which generate logistical, regulatory and ethical challenges less frequently encountered in other areas of research. These challenges are present regardless of study design: observational or interventional study.

Informed consent to research is a major area of ethical debate in donor management research.[7] It is intended to promote patient autonomy and to protect patient from potential risk or harm without warning.[73, 74] Research on deceased donors generally implies (i) a low potential for harm after death, (ii) the absence of clarity on whether patients declared deceased by neurological criteria are considered human subjects or not, and (iii) unlike other research, studies on donor management intend to promote successful donation itself, which is consistent with the values, preferences and interests of those who become organ donors and potentially multiple transplant recipients.[75]

Beside these ethical arguments, research on donor management is made complicated by logistical challenges that are less frequently or never encountered in other research contexts. These challenges impact the manner in which clinical investigators and research personnel obtain/procure research consent. These

include, but are not limited to, (i) the involvement of multiple participants involved in the research study (study donor, donor's relatives and +/- numerous corresponding organ recipients),[76] (ii) the involvement of multiple sites (organ recovery centre and +/- numerous transplantation centres),[32, 77] (iii) the unknown identities of future recipients at the time of donor enrolment into a clinical study,[32, 75-77] (iv) the unpredictable nature of the timing of organ recovery/transplantation,[32, 75-77] and (v) the need to proceed quickly with transplant procedures.[76, 77] Therefore, some have argued that consent for research in organ donor care is impracticable and should be waived.[32, 75, 78]

However, there is variability in its application in Canada since an individual's consent to be an organ donor and/or to participate in a research study is based on provincial legal legislation.[79-81] For example, the province of Quebec, allow use of waived consent from individuals if a third "party" grant such authorization. This is an important distinguishing feature that is relevant to the conduct of observational research in Quebec. Because more than 30% of all deceased donors in Canada are from Quebec.[11]

For the DONATE pilot observational study, a waived model of research consent was developed, which takes into account the regulatory requirements in Quebec and the rest of Canada. This chapter summarizes a justification for a waiver of research consent for this minimal risk, observational study of the medical management of deceased organ donors in Quebec. The chapter is divided into two sections. The first section*, Guiding Principles*, summarizes the

relevant articles and principles of ethics, research ethics, research methodology, Quebec law, and precedents, and addresses these in the context of the proposed research. In the second section, *Research Consent for Specific Study Participants*, additional considerations are described that are relevant to each of the two groups of participants (deceased donors and recipients).

To develop the justification, we solicited legal advice from a lawyer with expertise in healthcare research, consulted two independent REB chairs and solicited advice from TQ's REB. After multiple discussions, we were able to submit a proposal to the REB that respects the legal aspects and research ethics principles. We obtained approval from Sherbrooke's REB to carry out the DONATE-pilot study. This authorization is extended to the other centres in Quebec. Therefore, our waived consent model has been accepted in all of our participating centres in Ontario and Quebec.

2. Guiding Principles

2.1 Ethical Principles

2.1.1 Respect for Autonomy

Study participants have a right to choose or to refuse the use of their personal health information for research purposes (respect for autonomy). Respect for autonomy is an important concern in addressing issues of research consent. It needs to be balanced with other equally important ethical principles that bear on the suitability of a waived consent model for the proposed research

study, which include beneficence, non-maleficence, justice and equity.[73]

2.1.2 Beneficence

According to the principle of Beneficence, a practitioner should act in the best interest of the patient.[73] Deceased donors who uphold the importance of organ donation to save lives would generally uphold the importance of rigorous clinical research aimed to develop the best standards of care to carry out organ donation and transplantation.

2.1.3 Non-maleficence

Non-maleficence means "first, do no harm". This principle applies to arguments against imposing research discussions on fragile persons (e.g., donor families and organ recipients) at particularly difficult times. Non-maleficence is the focus of section 4, below.

2.1.4 Justice

Justice concerns the distribution of scarce health resources, and the decision of which patients receives particular treatments.[73] The overarching aim of this study is to enhance the availability of cadaveric organs and their quality for the purpose of transplantation through better understanding of optimal care for organ donors within our national ICUs. Our collective and limited understanding of what constitutes optimal management of organ donors currently limits the availability of organs to patients who are in need of them.[4, 62]

2.1.5 Equity

Equity dictates that the same guiding principles should apply to

authorization for the use of personal health information for hospital quality improvement initiatives and for research initiatives. Quality improvement (QI) initiatives are local studies desgined to improve local health care practices; when conducted well, these projects amount to rigorous assessments that follow scientific principles, i.e., research in a single centre. Furthermore, if the majority of patients involved in a QI initiative are not expected to directly benefit from the knowledge to be gained from it or if additional risks or burdens are imposed to make the results of the QI initiative generalizable, it should be considered as a research study.[82]

Multicentre research studies differ in their potential breadth of influence, and frequently surpass QI initiatives in terms of scientific rigor. At the present time, various multicentre research initiatives in Quebec are carried out with a waiver of informed consent when they are presented and viewed as QI initiatives.

2.1.6 Summary

In summary, values of autonomy, beneficence, non-maleficence, justice and equity provide a framework for considering the ethical suitability of a waived consent model for observational research. There is a strong ethical argument supporting a waiver of informed consent for a national observational study of organ donor management.

2.2 Research Ethics

2.2.1 *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*

In 2001, Canada's three federal research agencies, the Canadian Institutes for Health Research (CIHR), the Natural Sciences and Engineering Research Council (NSERC), and the Social Sciences and Humanities Research Council (SSHRC), jointly developed the TCPS.[83] Endorsed by the Government of Canada, the mandate is to promote the ethical conduct of research involving human participants.

In accordance with this policy, the following requires an ethics review and Research Ethics Board (REB) approval before the research begins:

(i) Research involving living human participants

(ii) Research involving human biological materials, as well as human embryos, fetuses, fetal tissue, reproductive materials and stem cells. This applies to material derived from living and deceased individuals.

The TCPS defined human participants "*as those individuals whose data, or responses to interventions, stimuli or questions by the researcher are relevant to answering the research question"*.[16] Our research involves patients with catastrophic brain injury declared dead by neurological criteria and by cardiocirculatory criteria. Therefore, our proposal fulfills these requirements.

The TCPS (2nd edition) stipulates that a waiver of research consent is appropriate when:

(i) *The research involves no more than minimal risk to the participants*;

(ii) *The lack of the participant's consent is unlikely to adversely affect*

the welfare of the participant. The research poses a clear benefit to society;

(iii) It is impossible or impracticable to carry out the research and to answer the research question properly, given the research design, if the prior consent of the participant is required;

(iv) Whenever possible and appropriate, after participation, or at a later time during the study, participants will be debriefed and provided with additional pertinent information in accordance with Article 3.2.and 3.4, at which point they will have the opportunity to refuse consent in accordance with article 3.1;

(v) The research does not involve a therapeutic intervention, or other clinical or diagnostic interventions.

The Canada-DONATE study meets all of these requirements.

2.2.1.1 Benefit to Society

Every week, three Canadians die while waiting for an organ transplant.[84] Early observational studies have suggested the utility of donor management intervention to increase the number of organs recovered.[3, 26, 85, 86] Most transplants originate from patients who succumb to a tragic brain injury in the setting of an ICU.[10, 11, 16] One goal of the DONATE research program is to improve the health and quality of life of chronically ill persons registered on Canadian transplant waiting lists through clinical research of the highest possible quality, using Canadian knowledge translation strategies and Canadian clinical

trials. This research is likely to have a profound effect on a particularly vulnerable group of people.

2.2.1.2 Minimal Risk

There is no study intervention or alteration of clinical care as a result of this study. There is minimal risk of a privacy breach. To prevent privacy breaches, only essential personal identifiers are recorded: to the extent that it is possible, all personal health data are recorded in an anonymous (de-identified) manner. In addition, study data is encrypted during transfer to the experienced CLARITY Methods Centre at McMaster University, and study data are stored on a secure server at McMaster University and accessed from password-protected computers in locked offices. Moreover, specific participant groups will have minimal risk: (i) organ donors with brain death are not alive at the time that they are registered in the study, (ii) the vast majority of donors with a cardiocirculatory death will die within two days of registration in the study, and (iii) the organ recipients will be alive at the time of data collection (approximately one week and three months following organ transplantation); however, the data collected for these participants will be extremely limited.

2.2.1.3 Impracticability and Inappropriateness

Many researchers in donor management have confirmed the impracticability of getting informed consent.[7, 32, 77, 87] The Canada-DONATE study is no exception. The impracticability and inappropriateness of written informed research consent for each of the three groups of study participants will

be discussed in section 4, below.

2.3 Research Methodology – Bias in Registry Studies

Prior registry studies have established that excluding patients for lack of consent leads to biased study results.[88, 89] The goal of *Canada-DONATE* is to learn about usual care so that we can design future clinical trials with study procedures that (i) are sensitive to the needs of donor families and ICU clinicians, and (ii) align with usual care. The aim of this registry study is to enrol every deceased organ donor at participating hospitals, and all of their respective organ recipients, to reach the study objectives. Many of the donors that we would miss because of lack of consent would reflect particularly challenging situations. Many bioethicists assert that, in appropriate studies, the waiver of consent with strategies to minimize risks to patient privacy will retain high research ethics standards and avoid the problem of consent rate bias.[89]

2.4 Quebec Law

Unlike other Canadian provinces where laws are in the British common law tradition, the roots of Quebec law are based on French civil law.[90] Accordingly, Quebec has a distinctive legal system characterized by the co-existence of two legal systems (common law and civil law). The existence of the Civil Code has an important impact on research. Specifically, and as described below, the civil code recognize the absence of consent to research (waived consent), if the REB **and** a competent authority (i.e., director of the professional services) grant such authorization. This is different from the other provinces where TCPS, which is

based on common law (federal regulation), is use and does not require other authorizations. This section of the chapter describes the articles of the Civil Code that influence the model of consent in Quebec.

2.4.1 Article 19.2 from an Act Respecting Health Services and Social Services

"The director of professional services of an institution or, if there is no such director, the executive director may authorize a professional to examine the record of a user for study, teaching or research purposes.

Before granting such authorization, the director must, however, ascertain that the criteria determined under Section 125 of the Act respecting Access to documents held by public bodies and the Protection of personal information (chapter A-2.1) are satisfied. If the director is of the opinion that the professional's project is not in compliance with generally accepted standards of ethics or scientific integrity, the director must refuse to grant the authorization.

The authorization must be granted for a limited period and may be subject to conditions. It may be revoked at any time if the director has reason to believe that the authorized professional is violating the confidentiality of the information obtained or is not complying with the conditions imposed or with generally accepted standards of ethics and scientific integrity."[91]

2.4.2 Section 125 of the Act Respecting Access to Documents held by Public Bodies and the Protection of Personal Information

"The Commission may, on a written request, grant a person or an agency

the authorization to receive communication of personal information contained in a personal information file, for study, research or statistics purposes, without the consent of the persons concerned, if it is of the opinion…

> *(1) that the intended use is not frivolous and the ends contemplated cannot be achieved unless the information is communicated in nominative form;*
>
> *(2) that the personal information will be used in a manner that will ensure its confidentiality.*

The authorization is granted for such period and on such conditions as may be fixed by the Commission. It may be revoked before the expiry of the period granted if the Commission has reason to believe that the authorized person or body does not respect the confidentiality of the information disclosed or the other conditions."[92]

2.4.3 Interpretation

One interpretation of these statements from the Civil Code of Quebec is that an appropriate institutional representative has the authority to judge whether a waiver of research consent is appropriate and permitted in some situations. Examples of such institutional representatives may include the Chief Executive Officer of TQ, a hospital Chief of Critical Care, or the Medical Director of a transplant program (in conjunction with a Research Ethics Board review).

2.5 Examples of Ministry-Supported Waivers of Research Consent

A Quebec Ministry of Health website outlines appropriate exceptions to the

requirement for prospective informed research consent (http://ethique.msss.gouv.qc.ca/lethique-en-bref/la-recherche-sur-dossiers.html). More specifically, the ministry's document outline a situation in which written informed consent was judged to be inconvenient and/or unfeasible and defended article 19.2 in providing the authority to selected individuals to waive the requirement for research consent. Research relying on chart review ("revue de dossiers") poses a minimal risk to participants, who do not interact with research teams. In specific situations where it would be considered difficult or inadvisable to communicate with patients or their relatives, the director of professional services of an institution, in agreement with the institution's REB, may authorize the conduct of a study without the explicit consent of participants. Canada-*DONATE* falls into this category.

2.6 Precedents - Waived Research Consent for Prospective ICU Data in Quebec

Two examples are shown here of clinical research studies conducted in the ICUs of Sainte-Justine University Hospital Centre (CHU Sainte-Justine) with REB approval for a waived consent model. We have translated and copied text found in the form submitted to the CHU Sainte-Justine is REB.

Epidemiology, Determinants And Clinical Impact Of Transfusion Of Red Blood Cells, Fresh Frozen Plasma And Platelet Concentrates In Critically Ill Children: A One-Year Prospective Study

Design – Prospective cohort study

Patients – A cohort of critically ill children consecutively admitted to the Pediatric Intensive Care Unit (PICU) of CHU Sainte-Justine over a one-year period (2009-2010).

Ethical considerations – The study was designed to minimize disturbance of the patients, their parents and caregivers: the research project was strictly observational, it would not change the clinical approach of the attending physician, data were gathered from the hospital charts or by interviewing intensivists. There was no interaction between the patients or their families and the investigators. This study would be meaningless if consent is required because the investigators wished to compare the data collected in year 2009 to data collected in year 2000 when consent was not required and the two studies would not be comparable if the sample of patients was not similar, which would be the case if consent was required for 2009-2010 cohort.

Influenza-and H1N1-Related Critical Illness - Demand and Capacity in the Health Care System: the Canadian ICU-Flu Study [(93)]

Design – (1) A Canadian prospective descriptive study; (2) A survey of all acute care hospitals in Canada.

Patients – A cohort of critically ill children admitted to the PICU of CHU Sainte-Justine.

Ethical considerations – To describe the presenting patient characteristics, organ dysfunction, clinical outcomes and resource needs of influenza-

H1N1-related critical illness and acute lung injury among children and adults in Canada. The primary endpoint was survival and the secondary endpoint was critical care-free days, both evaluated 90 days after onset of critical illness. The investigators successfully argued, as in the example above, to use a waived consent model.

3. Research Consent For Specific Study Participants

This section addresses practical considerations for two distinct groups; (i) deceased organ donors and (ii) organ transplant recipients. For each group, challenges to both a *prospective* research consent model and to a *deferred* research consent model are presented.

3.1 Deceased Donors

3.1.1 Prospective Research Consent with Deceased Donors

A prospective research consent model would require discussion of research consent during the same meeting or at a similar time during which discussions regarding consent for organ donation occurs.

3.1.1.1 Emotional Burden of Substitute Decision Makers

The discussion of organ donation in the context of a sudden fatal illness is often emotionally intense for families of patients in the ICU. Additional lengthy discussions about research are generally not be welcomed or well received at the time of such delicate discussions with distressed family members. This has been confirmed in a recent study on research consent and substitute decision

makers.[94] The following examples are quotes from family members to critical care investigators on the topic of the optimal timing to seek consent for research participation:

"*I think you need to check with the nursing staff to see if the patient has somewhat stabilized because, if they are not, it maybe isn't the best time to approach a family member (about research). My son had stabilized so I could concentrate. It wasn't a bad time. Other times might have been a bad time."*

"You don't want anybody to come and tell you about any research...all I want is you to come and tell me what is going on with my husband. Don't tell me anything about research, please…it is not a priority for me. My priority is my husband."(Afterward, this family agreed to be part of the study)

3.1.1.2 Poor Use of Limited Time for Organ Donation Coordinators

Transplant Quebec Organ Donation Coordinators opine that even though we are working with TQ on this study, their very specialized OD Coordinators do not have the mandate, the time, or the training to obtain consent for participation in research studies. At the time of discussing consent for organ donation, they focus their attention and the families' attention on obtaining pertinent information relevant to the donation process and the patients' social and medical history.

3.1.1.3 Urgency Limits Research Staff Availability

Research staff are rarely present at the time of consent for deceased organ donation after a neurological determination of death. These discussions frequently occur with little warning, and very often on weekends or evenings.

3.1.2 Deferred Research Consent with Deceased Donors

A deferred research consent model requires discussion of research consent some time after the discussion of consent for organ donation.

3.1.2.1 Emotional Burden of Substitute Decision Makers

Organ donation after neurological death typically proceeds within 24-48 hours. This remains an emotionally intense period for grieving families.

3.1.2.2 Family Availability Limits Feasibility

Many families leave the hospital after providing consent for organ donation following neurological determination of death, and return home to grieve and make funeral arrangements. Contacting them by phone as they are focused on gathering family members and planning funeral arrangements would be very challenging and may be perceived as inappropriate and intrusive. If and when they return to the hospital, their focus is on attending to the donor, grieving with other loved ones, and planning their next steps. Moreover, ICU staff are very likely to resist access of research staff to families at this time.

3.1.2.3 Increased Risk of Study Bias

If the process of organ donation has been very complicated, relatives may be more likely to decline to participate in research, which increases the potential to bias study findings.

3.2 Transplant Recipients

Soliciting consent from transplant recipients is uniquely complicated by the fact that this research involves observing medical interventions among organ

donors and then following and measuring prospectively, ideally, the outcomes of these interventions among corresponding transplant recipients.

Moreover, the potential risk to organ recipients is very minimal. The planned data to be collected in recipients are extremely limited and only include, (i) organ received, (ii) hospital of transplant surgery, (iii) date of transplant, (iv) year of birth, (v) sex, (vi) one blood test (PRA) as a measure of immune risk, and (vii) a measurement at one week and (viii) three months after transplant to indicate the functioning of the donated organ. This functional outcome measure is conducted in the transplant centre and reported to the study's Methods Centre as a single check box on a 7-point scale. These data are not socially sensitive.

3.2.1 Prospective Research Consent for Transplant Recipients

Prospective research consent requires decision making prior to transplantation.

3.2.1.1 Approach for Consent in Pre-Transplant Clinics is not Feasible

This model requires engagement and training of multiple people at 12 Quebec transplant programs (and 60 programs for the rest of Canada) to discuss consent for this research among potential transplant recipients, many of whom will receive their organs from centres that will not be participating in this research.

3.2.1.2 Approach for Consent at the Time of Organ Offer Might be Perceived as Coercive, and an Unnecessary Burden

If recipient consent is being sought while on the waiting list or at the time of the allocation, it could create undue influences that cannot be reconciled with the

consent process and the underlying principle of autonomy. Recipients could feel pressured to agree to participate or concerned that their chance of receiving an organ might decrease if they declined.

3.2.2 Deferred Research Consent for Transplant Recipients

Deferred research consent requires decision making after transplantation.

3.2.2.1 Approaching Recipients for Consent During the Transplant Hospitalization may also be Perceived as Coercive, and/or an Unnecessary Burden on Recipients

The post-operative period is often associated with incapacity to consent to research due to narcotics, sedatives or other interventions affecting the participant's cognition. They could also feel pressured to agree to participate in order to keep the same level of care or to not be put at a disadvantage if they suffered a graft failure and needed to be re-listed on the transplant waiting list.

3.2.2.2 Increased Risk of Study Bias

If the transplant has been very complicated, these patients may be more likely to decline to participate in research, which increases the risk of biased study findings.

3.2.2.3 Approaching Recipients for Consent Later in Outpatient Clinics is not Feasible

This would require the organization and training of multiple people at 72 Canadian transplant programs to discuss consent for this research. Organs from a single organ donor are distributed to different transplant programs across the

region and even to other provinces. While some of these programs have appropriate research infrastructure in place to facilitate consent discussions for this study, most do not. Furthermore, it is not practical for the research team to keep track of clinic visits for each recipient at each program across the country, and to determine who in that program might be competent to have the research consent discussion, or educated appropriately to do so, then reminded to add this to their professional health care activities.

4. Summary

The successful implementation of this study looking at recipient outcomes at a national level will require answers to the following questions:

(i) Does data about a transplantation outcome require REB approval from the transplant centre?

(ii) Should research consent, for a purely observational study be sought at the same time of consent for organ donation?

(iii) Should research consent be waived for data collection on recipients?

This proposal is an important, innovative and nationwide program of research designed to improve the rates of deceased organ donation and the function of transplanted organs in recipients. This research program starts with a nationwide observational study of the medical management of deceased organ donors in 25 centres across Canada, including approximately 4 hospitals in Quebec. This observational study is akin to a registry study in which selective

non-participation would introduce significant bias in the study results and undermine the primary goals of Canada-DONATE. Moreover, discussions of research consent are uniquely inappropriate and impracticable for this research. In this situation, Quebec Law, principles of ethics, and the Canadian TCPS support waiving the requirement for informed research consent.

We proposed to carry out this research without explicit consent from the SDMs for deceased organ donors and without explicit consent from the recipients of organs from these deceased donors. There is a commitment to work with the Quebec REB, hospitals, and TQ to achieve these goals in accordance with the Civil Code of Quebec and with the upmost consideration for patient dignity and respect. Without approval to move forward, in the absence of written consent from the organ donor families and transplant recipients, this research will not be possible.

We included a waived model of research consent to enable consecutive consented deceased donors to be automatically be enrolled in the DONATE study through a notification system with the OPOs; corresponding organ recipients are identified by OPOs. Through a data sharing agreement with the OPOs, the research team obtains minimal data about the recipients which include the name of the transplant program where the corresponding recipient is located. Therefore, one research coordinator could communicate with transplant program and assess the graft function of the recipients.

In summary, the normative frameworks (legal and ethical) for ethics in

research are not rigid. The development and adaptation of these schemes is possible if stakeholders perceive these changes as desirable. The DONATE-pilot waiver of consent model illustrates this matter. To our knowledge, this is the first model of this sort in Quebec.

Thesis Conclusion

The aims of this thesis was to build the foundations of the first national research program on critical care of deceased donors.

The first chapter offered an overview of the current organ donation process in Canada. It highlighted the gap between organ supply and the need for transplantation. Moreover, it described the organizational structure of organ donation in Canada and highlighted the paucity of research in the field of donor management. Therefore, it demonstrated the limitation of current clinical practice to inform practices, we are left with important, unresolved clinical questions.

The second chapter described the rationale for a prospective cohort study and reported the design of the vanguard phase for a national prospective observational study on clinical practices in organ donation called DONATE. This study is the first step of a national study on organ donation and created the foundation for a national research program in donor management research.

The third chapter adressed the challenge of research consent on prospective observational study on donor management with recipient outcomes. Specifically, it summarized the justification for a waived model of consent.

Overall, this thesis reported the foundation of a national research program on organ donor care. Clinical research will inform best practices in organ donation with the goal of increasing the number of organs recovered and transplanted from donors and graft function in transplant recipients.

Organ donor management is an important aspect of critical care medicine. The optimal management of this population is unclear because clinical evidence are lacking. This national research program on organ donor care will have a broad impact as follow:

Clinical: Will improve medical management of organ donors potentially leading to an improvement in the number of organs transplanted and the functional quality of transplanted allografts. Moreover, it will benchmark and establish determinants of success across centres.

Research: Will foster a network of collaborators, and raise the awareness of the type and quality of information available in the different databases.

There is no one solution to increasing organ donation. However, through rigorous clinical research, we will develop strategies that will ultimately narrow the gap between supply and demand of organs for transplantation.

In summary; « *It is when asking questions about therapy that we should try to avoid the non-experimental approaches, since these routinely lead to false positive conclusions about efficacy ». David Sackett 1996, Jan 13th.*

References

1. Kutsogiannis DJ, Asthana S, Townsend DR, Singh G, Karvellas CJ. The incidence of potential missed organ donors in intensive care units and emergency rooms: a retrospective cohort. Intensive care medicine. 2013 Aug;39(8):1452-9. PubMed PMID: 23702637. Epub 2013/05/25. eng.
2. Kramer AH, Zygun DA, Doig CJ, Zuege DJ. Incidence of neurologic death among patients with brain injury: a cohort study in a Canadian health region. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2013 Dec 10;185(18):E838-45. PubMed PMID: 24167208. Pubmed Central PMCID: PMC3855144. Epub 2013/10/30. eng.
3. Rosendale JD, Chabalewski FL, McBride MA, Garrity ER, Rosengard BR, Delmonico FL, et al. Increased transplanted organs from the use of a standardized donor management protocol. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2002 Sep;2(8):761-8. PubMed PMID: 12243497. Epub 2002/09/24. eng.
4. Dhanani S, Shemie SD. Advancing the science of organ donor management. Critical care (London, England). 2014;18(6):612. PubMed PMID: 25672523. Pubmed Central PMCID: PMC4331331. Epub 2015/02/13. eng.
5. Wheeldon DR, Potter CD, Oduro A, Wallwork J, Large SR. Transforming the "unacceptable" donor: outcomes from the adoption of a standardized donor management technique. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 1995 Jul-Aug;14(4):734-42. PubMed PMID: 7578183. Epub 1995/07/01. eng.
6. Shemie SD, Hornby L, Baker A, Teitelbaum J, Torrance S, Young K, et al. International guideline development for the determination of death. Intensive care medicine. 2014 Jun;40(6):788-97. PubMed PMID: 24664151. Pubmed Central PMCID: PMC4028548. Epub 2014/03/26. eng.
7. Mora-Esteves C, Koneru B. Resolving issues of consent and oversight: one step closer to terra firma in deceased organ donor research. Critical care medicine. 2011 Feb;39(2):400-1. PubMed PMID: 21248520. Epub 2011/01/21. eng.
8. S K. Fewer 'brain dead' patients mean less organ donors when need for transplant is at 'all-time high': researchers. National Post. 2013 Oct 28 th.
9. e-statistics on Organ Transplants, Waiting Lists and Donors [Internet]. 2012.
10. Quebec T. Statistiques officielles 2014 http://www.transplantquebec.ca/en/statistics-02014 [cited 2015].
11. Anonymous. Deceased Organ Donor Potential in Canada. Canadian Institute for Health Information, 2014.
12. Institute DaT. International Registry in Organ Donation and Transplantation 2015 [cited 2015 November 23 th]. Available from: http://www.irodat.org/.

13. Anonymous. TGLN Annual Report 2014/15. 2015.
14. Chavalitdhamrong D, Gill J, Takemoto S, Madhira BR, Cho YW, Shah T, et al. Patient and graft outcomes from deceased kidney donors age 70 years and older: an analysis of the Organ Procurement Transplant Network/United Network of Organ Sharing database. Transplantation. 2008 Jun 15;85(11):1573-9. PubMed PMID: 18551062. Epub 2008/06/14. eng.
15. Huynh MJ, Violette PD, Rowe NE, Weernink C, MacLean K, Sener A, et al. Donation after Circulatory Death Renal Allografts--Does Donor Age Greater than 50 Years Affect Recipient Outcomes? The Journal of urology. 2015 Oct;194(4):1057-61. PubMed PMID: 25981804. Epub 2015/05/20. eng.
16. Anonymous. Trillium Gift of Life Network 2015. Available from: http://www.giftoflife.on.ca/en/.
17. Anonymous. Transplant Quebec Annual Report. 2014.
18. Matas AJ, Delmonico FL. Living donation: the global perspective. Advances in chronic kidney disease. 2012 Jul;19(4):269-75. PubMed PMID: 22732048. Epub 2012/06/27. eng.
19. Teitelbaum J, Shemi SD. Neurologic determination of death. Neurologic clinics. 2011 Nov;29(4):787-99. PubMed PMID: 22032661. Epub 2011/10/29. eng.
20. Manara AR, Murphy PG, O'Callaghan G. Donation after circulatory death. British journal of anaesthesia. 2012 Jan;108 Suppl 1:i108-21. PubMed PMID: 22194426. Epub 2012/01/04. eng.
21. Dominguez-Gil B, Delmonico FL, Shaheen FA, Matesanz R, O'Connor K, Minina M, et al. The critical pathway for deceased donation: reportable uniformity in the approach to deceased donation. Transplant international : official journal of the European Society for Organ Transplantation. 2011 Apr;24(4):373-8. PubMed PMID: 21392129. Epub 2011/03/12. eng.
22. Anonymous. Canadian Blood Services 2015. Available from: https://http://www.blood.ca/en/organs-tissues/donating-future.
23. Kotloff RM, Blosser S, Fulda GJ, Malinoski D, Ahya VN, Angel L, et al. Management of the Potential Organ Donor in the ICU: Society of Critical Care Medicine/American College of Chest Physicians/Association of Organ Procurement Organizations Consensus Statement. Critical care medicine. 2015 Jun;43(6):1291-325. PubMed PMID: 25978154. Epub 2015/05/16. eng.
24. Mascia L, Pasero D, Slutsky AS, Arguis MJ, Berardino M, Grasso S, et al. Effect of a lung protective strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial. Jama. 2010 Dec 15;304(23):2620-7. PubMed PMID: 21156950. Epub 2010/12/16. eng.
25. Sally M, Malinoski D. Current research on organ donor management. Anesthesiology clinics. 2013 Dec;31(4):737-48. PubMed PMID: 24287350. Epub 2013/11/30. eng.
26. Shah VR. Aggressive management of multiorgan donor. Transplantation proceedings. 2008 May;40(4):1087-90. PubMed PMID: 18555120. Epub 2008/06/17. eng.

27. Al-Khafaji A, Elder M, Lebovitz DJ, Murugan R, Souter M, Stuart S, et al. Protocolized fluid therapy in brain-dead donors: the multicenter randomized MOnIToR trial. Intensive care medicine. 2015 Mar;41(3):418-26. PubMed PMID: 25583616. Pubmed Central PMCID: PMC4351113. Epub 2015/01/15. eng.
28. Shemie SD, Ross H, Pagliarello J, Baker AJ, Greig PD, Brand T, et al. Organ donor management in Canada: recommendations of the forum on Medical Management to Optimize Donor Organ Potential. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2006 Mar 14;174(6):S13-32. PubMed PMID: 16534070. Pubmed Central PMCID: PMC1402396. Epub 2006/03/15. eng
fre.
29. Rech TH, Moraes RB, Crispim D, Czepielewski MA, Leitao CB. Management of the brain-dead organ donor: a systematic review and meta-analysis. Transplantation. 2013 Apr 15;95(7):966-74. PubMed PMID: 23545508. Epub 2013/04/03. eng.
30. Iwai A, Sakano T, Uenishi M, Sugimoto H, Yoshioka T, Sugimoto T. Effects of vasopressin and catecholamines on the maintenance of circulatory stability in brain-dead patients. Transplantation. 1989 Oct;48(4):613-7. PubMed PMID: 2799913. Epub 1989/10/01. eng.
31. Singer P, Shapiro H, Cohen J. Brain death and organ damage: the modulating effects of nutrition. Transplantation. 2005 Nov 27;80(10):1363-8. PubMed PMID: 16340775. Epub 2005/12/13. eng.
32. Abt PL, Marsh CL, Dunn TB, Hewitt WR, Rodrigue JR, Ham JM, et al. Challenges to research and innovation to optimize deceased donor organ quality and quantity. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2013 Jun;13(6):1400-4. PubMed PMID: 23617244. Epub 2013/04/27. eng.
33. Dupuis S, Amiel JA, Desgroseilliers M, Williamson DR, Thiboutot Z, Serri K, et al. Corticosteroids in the management of brain-dead potential organ donors: a systematic review. British journal of anaesthesia. 2014 Sep;113(3):346-59. PubMed PMID: 24980425. Epub 2014/07/02. eng.
34. Dikdan GS, Mora-Esteves C, Koneru B. Review of randomized clinical trials of donor management and organ preservation in deceased donors: opportunities and issues. Transplantation. 2012 Sep 15;94(5):425-41. PubMed PMID: 22892991. Epub 2012/08/16. eng.
35. Macdonald PS, Aneman A, Bhonagiri D, Jones D, O'Callaghan G, Silvester W, et al. A systematic review and meta-analysis of clinical trials of thyroid hormone administration to brain dead potential organ donors. Critical care medicine. 2012 May;40(5):1635-44. PubMed PMID: 22511141. Epub 2012/04/19. eng.
36. McElhinney DB, Khan JH, Babcock WD, Hall TS. Thoracic organ donor characteristics associated with successful lung procurement. Clinical transplantation. 2001 Feb;15(1):68-71. PubMed PMID: 11168319. Epub 2001/02/13. eng.

37. Follette DM, Rudich SM, Babcock WD. Improved oxygenation and increased lung donor recovery with high-dose steroid administration after brain death. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 1998 Apr;17(4):423-9. PubMed PMID: 9588588. Epub 1998/05/20. eng.
38. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. The New England journal of medicine. 2002 Feb 21;346(8):549-56. PubMed PMID: 11856793. Epub 2002/02/22. eng.
39. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. The New England journal of medicine. 2013 Dec 5;369(23):2197-206. PubMed PMID: 24237006. Epub 2013/11/19. eng.
40. Jiao B, Liu S, Liu H, Cheng D, Cheng Y, Liu Y. Hypothermic machine perfusion reduces delayed graft function and improves one-year graft survival of kidneys from expanded criteria donors: a meta-analysis. PloS one. 2013;8(12):e81826. PubMed PMID: 24339970. Pubmed Central PMCID: PMC3858268. Epub 2013/12/18. eng.
41. Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. Critical care medicine. 2009 Jul;37(7 Suppl):S186-202. PubMed PMID: 19535947. Epub 2009/06/26. eng.
42. Niemann CU, Feiner J, Swain S, Bunting S, Friedman M, Crutchfield M, et al. Therapeutic Hypothermia in Deceased Organ Donors and Kidney-Graft Function. The New England journal of medicine. 2015 Jul 30;373(5):405-14. PubMed PMID: 26222557. Epub 2015/07/30. eng.
43. Shemie SD, Baker AJ, Knoll G, Wall W, Rocker G, Howes D, et al. National recommendations for donation after cardiocirculatory death in Canada: Donation after cardiocirculatory death in Canada. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2006 Oct 10;175(8):S1. PubMed PMID: 17124739. Pubmed Central PMCID: PMC1635157. Epub 2006/11/25. eng.
44. Reich DJ, Mulligan DC, Abt PL, Pruett TL, Abecassis MM, D'Alessandro A, et al. ASTS recommended practice guidelines for controlled donation after cardiac death organ procurement and transplantation. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2009 Sep;9(9):2004-11. PubMed PMID: 19624569. Epub 2009/07/25. eng.
45. Chen GD, Shiu-Chung Ko D, Wang CX, Qiu J, Han M, He XS, et al. Kidney transplantation from donors after cardiac death: an initial report of 71 cases from China. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2013 May;13(5):1323-6. PubMed PMID: 23464380. Epub 2013/03/08. eng.
46. Kumar R, Shekar K, Widdicombe N, Fraser JF. Donation after cardiac death in Queensland: review of the pilot project. Anaesthesia and intensive care.

2012 May;40(3):517-22. PubMed PMID: 22577919. Epub 2012/05/15. eng.
47. Bellingham JM, Santhanakrishnan C, Neidlinger N, Wai P, Kim J, Niederhaus S, et al. Donation after cardiac death: a 29-year experience. Surgery. 2011 Oct;150(4):692-702. PubMed PMID: 22000181. Pubmed Central PMCID: PMC3357118. Epub 2011/10/18. eng.
48. Hernadez-Alejandro R, Wall W, Jevnikar A, Luke P, Sharpe M, Russell D, et al. Organ donation after cardiac death: donor and recipient outcomes after the first three years of the Ontario experience. Canadian journal of anaesthesia = Journal canadien d'anesthesie. 2011 Jul;58(7):599-605. PubMed PMID: 21538211. Epub 2011/05/04. eng.
49. Kim JM, Kim SJ, Joh JW, Kwon CH, Song S, Shin M, et al. Kidney donation after cardiac death in Korea. Transplantation proceedings. 2011 Jun;43(5):1434-7. PubMed PMID: 21693213. Epub 2011/06/23. eng.
50. Pine JK, Goldsmith PJ, Ridgway DM, Cockbain AJ, Farid S, Fraser S, et al. Comparable outcomes in donation after cardiac death and donation after brainstem death: a matched analysis of renal transplants. Transplantation proceedings. 2010 Dec;42(10):3947-8. PubMed PMID: 21168594. Epub 2010/12/21. eng.
51. Alonso A, Fernandez-Rivera C, Villaverde P, Oliver J, Cillero S, Lorenzo D, et al. Renal transplantation from non-heart-beating donors: a single-center 10-year experience. Transplantation proceedings. 2005 Nov;37(9):3658-60. PubMed PMID: 16386496. Epub 2006/01/03. eng.
52. Keizer KM, de Fijter JW, Haase-Kromwijk BJ, Weimar W. Non-heart-beating donor kidneys in the Netherlands: allocation and outcome of transplantation. Transplantation. 2005 May 15;79(9):1195-9. PubMed PMID: 15880069. Epub 2005/05/10. eng.
53. Sudhindran S, Pettigrew GJ, Drain A, Shrotri M, Watson CJ, Jamieson NV, et al. Outcome of transplantation using kidneys from controlled (Maastricht category 3) non-heart-beating donors. Clinical transplantation. 2003 Apr;17(2):93-100. PubMed PMID: 12709073. Epub 2003/04/24. eng.
54. L B. Donation After Cardiocirculatory Determination of Death: A Review. CCDT, 2005.
55. Gurusamy KS, Kumar Y, Sharma D, Davidson BR. Ischaemic preconditioning for liver transplantation. The Cochrane database of systematic reviews. 2008 (1):CD006315. PubMed PMID: 18254099. Epub 2008/02/07. eng.
56. Schnuelle P, Gottmann U, Hoeger S, Boesebeck D, Lauchart W, Weiss C, et al. Effects of donor pretreatment with dopamine on graft function after kidney transplantation: a randomized controlled trial. Jama. 2009 Sep 9;302(10):1067-75. PubMed PMID: 19738091. Epub 2009/09/10. eng.
57. Malinoski DJ, Daly MC, Patel MS, Oley-Graybill C, Foster CE, 3rd, Salim A. Achieving donor management goals before deceased donor procurement is associated with more organs transplanted per donor. The Journal of trauma. 2011 Oct;71(4):990-5; discussion 6. PubMed PMID: 21808207. Epub 2011/08/03. eng.

58. Malinoski DJ, Patel MS, Ahmed O, Daly MC, Mooney S, Graybill CO, et al. The impact of meeting donor management goals on the development of delayed graft function in kidney transplant recipients. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2013 Apr;13(4):993-1000. PubMed PMID: 23406284. Epub 2013/02/15. eng.
59. Malinoski DJ, Patel MS, Daly MC, Oley-Graybill C, Salim A. The impact of meeting donor management goals on the number of organs transplanted per donor: results from the United Network for Organ Sharing Region 5 prospective donor management goals study. Critical care medicine. 2012 Oct;40(10):2773-80. PubMed PMID: 22846779. Epub 2012/08/01. eng.
60. Patel MS, Zatarain J, De La Cruz S, Sally MB, Ewing T, Crutchfield M, et al. The impact of meeting donor management goals on the number of organs transplanted per expanded criteria donor: a prospective study from the UNOS Region 5 Donor Management Goals Workgroup. JAMA surgery. 2014 Sep;149(9):969-75. PubMed PMID: 25054379. Epub 2014/07/24. eng.
61. Anonymous. Organ and Tissue Donation and Transplantation National Consultation: Executive Summary. Canadian Blood Services, 2008.
62. Feng S. Got It! Let's Cool It! But What's Next in Organ Donor Research? American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2016 Jan;16(1):5-6. PubMed PMID: 26551003. Epub 2015/11/10. eng.
63. Carpenter J KM. Multiple imputation and its application 2012. Available from: http://missingdata.lshtm.ac.uk.
64. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ (Clinical research ed). 2007 Oct 20;335(7624):806-8. PubMed PMID: 17947786. Pubmed Central PMCID: PMC2034723. Epub 2007/10/20. eng.
65. Callahan DS, Neville A, Bricker S, Kim D, Putnam B, Bongard F, et al. The effect of arginine vasopressin on organ donor procurement and lung function. The Journal of surgical research. 2014 Jan;186(1):452-7. PubMed PMID: 24176209. Epub 2013/11/02. eng.
66. Christmas AB, Bogart TA, Etson KE, Fair BA, Howe HR, Jacobs DG, et al. The reward is worth the wait: a prospective analysis of 100 consecutive organ donors. The American surgeon. 2012 Mar;78(3):296-9. PubMed PMID: 22524766. Epub 2012/04/25. eng.
67. Perico N, Cattaneo D, Sayegh MH, Remuzzi G. Delayed graft function in kidney transplantation. Lancet (London, England). 2004 Nov 13-19;364(9447):1814-27. PubMed PMID: 15541456. Epub 2004/11/16. eng.
68. Latchana N, Peck JR, Whitson B, Black SM. Preservation solutions for cardiac and pulmonary donor grafts: a review of the current literature. Journal of thoracic disease. 2014 Aug;6(8):1143-9. PubMed PMID: 25132982. Pubmed

Central PMCID: PMC4133544. Epub 2014/08/19. eng.
69. Parsons RF, Guarrera JV. Preservation solutions for static cold storage of abdominal allografts: which is best? Current opinion in organ transplantation. 2014 Apr;19(2):100-7. PubMed PMID: 24553501. Epub 2014/02/21. eng.
70. Anonymous. NHLBI Policy for Data and Safety Monitoring of Extramural Clinical Studies 2016. Available from: http://www.nhlbi.nih.gov/research/funding/human-subjects/data-safety-monitoring-policy.
71. Woolf SH, Zimmerman E, Haley A, Krist AH. Authentic Engagement Of Patients And Communities Can Transform Research, Practice, And Policy. Health affairs (Project Hope). 2016 Apr 1;35(4):590-4. PubMed PMID: 27044956. Epub 2016/04/06. eng.
72. Cobb EM, Meurer W, Harney D, Silbergleit R, Lake BP, Clark C, et al. Patient Engagement in Neurological Clinical Trials Design: A Conference Summary. Clinical and translational science. 2015 Dec;8(6):776-8. PubMed PMID: 26083566. Epub 2015/06/18. eng.
73. Tom L. Beauchamp JFC. Principles of Biomedical Ethics. Seventh ed2012.
74. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? Jama. 2000 May 24-31;283(20):2701-11. PubMed PMID: 10819955. Epub 2000/05/20. eng.
75. Rey MM, Ware LB, Matthay MA, Bernard GR, McGuire AL, Caplan AL, et al. Informed consent in research to improve the number and quality of deceased donor organs. Critical care medicine. 2011 Feb;39(2):280-3. PubMed PMID: 20975549. Pubmed Central PMCID: PMC3717371. Epub 2010/10/27. eng.
76. Warrens AN, Lovell H. Addressing problems in transplantation research in the United kingdom. Transplantation. 2012 May 15;93(9):860-4. PubMed PMID: 22411561. Epub 2012/03/14. eng.
77. Feng S. Donor intervention and organ preservation: where is the science and what are the obstacles? American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2010 May;10(5):1155-62. PubMed PMID: 20420628. Epub 2010/04/28. eng.
78. Glazier AK, Heffernan KG, Rodrigue JR. A Framework for Conducting Deceased Donor Research in the United States. Transplantation. 2015 Nov;99(11):2252-7. PubMed PMID: 26244717. Epub 2015/08/06. eng.
79. Rodrigue JR, Feng S, Johansson AC, Glazier AK, Abt PL. Deceased Donor Intervention Research: A Survey of Transplant Surgeons, Organ Procurement Professionals, and Institutional Review Board Members. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2016 Jan;16(1):278-86. PubMed PMID: 26484950. Epub 2015/10/21. eng.
80. Toews M CT, Nelson E, Ogbogu U, Hartnell D. Fast Policy Facts: Human Bodies and Biological Materials. In: Program CNTR, editor. 2015.

81. Goldfeld B CT, Nelson E, Wright L. Fast Policy Facts: Consent. Canadian National Transplant Research Program, 2013.
82. Casarett D, Karlawish JH, Sugarman J. Determining when quality improvement initiatives should be considered research: proposed criteria and potential implications. Jama. 2000 May 3;283(17):2275-80. PubMed PMID: 10807388. Epub 2000/05/12. eng.
83. Anonymous. Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. Governement of Canada; 2014.
84. Anonymous. Canadian Organ Replacement Register Annual Report: Treatment of End-Stage Organ Failure in Canada, 2004-2013. Canadian Institute for Health Information, 2015.
85. Salim A, Martin M, Brown C, Inaba K, Roth B, Hadjizacharia P, et al. Using thyroid hormone in brain-dead donors to maximize the number of organs available for transplantation. Clinical transplantation. 2007 May-Jun;21(3):405-9. PubMed PMID: 17488392. Epub 2007/05/10. eng.
86. Angel LF, Levine DJ, Restrepo MI, Johnson S, Sako E, Carpenter A, et al. Impact of a lung transplantation donor-management protocol on lung donation and recipient outcomes. American journal of respiratory and critical care medicine. 2006 Sep 15;174(6):710-6. PubMed PMID: 16799075. Epub 2006/06/27. eng.
87. Mone T, Heldens J, Niemann CU. Deceased organ donor research: the last research frontier? Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2013 Feb;19(2):118-21. PubMed PMID: 23193057. Epub 2012/11/30. eng.
88. Tu JV, Willison DJ, Silver FL, Fang J, Richards JA, Laupacis A, et al. Impracticability of informed consent in the Registry of the Canadian Stroke Network. The New England journal of medicine. 2004 Apr 1;350(14):1414-21. PubMed PMID: 15070791. Epub 2004/04/09. eng.
89. El Emam K, Jonker E, Moher E, Arbuckle L. A review of evidence on consent bias in research. The American journal of bioethics : AJOB. 2013;13(4):42-4. PubMed PMID: 23514396. Epub 2013/03/22. eng.
90. Jukier R. The Impact of Legal Traditions on Quebec Procedural Law: Lessons from Quebec's new code of civil procedure. McGill University, 2015.
91. An Act Respecting Health Services And Social Services, (2016).
92. An Act Respecting Access to Documents Held by Public Bodies and the Protection of Personal Information, (2016).
93. Muscedere J, Ofner M, Kumar A, Long J, Lamontagne F, Cook D, et al. The occurrence and impact of bacterial organisms complicating critical care illness associated with 2009 influenza A(H1N1) infection. Chest. 2013 Jul;144(1):39-47. PubMed PMID: 23392627. Epub 2013/02/09. eng.
94. Burns KE, Rizvi L, Smith OM, Lee Y, Lee J, Wang M, et al. Is there a role for physician involvement in introducing research to surrogate decision makers in the intensive care unit? (The Approach trial: a pilot mixed methods study).

Intensive care medicine. 2015 Jan;41(1):58-67. PubMed PMID: 25491659. Epub 2014/12/11. eng.

Appendix

Observational Study of Clinical Practices in Deceased Organ Donation

Operations Manual
(Version 2 – March 1st , 2016)

TABLE OF CONTENTS

STUDY ACRONYMS AND TERMINOLOGY

OD	Organ Donation	Process of transferring organs from one person (donor) to another (recipient).
ICU	Intensive Care Unit *(will be used interchangeably with critical care area)	AKA critical care area. Organ donor care may be managed in a variety of ICUs or critical care areas depending on the study site. ICU types include medical, surgical, pediatric, neurosurgical, trauma, cardiac care and cardiac surgery.
DND	Donation after Neurological Death	AKA brain death, death by neurological criteria, neurological determination of death.
DCD	Donation after Cardiac Death	AKA cardiac death, death by cardiac criteria.
OPO	Organ Procurement Organization	Provincial bodies that oversee organ donation.
TGLN	Trillium Gift of Life Network	The OPO for Ontario.
TQ	Transplant Quebec	The OPO for Quebec.
Waived Consent		A consent model that does not require an informed consent from the deceased donor's substitute decision maker.
MC	Methods Centre	Coordination site for DONATE located at McMaster University
REB	Research Ethics Board	An institutional panel responsible for approving the conduct of research
CRFs	Case Report Forms	Study documents for recording participant data
EBs	Evidence Bulletins	Summaries of Canadian practices of medical interventions relevant to organ donation
RC	Research Coordinator	Personnel at study sites responsible for any or all of; patient screening, recruitment and data collection
OPO Coordinator	Organ Procurement Organization Coordinator	Representatives from provincial bodies that oversee organ donation. Responsible for coordinating care of organ donors in hospital.
PI(s)	Principal Investigator(s)	Oversee all aspects of the study.
SI(s)	Site Investigator(s)	Local investigator for a particular site, playing supervisory role.
IR	Infirmieres Ressources	Similar to OPO coordinator,

		specific to Quebec
Potential Donor(s)		Patient with severe non-recoverable brain trauma, brain death or severe non-recoverable injury whom may be a candidate for organ donation. Consent for organ donation yet to be acquired.
Consented Donor(s)		Potential donor for whom consent for organ donation has been obtained.
Patient ID	Patient Identification Number	A unique number assigned to each patient upon consent for organ donation
Study Site Number		The first two digits of the patient ID. Study Site Numbers are assigned in Section 6.2.2
Patient Number		The last three digits of the patient ID. Assigned consecutively to patients enrolled in the study (i.e. 001, 002, 003 etc.)
Co-enrolment		Occurs when patient is enrolled in another study at the same time as DONATE.
Organ Recovery		Occurs when patient goes to the operating room to have organs harvested for donation.
WLS	Withdrawal of Life Support	Defining criteria listed in Section 9.3.7.1.
MAP	Mean Arterial Pressure	
CSF	Cerebral Spinal Fluid	
ICP	Intracranial Pressure	
PEEP	Positive End-Expiratory Pressure	
ECLS	Extra Corporeal Life Support	
ECMO	Extra Corporeal Membrane Oxygenation	
HFO	High Frequency Oscillatory Ventilation	
APRV	Airway Pressure Release Ventilation	
bpm	beats per minute	
GIK	Glucose – Insulin - Potassium	
WBC	White Blood Cells	
Hgb	Hemoglobin	
INR	Prothrombin Time	
PTT	Partial Thromboplastin Time	
ABG	Arterial Blood Gases	
AST	Aspartate aminotransferase	
ALT	Alanine aminotransferase	

CVP	Central Venous Pressure	
PVC	Premature Ventricular Contraction	
PALS	Pediatric Advanced Life Support	Guideline for pediatric reference ranges of blood pressure.

1 STUDY OVERVIEW

The DONATE Pilot study is an observational study of clinical practices in organ donation (**OD**), for an overview see Figure 1. Over the course of the one-year pilot, feasibility of study procedures and data collection will be assessed. Relevant changes based on this feasibility assessment will be made before launching a nation-wide program of research.

1.1 Research Question

Within organ donation centres in Canada, what are the current practices for declaring death, caring for organ donors, and assessing organ suitability for transplantation?

1.2 Objectives

The overarching goal of the DONATE study is to observe the medical management of organ donors in intensive care areas/**ICU**s of the most active organ donation centres in Canada. We have 4 general objectives: 1) evaluation of medical interventions, 2) knowledge translation, 3) quality assurance, and 4) advancement of clinical research in the field.

1.2.1 Evaluation of Medical Interventions

One objective of the study is to evaluate several management strategies for organ donors that are perceived to improve transplant rates. Some management strategies or interventions are specific to donor management after death by neurologic criteria (brain death; **DND**); others are specific to donor management that precedes imminent death by circulatory criteria (i.e., after the withdrawal of life support; **DCD**).

1.2.2 Knowledge Translation

Another objective of the study is to describe the medical management of organ donors in Canada. Reports of current practices (including consistencies and variability) will help clinicians (by providing a benchmark for care, and offering practice alternatives), educators (by revealing knowledge gaps) and policy makers (by providing accurate provincial data).

1.2.3 Quality Assurance

A third objective is to assess the accuracy and completeness of organ donor data collected by organ procurement organizations (**OPO**s), specifically the Trillium Gift of Life Network (**TGLN**) and Transplant Quebec (**TQ**). Data are collected inconsistently and, at times, remotely and retrospectively by non-clinical staff. Findings, may support utilization of **OPO** databases for future randomized controlled trials.

1.2.4 Advancing Clinical Research

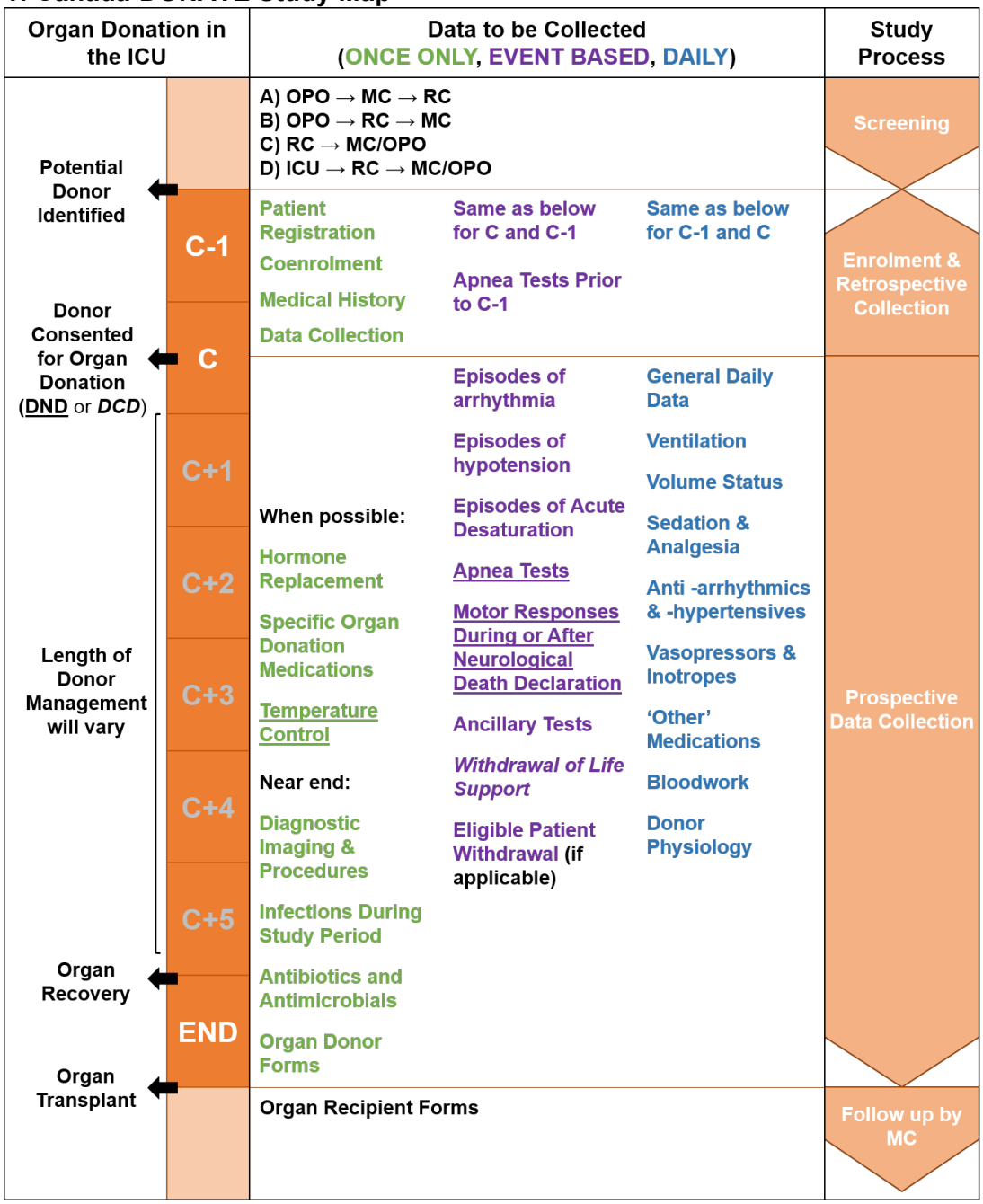
Follow-up of organ function in transplant recipients provides the most clinically important outcome for studies of organ donor management. Current **OPO** databases do not link donor and recipient data in this manner, which limits the potential for multicentre research. The aim of Canada-DONATE is to link donor and recipient data.

1.3 Lay Summary

Organ donation saves lives and is the most effective therapy available to treat end stage failure of a number of organs. Unfortunately, there is a growing gap between the number of donors and the number of patients waiting for transplantation. The objectives of this observational study within critical care areas/**ICU**s of the most active organ donation centres in Canada are multifaceted. We aim to 1) evaluate the benefit of strategies that are perceived to improve the rate of organ recovery and transplantation, 2) provide a benchmark for clinical care management of organ donors, 3)

assess the feasibility of follow-up of transplant recipients up to three months post-surgery and 4) assess the quality of provincial administrative patient data for clinical research purposes. Results will inform investigators for future clinical trials on organ donor management, improve care and help reduce the gap between transplant needs and organ supply.

Figure 1: Canada-DONATE Study Map



2 GETTING STARTED

2.1 Research Ethics Board (REB) Review

The study will not begin at any site without local Research Ethics Board (REB) approval. Be aware

that the DONATE-Pilot study uses a **waived consent** model for potential donors and recipients. For assistance with your REB application or amendments in Ontario please contact the Study Project Manager (Erika Arseneau) at McMaster University. Quebec sites can also contact the Study Project Manager (Marie-Helene Masse) at Le Centre Hospitalier Universitaire de Sherbrooke. Please forward all local REB approval letters to the CLARITY Research Methods Centre (**MC**) via e-mail or fax (e-mail: arsenee@mcmater.ca or fax: 905-252-3841).

2.2 Study Reimbursements and Data Transfer Agreements

Participating centres will receive reimbursements for each enrolled participant in the study, upon completion of all related Case Report Forms (**CRFs**). A Data Transfer Agreement (site contract) will be provided to all of the sites participating in the DONATE Pilot. Each site will be asked to review the site contract and provide approval from designated signatories.

2.3 Teaching Materials

Prior to commencing the study, each site will be asked to inform local medical personnel about DONATE. Each site will receive training on DONATE procedures and will be provided with resources to inform local personnel. During the course of the study each site will also be given Evidence Bulletins (**EB**s) which will summarize current practice of relevant medical interventions in organ donation.

2.3.1 Site Training on DONATE protocols

Prior to beginning enrolment, each study site will receive a site visit from one of the principal investigators and MC personnel. During this site visit all DONATE protocols and procedures will be discussed, including an iDataFax tutorial if necessary. Ongoing updates and meetings will be held by teleconference. **RC**s are encouraged to contact the study administration team with any questions they may have (Section 3.1).

2.3.2 Informing Local Personnel

Research coordinators (**RC**s) are asked to communicate to local medical personnel in their hospital and participating **ICUs** about DONATE's existence. The **MC** will provide each site with a short power point presentation that may be used to present to ICU physicians, nurses, on-site organ procurement organization coordinators (**OPO coordinators**) and central OPO staff. This presentation can be presented at departmental staff meetings, grand rounds, over lunch or morning meetings. All sites will also be provided with a one-page summary of DONATE that may be provided to **OPO coordinators** or hospital staff interested in DONATE. It is recommended that each site send an e-mail to **ICU** staff to notify them of DONATE's presence and that each site display posters and reminders in **ICU(s)** where possible.

2.3.3 Evidence Bulletins (EBs)

The CLARITY **MC** will provide sites with Evidence Bulletins on a quarterly basis. The focus of each **EB** will be a separate medical intervention related to organ donor management. Each site is encouraged to share the **EB**s with hospital, medical and **ICU** staff.

3 STUDY ADMINISTRATION

3.1 Who to Contact

3.1.1 Administrative Requests (data management, documents, reimbursements, etc.)

Ontario Sites
Erika Arseneau
Study Project Manager
CLARITY Research Methods Centre
McMaster University
1280 Main Street W
Health Sciences Centre (HSC-2C3)
Hamilton ON L8S 3K1
E-mail: arsenee@mcmaster.ca
Tel: 905-525-9140 x24945
Fax: 905-525-3841

Quebec Sites
Marie-Helene Masse
CR-CHUS Soins Intensifs
3001, 12e Avenue Nord
Sherbrooke, QC, Canada
J1H 5N4
Local 2906 bureau 40
E-mail: mhasse.chus@ssss.gouv.qc.ca
Tel: 819-346-1110 poste 14174
Pagette: 2153

3.1.2 Protocol/Data Inquiries (clinical protocol clarifications, clinical data queries, etc.)

Ontario Sites
Lori Hand, RRT
Clinical Research Coordinator (RC)
Hamilton General Hospital
237 Barton St E
Hamilton ON L8L 2X2
E-mail: handlori@hhsc.ca
Tel: 905-527-4322 x44553
*Mobile: 905-563-2777 (24 hrs/7days)
*Call first

Quebec Sites
Marie-Helene Masse
CR-CHUS Soins Intensifs
3001, 12e Avenue Nord
Sherbrooke, QC, Canada
J1H 5N4
Local 2906 bureau 40
E-mail: mhasse.chus@ssss.gouv.qc.ca
Tel: 819-346-1110 poste 14173
Pagette: 2153

3.2 Principal Investigators

The principal investigators oversee all aspects of the study, working directly with the Steering Committee, the Study Project Manager, Clinical Research Coordinators, coinvestigators, OPOs and transplant programs. The principal investigators report to the Canadian Critical Care Trials Group (CCCTG) and the Canadian National Transplant Research Program (CNTRP).

Frederick D'Aragon, MD
E-mail: frederick.daragon@usherbrooke.ca
Tel: 819-821-8000 x70103
Mobile: 647-525-7644

Maureen Meade, MD, MSc
E-mail: meadema@hhsc.ca
Tel: 905-525-9140 x23162
Mobile: 289-237-4997

3.3 Steering Committee

The steering committee members include Frederick D'Aragon, Maureen Meade, Sonny Dhanani, Francois Lamontagne and Erika Arseneau. The steering committee will meet by conference call a minimum of three times and as needed during the study. Performance reports summarizing patient enrollment, data accuracy and completeness will be reviewed. The Steering Committee will also address the need for any protocol modifications, adherence to study timelines, and any other necessary methodologic or practical decisions. Each quarter the steering committee will provide each site with a site report that describes: i) their current practice and ii) the overall progress of the study.

3.4 Personnel at all DONATE Pilot Sites

Research Coordinators (**RC**s) are responsible for recruitment and data collection of all patients at

their corresponding site(s). Local site investigators (**SI**s) play a supervisory role in study oversight.

Hamilton Health Sciences
Hamilton ON
RC: Lori Hand
SI: Dr. Maureen Meade

St. Joseph's Healthcare
Hamilton ON
RC: France Clarke
SI: Dr. Deborah Cook

London Health Sciences Centre
London ON
RC: Eileen Campbell
SI: Dr. Ian Ball

Hopital Sacre Coeur de Montreal
Montreal QC
RC: Virginie Williams
SI: Anne Julie Frenette

CHU de Sherbrooke
Sherbrooke QC
RC: Marie-Helene Masse
SI: Dr. Frederick D'Aragon

CHU de Montreal-Notre Dame
Montreal, QC
RC: TBD
SI: Dr. Jean Francois Lize

CHU de Quebec-Hotel Dieu
Quebec City, QC
RC: TBD
SI: Dr. Michael Chasse

4 STUDY POPULATION

All adult deceased donors from participating sites are to be enrolled in DONATE. McMaster Children's Hospital will also enroll pediatric deceased donors for the pilot study.

4.1 Inclusion Criteria

i) Admitted to a critical care area (ICU, PICU, CCU, ER)
ii) ≥ 18 years of age (except at McMaster Children's Hospital)
iii) Patient pronounced dead by neurological death criteria or has suffered a brain injury reflective of imminent death (**DND**) OR patient has sustained a non-recoverable injury where death is suspected within 2 hours or less of withdrawing life support (**DCD**)
iv) Consent has been obtained for organ donation

4.2 Exclusion Criteria

i) Neonate < 36 weeks gestation
ii) <18 years of age (except at McMaster Children's Hospital)

5 SCREENING

A multi-faceted screening approach will be performed on an ongoing basis.

5.1 Overview

To minimize selection bias, ensure a representative sample, obtain sufficient statistical power and to ensure every consented adult donor is enrolled in DONATE we will use four screening approaches (A-D).

5.1.1 Approach A: OPO → MC → RC

This approach is the most common method for Ontario sites. The provincial **OPO**, **TGLN**, has

set up an automatic notification system whereby the DONATE methods centre (**MC**) receives an e-mail notification once consent for organ donation has been given for a potential donor. Once received, the **MC** will send the notification to the corresponding site **RC** for them to begin data collection. It is possible that the local **RC** will become aware of **potential donors** prior to this automatic notification (Approaches B-D).

5.1.2 Approach B: OPO → RC → MC

This approach is the most common method for Quebec sites. The provincial **OPO**, **TQ**, has personnel called 'infirmieres ressources' (**IR**) very similar to the role of **OPO coordinator** at TGLN. The IR will notify local **RC**s of any newly consented organ donors at participating sites. In Ontario, **OPO coordinators** may notify **RC** of **potential donors** before consent has been acquired and before the automatic notification is sent. Additionally, it is possible that the **RC** or **ICU** staff become aware of potential donors before the **OPO coordinators** or the **MC**, while working day to day in critical care areas (Approaches C&D).

5.1.3 Approach C: RC → MC/OPO

When in the **ICU RC**s should be screening daily for any potential donors at their site. It is possible that **RC**s become aware of a potential organ donor before **MC** or **OPO** staff. If this happens the **OPO**s should be contacted according to standard hospital and provincial regulations.

5.1.4 Approach D: ICU Staff → RC → MC/OPO

In some cases, it may be possible that **ICU** staff inform local **RC**s or local **OPO coordinator**s of **potential donors** that arrive in the **ICU.** If the **OPO coordinator** has not already been notified of this patient, the local **RC**s should notify the correct personnel. It is thus important to inform local personnel of DONATE as mentioned previously to aid in this method of screening.

5.2 Enrolment & Data Collection Following Consent

Local **RC**s, although they can only begin data collection after consent, should attempt to be aware of potential organ donors within their participating critical care areas/**ICU**s in the event that they are consented and can be enrolled in DONATE.

6 ENROLMENT

6.1 Process

Once a **potential donor** (identified through the screening process described in Section 5) has consented for organ donation they become a **consented donor.** At this point, **RCs** will enroll the patient in DONATE by assigning them a **patient ID**. Any **patient ID**s assigned should be recorded in the site's screening log (Appendix A) and reported to the **MC** on a monthly basis. Once consent is obtained and the **patient ID** has been assigned, data collection can begin.

6.2 Model of Consent

DONATE has obtained research and ethics board approval for **waived consent**. No consent is required from the potential organ donors' substitute decision maker or the organ recipients.

6.2.1 Patient IDs

Once consent for organ donation is obtained a unique **Patient ID** must be assigned. The template ## - 1 - ### is to be used. The first two numbers indicate the assigned study site number. Please refer to the designated **study site numbers** below in section 6.2.2 when assigning **patient ID**s.

The **study site number** is followed by the number 1 and then a three-digit number that corresponds to the **patient number**. Consecutive numbers are to be assigned to consecutive organ donors at each specific site starting with 001.

6.2.2 Site Numbers

Each participating site has a **site number** assigned to their respective health care centre.

Health Care Centre	Study Site	Study Site Number
Hamilton Health Sciences	Hamilton General	01
	Juravinksi	02
	McMaster University Medical Centre	03
	St. Joseph's Healthcare	04
London Health Sciences	Victoria Hospital	05
	London Health Sciences Centre	06
CHU de Sherbrooke	Fleurimont	07
	Hotel Dieu	08
	Hopital de Sacre-Coeur	09
	CHU de Montréal- Notre Dame	10
	CHU de Québec- Hôtel Dieu	11

6.2.3 Screening Log

All sites are to notify the **MC** of newly consented donors and their assigned **patient ID**s on a monthly basis by recording them in the **screening log**. See Appendix A – Monthly Screening Log. At the end of every calendar month **RC**s are to send their screening logs to Erika Arseneau at arsenee@mcmaster.ca.

6.3 Co-Enrolment

No current studies will be compromised in cases of **co-enrolment** with the DONATE pilot study, including any Canadian Critical Care Trials Group (CCCTG) studies. Subsequently, enrolment of participants in other CCCTG studies should not affect enrolment in the DONATE pilot study. Whether a patient enrolled in DONATE is coenroled in another study must be indicated on the Coenrolment Form 34.1.

6.4 Withdrawal

Events of withdrawal from the DONATE pilot should be extremely rare given the **waived consent** model. If, however a family, substitute decision maker or physician explicitly requests that the patient be withdrawn from DONATE then data collection will stop at this point. A detailed reason for withdrawal is to be elicited from the individual who made the decision to withdraw and it should be discussed what data collected, if any, are able to be retained. In cases of withdrawal, complete the withdrawal form (Eligible Patient Withdrawn Form 45.1).

7 DATA COLLECTION

7.1 General Approach for Donors

Since patients are enrolled following consent for organ donation, some data will need to be collected retrospectively. This retrospective data includes, past medical history and chronic illnesses, details related to the illness necessitating hospital admission, data related to cardiorespiratory stability, and key aspects of care in the critical care area up to the time of consent. All other data should be collected prospectively. This includes; cardiopulmonary monitoring, organ donor interventions and assessments of organ suitability.

7.2 General Approach for Recipients

We will also collect data on recipients of organs transplanted from enrolled donors. We will collect data on organ function among transplant recipients within the first seven days (timing will vary according to the organ recovered) and at three months' post-transplantation.

7.3 Data Collection Frequency

Data collection begins at time of consent and continues until the time of **organ recovery** or the time at which all organs have been excluded from organ donation (this could be due to a variety of reasons).

7.3.1 Day of Study

Each day of study is referenced to the day of consent for organ donation.

7.3.1.1 C-1

C-1 corresponds to the day before the day of consent for organ donation. Any data collected for this day will be collected retrospectively.

7.3.1.2 C

C is the day of consent for organ donation. All other study days are in reference to this day. Data from this point onward should be collected prospectively as much as possible. The day and time of consent is defined as the day and time when consent for organ donation was obtained by the OPO staff and/or intensivist. To the extent that it is possible data collection should start within 2 hours of consent.

Day of consent will continue to midnight of the same calendar day. The previous calendar day is C-1 and the next calendar day is C+2. For example, a new organ donor consents on April 12th at 17:00. Day "C" is defined as April 12th, from 00:00 to 23:59. Day C+1 would then be defined as April 13th beginning at 00:00 extending to 23:59. Day C-1 would be defined as April 11th beginning at 00:00 extending to 23:59.

7.3.1.3 C+1, C+2, C+3, C+4, C+5

Labelling of study day will continue (as described above) up until the final day of data collection. **CRF**s have been designed to collect data up to 5 days' post-consent (Figure 1) however management of organ donors in critical care areas rarely extends more than 48 hours beyond the time of consent.

7.3.2 Final Day of Data Collection

The final day of data collection corresponds to the day the patient goes to the operating room for **organ recovery**. In other cases, it may be that all of the patient's organs were declined prior to **organ recovery** or they suffered a complication prior to **organ recovery** that excludes them from organ donation (i.e. cardiac arrest). In these instances, the day all organs are

declined or the day the complication occurs is labelled the final day of data collection.

7.4 Types of Data Collected

Data collected as part of DONATE can be categorized into Daily data, Once Only data and Event Based data. Daily data and Once Only data are captured on required forms that are required for every patient. Event Based data is captured on optional forms that become required based on how specific questions are answered for a given patient.
Generally speaking, there are two instances where Once Only data is collected, at enrolment and at the end of data collection (day of organ procurement or day all organs declined). Outcome data can also be considered Once Only data.

7.4.1 Once Only Data (At Enrolment)

When a participant is enrolled in the study, data regarding patient registration, co-enrolment, and medical history are collected. The first day of data collection should also be recorded at this time on the Data Collection Form 2.1. At the end of data collection, it is important to go back to this form and indicate the final day of data collection. All of this data is captured on the following CRFs:

- Patient Registration Form 1.1
- Data Collection Form 2.1
- Medical History Form 3.1 – 3.2
- Co-Enrolment Form 34.1

If C-1 data is available, all C-1 data is to be captured on daily forms. Also at this time determine if the patient had an apnea test prior to C-1. If so, document the apnea test prior to C-1 on the following Event Based form:

- Apnea Tests Prior to C-1 Form 25.1 – 25.6 (2 pages per apnea test)

7.4.2 Daily Data

There are specific data to be captured every study day for which a patient is enrolled beginning at C-1. This includes physiological and bloodwork data, use of medications, details on ventilation and other donor management interventions. This data is captured on the following CRFs:

- Daily Data Form 4.1 – 4.2
- Daily Ventilation Form 5.1
- Daily Blood Products & Colloid Therapy Form 6.1
- Daily Volume Status Form 7.1
- Daily Sedation & Analgesia Form 8.1
- Daily Vasopressors & Inotropes Form 10.1
- Daily ‘Other Medications’ Form 11.1
- Hematology Bloodwork Form 14.1
- Acid Base Bloodwork Form 15.1
- Electrolyte Bloodwork Form 16.1 – 16.2
- Renal/Liver Bloodwork Form 17.1 – 17.2
- Troponin Bloodwork Form 18.1
- Hormone Bloodwork Form 19.1
- Glycemic Bloodwork Form 20.1

- Donor Physiology Form 21.1 – 21.8

7.4.3 Event Based Data

All **RC**s should be aware of and record relevant data upon occurrence of events such as apnea tests, ancillary tests, motor responses during or after neurological death determination, episodes of arrhythmia, hypotension and acute desaturation and the withdrawal of life support. Withdrawal from the study, as rare as it is, is also considered event based data. This data is captured on the following CRFs:

- Episodes of Arrhythmia Form 22.1 – 22.8 (1 form per episode, may be more than 1 episode/form per study day)
- Episodes of Hypotension Form 23.1 – 23.8 (1 form per episode, may be more than 1 episode/form per study day)
- Episode of Acute Desaturation Form 24.1 – 24.8 (1 form per episode, may be more than 1 episode/form per study day)
- Apnea Tests Prior to C-1 Form 25.1 – 25.6 (2 pages per apnea test)
- Apnea Test Form 26.1 – 26.10 (2 pages per apnea test, may be more than 1 test/form per study day)
- Motor Response During Determination of Neurological Death Form 27.1 – 27.10 (2 pages per motor response, may be more than 1 motor response form per study day)
- Ancillary Tests Form 28.1 – 28.2
- Withdrawal of Life Support Form 31.1 – 31.6
- Eligible Patient Withdrawn Form 45.1

7.4.4 Once Only Data

The initiation of hormone replacement therapy, insulin, vasopressin DDAVP, and temperature control are captured on once only forms. This data may be able to be collected as early as day C and needs to be collected by the end of study. On the last day of study data on diagnostic procedures and imaging, infections and antibiotic use and data on organ suitability needs to be recorded. This data is captured on the following CRFs:

- Hormone Replacement Therapy Form 12.1
- Specific Organ Donation Medications Form 13.1
- Temperature Control After Brain Death Declaration Form 29.1
- Diagnostic Imaging & Procedures Form 30.1 – 30.2
- Infections During Study Period Form 32.1 – 32.2
- Antibiotic/Antimicrobial Form 33.1 – 33.4
- Lung Donor Form 35.1
- Liver Donor Form 36.1
- Kidney Donor Form 37.1
- Heart Donor Form 38.1
- Pancreas/Islet Cell Donor Form 39.1

7.4.5 Once Only Data (Outcome Data)

Outcome data will be collected on recipients to assess organ function at approximately one week and three months after transplant. The following CRFs will be completed by the **MC** by

corresponding with the transplant programs:

- Lung Recipient Form 40.1 – 40.2 (one form per lung)
- Liver Recipient Form 41.1 – 41.2 (one form per lobe)
- Kidney Recipient Form 42.1 – 42.2 (one form per kidney)
- Heart Recipient Form 43.1
- Pancreas/Islet Cell Recipient Form 44.1

7.5 Data Specific to Donor Type

Specific data is needed based on the type of organ donor, depending on whether they are **DND** or **DCD.**

7.5.1 DND Specific Data

DND donors require certain data to be collected that **DCD** donors do not. This includes data regarding apnea tests, motor responses during neurological death declaration, ancillary tests, and temperature control. Therefore, the following CRFs will only be required for DND donors:

- Apnea Test Form 25.1 – 26.10 (Prior to C-1 and C-1 onward)
- Motor Responses During or After Neurological Death Declaration Form 27.1 – 27.10
- Ancillary Tests Form 28.1 – 28.2
- Temperature Control After Brain Death Declaration Form 29.1

7.5.2 DCD Specific Data

DCD donors require certain data to be collected that **DND** donors do not. In this case the DND specific forms are not required but data on withdrawal of life support will be required and captured on the following CRF:

- Withdrawal of Life Support Form 31.1 – 31.6

7.5.3 Changes in Donor Type

In the event that a potential **DND** donor fails an apnea test and cannot be confirmed neurologically dead by ancillary testing the potential **DND** donor may become a **DCD** donor. It is also possible that a potential donor initially thought to be a **DCD** donor progresses to neurological death and becomes a **DND** donor. In either case, both the **DND** and **DCD** specific forms (as listed above) are to be completed.

7.6 Special Considerations for Prospective Data Collection

To facilitate prospective data collection, it is imperative that **RC**s be aware of certain events (neurological assessments, withdrawals of life support etc.) so that they can be present, when possible, to collect time sensitive data. These items are listed on Form 2.1. Although it is encouraged that **RC**s facilitate data collection without relying on OPO or other critical care staff we understand this may not always be possible and consultation with the OPO, nursing or physician staff may be required. **RC**s are encouraged to collect as much prospective data as possible being mindful of time sensitive data.

7.6.1 Time Sensitive Data

The following is a list of events that require real-time (prospective) data collection:

- Patient Registration
- Presence of Organ Donation Coordinator in ICU
- ICU Echos
- Catecholamine Storms
- Episodes of Arrhythmia, Hypotension & Acute Desaturation
- Recruitment Maneuvers
- Apnea Tests (if applicable)
- Motor Movements During Apnea Tests (if applicable)
- Ancillary Testing of Neurological Death
- Withdrawal of Life Support (if applicable)
- Suspected Presence of Infection
- Withdrawal of Patients

The following items are to be collected prospectively:

Item	Form	Question
Patient Registration		
Actual weight at critical area admission	Patient Registration Form 1.1	14
Height (to be measured if not documented)	Patient Registration Form 1.1	15
Presence of Organ Donation Coordinator in ICU		
Is there an organ donation coordinator in the critical care area today?	Daily Data Form 4.1	3
ICU Echos		
Number of critical care echos today (informal, image not saved)	Daily Data Form 4.2	12.7
Catecholamine Storms		
Were any of these medications administered during a catecholamine storm? (based on opinion of intensivist)	Daily Antiarrhythmics & Antihypertensives Form 9.1	4
Recruitment Maneuvers		
Number of recruitment maneuvers	Daily Ventilation Form 5.1	10
Episodes of Arrhythmia, Hypotension & Acute Desaturation		
Number of episodes of arrhythmia today	Daily Data Form 4.2	13
Number of episodes of hypotension today	Daily Data Form 4.2	14
Event of hypotension preceded by…	Hypotension Form 23.1	3
Number of episodes of acute desaturation today	Daily Data Form 4.2	15
Apnea Tests (Items apply to apnea tests prior to C-1 as well, numbering is different)		
Number of apnea tests performed today	Daily Ventilation Form 5.1	11
End tidal CO_2 monitoring	Apnea Test Form 26.1	6.2
PEEP valve in use	Apnea Test Form 26.1	7.2
Did a motor response occur during or after brain death declaration?	Apnea Test Form 26.2	10 (+ Form 27.1-27.2)
Number of physicians in attendance confirming brain death	Apnea Test Form 26.2	11
Ancillary Testing of Neurological Death		

Number of Ancillary Tests	Daily Data Form 4.2	16
Reason for ancillary testing	Ancillary Tests of Neurological Death Form 28.1	1
Withdrawal of Life Support (if applicable)		
All	Withdrawal of Life Support 31.1-31.6	All
Neck circumference (DCD)	Withdrawal of Life Support 31.2	7
Donor physiology after WLS	Withdrawal of Life Support 31.6	All
Suspected Presence of Infection		
Clinical suspicion of pneumonia from most responsible intensive care physician	Infections During Study Period Form 32.1	1
Clinical suspicion of 'other' infection from most responsible intensive care physician	Infections During Study Period Form 32.2	10
Withdrawal of Patients		
Reason patient withdrawn	Eligible Patient Withdrawn Form 45.1	2
Data collection to be allowed	Eligible Patient Withdrawn Form 45.1	3

7.6.2 Data that may Require Consultation with Organ Donation Coordinators

During data collection **RC**s should not rely on OPOs. However, they may need to consult with the organ donation coordinator at the time of consent for organ donation, only AFTER all possible information from hospital records has been obtained. The following is data that may require consultation with organ donation coordinators:

Item	Form	Question
First referral (telephone call or page) to OPO	Patient Registration Form 1.1	2
First 'family/friend' expression of approval/authorization for organ donation	Patient Registration Form 1.1	3
Lung recovery considered any time after consent	Diagnostic Imaging & Procedures Form 30.1	1.1
Kidneys, liver and/or pancreas recovery considered any time after consent	Diagnostic Imaging & Procedures Form 30.1	2.1
Details of organ recovery/decline	Lung Donor Form 35.1 Liver Donor Form 36.1 Kidney Donor Form 37.1 Heart Donor Form 38.1 Pancreas/Islet Cell Donor Form 39.1	All

7.6.3 Data that may Require Consultation with Critical Care Staff

During data collection **RC**s should not rely on critical care staff. However, **RC**s may ask critical care staff about the following items if they were not present for the event:

Item	Form	Question
Number of ICU echos today (Informal, or images not saved)	Daily Data Form 4.1 of 2	12.7
Number of recruitment maneuvers and associated reason	Daily Ventilation Form 5.1	10
Withdrawal of Life Support		
Heparin therapy for DCD	Cessation of Life Support for DCD Form 31.1 of 6	2
Family presence during withdrawal of life support	Cessation of Life Support for DCD Form 31.1 of 6	4

Endotracheal tube cuff leak	Cessation of Life Support for DCD Form 31.2 of 6	6
Initial body position after extubation	Cessation of Life Support for DCD Form 31.3 of 6	12
Monitoring after cessation of life support	Cessation of Life Support for DCD Form 31.3 of 6	17
Was there a premature determination of cardiocirculatory death?	Cessation of Life Support for DCD Form 31.4 of 6	20
Subsequent premature diagnosis of death	Cessation of Life Support for DCD Form 31.4 of 6	20.4
Was there any evidence of bleeding during the withdrawal of life support?	Cessation of Life Support for DCD Form 31.5 of 6	22
Was there bleeding intraoperatively that complicated organ recovery or that required transfusions/	Cessation of Life Support for DCD Form 31.5 of 6	23
Describe any noteworthy aspects of the withdrawal of life support including unique procedures (that may or may not have worked well), interpersonal challenges (with family, staff, operating room teams), or technical difficulties	Cessation of Life Support for DCD Form 31.5 of 6	24

7.6.4 Data that may Require Consultation with Critical Care Physician Staff

There are few items that **RC**s will need to consult a critical care physician about during data collection. They include:

Item	Form	Question
DND Patients		
Were any antiarrhythmics or antihypertensives administered during a catecholamine storm?	Daily Antiarrhythmics & Antihypertensives Form 9.1	4
Estimated delay from perceived time of brain death to time of first apnea test (as judged by the attending intensivist).	Apnea Test Form 25.1 & 26.1	4 & 3 respectively
Estimated delay from perceived time of brain death to time of death confirmed by ancillary testing (as judged by the attending intensivist).	Ancillary Tests of Neurological Death Form 28.2 of 2	13

7.7 Recipient Outcome Data

Outcome data will be collected at one week and three months after transplant to assess function of the transplanted organ. This will be captured on the recipient CRFs Forms 40.1 – 44.1 by staff at the Methods Centre through contact with transplant programs.

7.8 iDATAFAX

The iDATAFAX clinical trial management system will be used for the DONATE pilot study. Sites should enter the data manually into the iDATAFAX system. If necessary, sites may upload hand written pdf files to the database using DFSend. Regardless, timely data collection and transmission is very important for this study. The **MC** personnel will review and validate data in real time as it arrives, for completion and accuracy, and will generate data queries (sent on a bi-weekly or monthly basis depending on patient volume) for local **RC**s.

7.8.1 Completing Hard Copy DATAFAX Case Report Forms (CRFs)

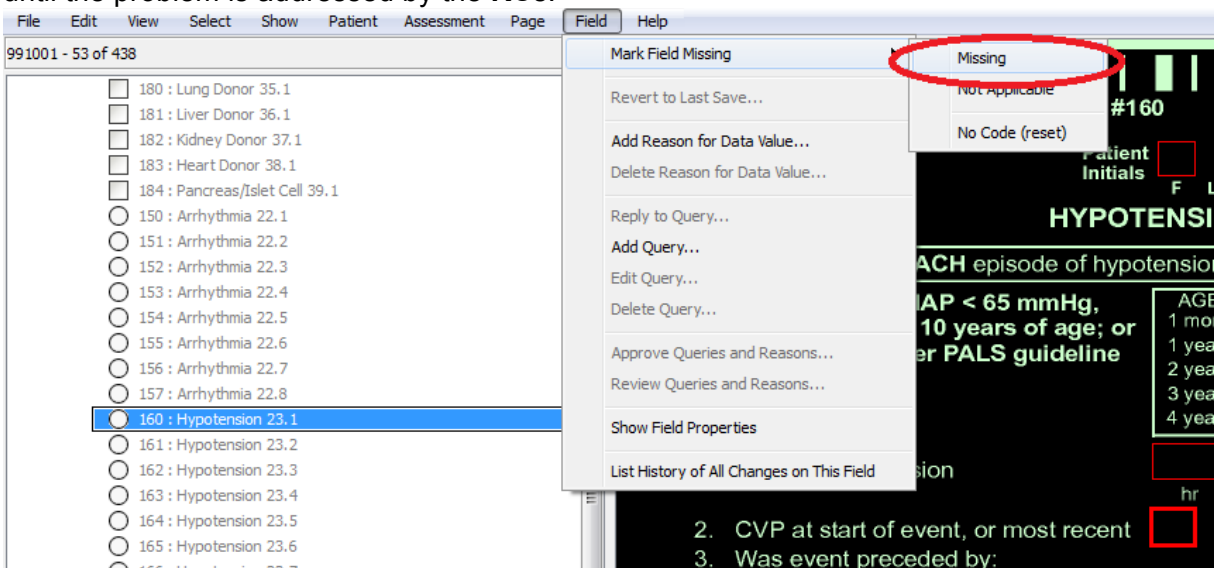
If pdf files are going to be uploaded using DFSend it is important for the data collected on **CRF**s to be completed by certain guidelines for the software to read the data fields appropriately. Refer to Appendix B for Instructions for Completing Hard Copy DATAFAX Case Report Forms (CRFs). Please note that only files with the extension .pdf can be uploaded this way.

7.8.2 Using iDATAFAX

All sites will be given access to the iDATAFAX software for completing electronic records of the **CRF**s. It is important not to share your password or username with anyone, including other members of your research team. Any issues regarding iDATAFAX should be sent to Erika Arseneau. Instructions on how to use iDATAFAX can be found under the help menu under 'about iDATAFAX'.

Any field that is required will appear in red. If no answer is provided for these fields, the form will not be able to be marked as final. Optional fields will appear yellow.

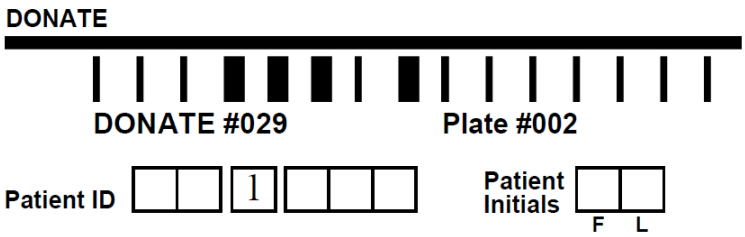
If data is unavailable mark the appropriate fields as missing. Any empty fields not marked as missing, any incorrect, or partially filled fields will be queried by the **MC** and will appear blue until the problem is addressed by the **RC**s.



8 DESCRIPTION OF CASE REPORT FORMS (CRFs)

8.1 Common Items

Each CRF has a header at the top of the page (shown below) that contains a barcode, the **patient ID**, and the patient initials.



8.1.1 Barcode

The barcode is necessary for DATAFAX to electronically pull information from CRFs. The plate number is part of the barcode that makes each CRF form unique, every page number has a different plate number that is not repeated.

8.1.2 Patient ID

The patient ID is the unique number assigned to each patient as described in section 6.2.1. The first two digits correspond to the site number as listed in section 6.2.2. The last three digits correspond to the sequential numbering of enrolled patients at each site.

8.1.3 Patient Initials

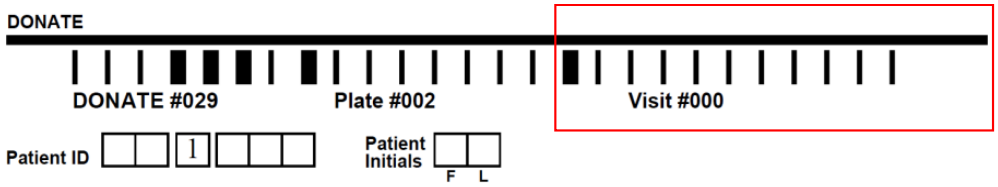
Enter the first initial of the patient's first name in the first space and the first initial of the patient's surname in the second space provided. Alternatively, fabricated initials, keeping a separate log of real versus fabricated initials, may be used according to local research ethics practice.

8.2 Difference Between Once Only, Daily & Event Based Forms

The three types of data (Once Only, Daily and Event Based), described in Section 7.4, are collected on one of two different types of forms.

8.2.1 Once Only Forms

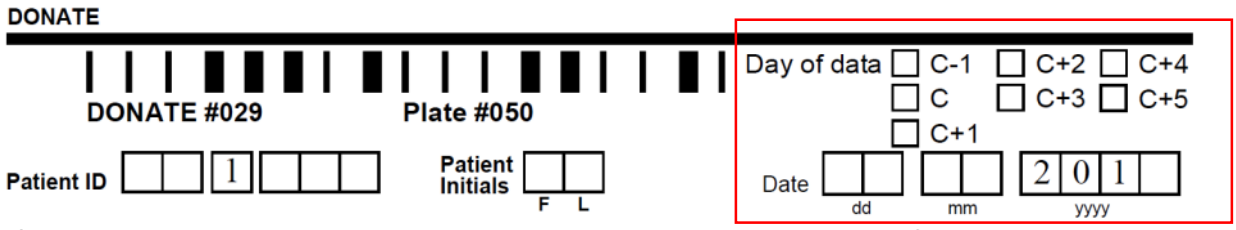
Once Only forms differ from daily forms in that they do not necessitate a study day to be associated with them. For that reason, they each contain the label 'Visit #000' in the barcode as shown below.



All Once Only forms appear in iDATAFAX as required forms under the study day C.

8.2.2 Daily Forms

Daily Forms require a study day be associated with the form (i.e. C-1, C, C+1 etc). See Section 7.3.1 for the definition of each study day. The option to indicate which study day is being recorded can be found at the top right of the barcode as shown below.



After checking the study day, you are prompted to complete the date field. Enter the calendar

day that corresponds to the study day. For example, if a potential donor was consented on November 27th, 2015 and data is to be entered for the previous day, you would check C-1 and the date field would read 26 11 2015.
All Daily forms appear in iDATAFAX as required forms under the study day to which they are assigned.

8.2.3 Event Based Forms

Event Based data is captured on both types of forms described above. All Event Based forms appear in iDATAFAX as optional forms.

8.2.3.1 Event Based 'Once Only' Forms

If the event is something that only occurs once such as the withdrawal of life support the data is captured on a 'once only' form. Below is a list of Event Based data captured on Once Only Forms:

- Apnea Tests Prior to C-1 Forms 25.1 – 25.6 (2 forms per apnea test)
- Ancillary Tests Forms 28.1 - 28.2
- Withdrawal of Life Support Forms 31.1 – 31.6
- Eligible Patient Withdrawn Form 45.1

All of the above forms appear in iDATAFAX under study day C.

8.2.3.2 Event Based 'Daily' Forms

If the event is to be recorded each day of occurrence such as episodes of arrhythmia, the data is captured on a 'daily form'. Below is a list of Event Based data captured on Daily Forms:

- Arrhythmia Forms 22.1 – 22.8 (1 form per episode of arrhythmia)
- Hypotension Forms 23.1 – 23.8 (1 form per episode of hypotension)
- Acute Desaturation Forms 24.1 – 24.8 (1 form per episode of acute desaturation)
- Apnea Tests Forms 26.1 – 26.10 (2 forms per apnea test)
- Motor Responses During or After Neurological Death Declaration Forms 27.1 – 27.10 (2 forms per motor response)

Note that there are multiple numbered forms for each event (i.e. Arrhythmia Form 22.1, Arrhythmia Form 22.2 etc.). The purpose of this is to be able to capture multiple events that occur within the same study day. If more than one event occurs in a study day the subsequent forms must be completed. Start back at form 1 for the next study day. For example, on day C-1 patient X experiences 2 episodes of hypotension. In this case Hypotension Form 23.1 and Hypotension Form 23.2 are to be completed with C-1 checked off as the day of study. On day C the patient experiences 1 episode of hypotension. A second Hypotension Form 23.1 is now completed with C checked as the day of study.
All of the above forms appear in iDATAFAX under the day of study to which they are assigned.

9 HOW TO COMPLETE CASE REPORT FORMS

This section will describe specific directions on how to answer questions posed in the CRFs. Each CRF is presented similar to the order **RC**s will be completing them and are separated into the four types of data described in Section 7.4. References to specific items on each form will be referenced by question number (i.e. Q1). All dates should follow the format specified (dd/mm/yyyy) and all times should be entered according to a 24 hour clock (hr:mm).

9.1 Once Only CRFs (at Enrolment)

The following forms are to be completed as soon as a patient is enrolled in the study.

9.1.1 Site Form

This form is completed annually for all each individual study site. Completed forms may be scanned and e-mailed to Erika Arseneau (arsenee@mcmaster.ca) or faxed to Lori Hand at (905) 527- 0250.

9.1.1.1 Organs transplanted at hospital site (Q6)

A transplant program in the same hospital site as the critical care area/ICU where the patient is.

9.1.1.2 Conscientious Objection (Q7)

Some physicians may have an opposition to a part or parts of the organ donation process. It is possible in this case that some physicians may transfer care to an alternative ICU physician.

9.1.1.3 Local organ donation coordinator (Q8)

The local Organ Donation Coordinator (OD Coordinator) or "Infirmiere ressource" for Quebec sites, is a healthcare provider overseeing all aspects of organ donation in the hospital on a daily basis.

9.1.1.4 Protocols in the ICU (Q9)

For each protocol (Q9.1 to 9.7) it is important to indicate if there is a corresponding order set or guideline/checklist.
An *order set* is a document that must be signed off by a physician in order to be implemented.
A *guideline/checklist/protocol* is a hospital document not requiring medical signature for implementation.

9.1.2 Patient Registration Form 1.1

When a patient is consented for organ donation, they are enrolled in the study and a patient ID is assigned as described in Section 6.2.

9.1.2.1 Organ Procurement Organization (OPO) identification number (Q1)

The OPO identification number is a unique number assigned to each organ donor by the corresponding OPO. Depending on the province the number of alpha or numeric digits may vary. Please right justify this number preceded by zeros, if applicable (i.e. 0000123456789).

9.1.2.2 First referral (Q2)

First referral to OPO is defined as the first notification from any healthcare provider to the OPO centre or the local coordinator (if any). If both are notified, consider the first one. Remember, if any piece of data is unavailable, mark as `missing`.

9.1.2.3 First family/friend expression of approval (Q3)

Expression of approval to consent for organ donation is defined as the first time a substitute decision maker verbally expressed their consent for organ donation. This could be expressed during discussions with any of; physicians, critical care/**ICU** staff, or **OPO**

staff.

9.1.2.4 Formal consent to organ donation (Q6)

The time on the provincial **OPO** consent form for organ donation. If not documented, consult the appropriate **OPO** staff.

9.1.2.5 Research coordinator initiated data collection (Q7)

The day and time the local **RC** recorded the first value of data on the patient other than assigning their **patient ID**. This will not be used in any way to assess performance of **RC**s, but will be used to assess the feasibility of collecting prospective data for this study.

9.1.2.6 Expected donor type at study registration (Q9)

Indicate whether the patient is expected to be a **DND** or **DCD** donor at the time of registration. If the expected donor type changes at any point, indicate when this change occurs on the Daily Data Form 4.1 (Q2).

9.1.2.7 Admission to the study hospital ICU (Q10)

Refers to the date of admission to hospital where the study critical care area is located.

9.1.2.8 Intubation date (Q11)

Refers to the date of endotracheal intubation associated with the presenting illness resulting in admission to a critical care area.
For patients that have failed extubation, or self-extubated and are re-intubated, please include the original date of intubation.

9.1.2.9 Height (Q15)

If height of the patient is not documented, make sure to measure it and record appropriately.

9.1.2.10 Apnea tests prior to C-1 (Q16)

At the time of registration, it is important to indicate whether an apnea test was performed prior to the first day of data collection (C-1). If an apnea test was performed prior to C-1 indicate this on the registration form and record how many. Fill out the Apnea Test Prior to C-1 Forms 25.1 – 25.6 (2 forms for every apnea test performed).

9.1.3 Data Collection Form 2.1

For organ donation during evenings or weekends actual data collection may not be able to begin at the time of or day of consent for organ donation.

9.1.3.1 Earliest time point data is available (Q1)

In some cases, data from day C-1 may not be available or may not be applicable. Indicate the earliest time point at which data is available in terms of study day.

9.1.3.2 Final day of data collection (Q2)

When the final day of study occurs (refer to Section 9.2.1.1) indicate which study day is the final day of data collection.

9.1.3.3 Time sensitive data

On this form is the list of time sensitive data to be collected (Section 7.6.1). This is to be used as a reference.

9.1.4 Medical History Forms 3.1 & 2.3

9.1.4.1 Principal diagnosis leading to deceased organ donation (Form 3.1 Q1)

Refers to the diagnosis reported on the death certificate. Check the ONE option that most closely represents the principal diagnosis. If not in list of diagnoses, check 'other' and specify the diagnosis.

9.1.4.2 Pre-existing medical conditions (Form 3.2 Q1-18)

Pre-existing medical conditions may affect the number of organs available and the quality of organs recovered. For these reasons, review of the patient's past medical history is important. Check all conditions that apply based on your evaluation of medical notes and ask the medical team if in doubt.

9.1.5 Apnea Test Prior to Day C-1 Forms 25.1 – 25.6

This form is to be completed for all donors who underwent an apnea test prior to the day before consent. Instructions for filling out this form are the same as for Apnea Test Forms 26.1 – 26.10 except for Q1 which asks for the calendar date on which the apnea test prior to C-1 was performed.

9.2 Daily CRFs

The following forms are to be completed for each study day, from C-1 to the final day of data collection.

9.2.1 Daily Data Forms 4.1 & 4.2

9.2.1.1 Final day of study (Q1)

The day that the patient

i) goes for organ recovery surgery,
ii) suffers a complication that excludes them from organ donation or
iii) has all organs declined, is defined as the final day of study.

Each time this form is filled out, indicate whether any one of these events occurred and specify which one.
Types of *complications that may occur during organ donor management and exclude the patient from organ donation,* include but are not limited to the following; cardiac arrest, septic shock, cancer identified during organ assessment etc.

9.2.1.2 Change in expected donor type (Q2)

Refer to Section 7.5.3.

9.2.1.3 Motor response after neurologic death declaration (Q4)

For expected **DND** donors, any motor responses that occur after declaration of neurologic death should be recorded. In addition to recording the presence of the movement on this form, fill out the Motor Responses During or After Neurological Death Declaration Form 27.1-27.10 (2 forms per movement). If the patient is an expected **DND** donor but has not yet been declared brain dead check 'NA (neurologic death not confirmed)`. If the patient is a DCD donor, check 'NA (DCD)'.

9.2.1.4 Protocol/order sets used today (Q5)

Please indicate which order sets, guides or checklists used in donor management for the study day indicated on the daily data form. If none were used check "none".

9.2.1.5 Pneumonia prevention (Q6)

If the type of endotracheal tube or feeding tube changes at any point during the study day, check off the type that was used for the majority of that study day.

9.2.1.6 CSF (Q9.1)

CSF refers to cerebral spinal fluid.

9.2.1.7 ICP (Q9.2 & 10)

ICP refers to intracranial pressure. Types of alternative measurement devices include but are not limited to; intraparenchymal/subdural drains.

9.2.1.8 Target arterial pressure and systolic blood pressure (Q12.2. & 12.3)

For both questions, enter either the target mean pressure or the target pressure range.

9.2.1.9 Echocardiography (Q12.7)

Echocardiographs are often referred to in the CRFs as echos.
May need to consult with nursing or other ICU staff to obtain the number of critical care area/ICU echos on a study day.
Note that a cardiology echo is defined as an echocardiogram performed by a cardiologist. If patient is cared for within the cardiac care unit (CCU) it is probable that all echos are cardiology echos.
If more than one echo per day record the final ejection fraction from the last echo performed within that study day.
If no echos were performed, check off 'NA – no echos' for the final ejection fraction.

9.2.1.10 Number of episodes of arrhythmia, hypotension and acute desaturation (Q13-15)

Keep track of all episodes or arrhythmia, hypotension and acute desaturation by recording the details of the events on the respective Arrhythmia, Hypotension and Acute Desaturation Forms 22 – 24 and record the total that occurred within a study day on this form.

9.2.1.11 Ancillary tests of brain function performed today (Q16)

Ancillary tests of brain function include conventional 4-vessel cerebral angiography, CT angiography, MR angiography, and radionucleotide tests. Any other type of test used to assess blood flow in the brain is considered an ancillary test of brain function and should be considered when answering this question. Ancillary tests should be recorded for all donors.

9.2.2 Daily Ventilation Form 5.1

9.2.2.1 Tidal volume (Q1)

Record the exhaled tidal volume displayed on the ventilator for patients on pressure control or pressure support modes. Record the inspired tidal volume set on the ventilator for patients on volume control mode (including volume-targeted pressure regulated modes).

9.2.2.2 Positive end-expiratory pressure (PEEP) (Q2)

Record the positive end-expiratory pressure (PEEP) set on the ventilator.

9.2.2.3 Mean airway pressure (Q3)

Record the value displayed on the ventilator.

9.2.2.4 Plateau airway pressure (Q4)

For donors on pressure control or pressure support modes, plateau airway pressure = set drive pressure + PEEP. For donors on volume assist control or volume-targeted pressure regulated modes, perform an inspiratory hold of 0.5 – 1.0 seconds on the ventilator.

9.2.2.5 Highest FiO_2 recorded today (Q6)

Refers to the highest FiO_2 set on the ventilator within the last 24 hours.
Do not record FiO_2 set at 1.00 for the purpose of a bronchoscopy or lung transplant assessment.

9.2.2.6 Highest PaO_2 on FiO_2 1.00 recorded today & lowest PaO_2 on FiO_2 1.00 recorded today (Q7-8)

With or without FiO_2 set at 1.00 for transplant assessment, a procedure, or recruitment maneuver.

9.2.2.7 Other respiratory adjuncts used today (Q9)

Other respiratory adjuncts used today include the following; extra corporeal life support or membrane oxygenation (ECLS/ECMO), high frequency oscillatory ventilation (HFO), flolan, airway pressure release ventilation (APRV) or BiLEVEL.
If a different type of respiratory adjunct was used that is not listed, check other and specify the adjunct.

9.2.2.8 Number of recruitment maneuvers (Q10)

The goal of this intervention is to open the lung by applying a distending pressure for a prolonged period of time (seconds).
RCs are to record reasons for recruitment maneuvers (RMs).

9.2.2.9 Number of apnea tests performed today (Q11)

Apnea tests are performed at the time of the neurological declaration of death.
Keep track all apnea tests by recording the details of the tests on the Apnea Test Forms 26.1 – 26.10 (2 forms per test).
Record the total that occurred within a study day on this form.

9.2.3 Daily Blood Products & Colloid Therapy Form 6.1

Include on this form all blood products given. This includes any products on day C-1 that were given in the ER.

9.2.3.1 Differentiation of O negative blood and uncrossmatched blood (Q1&2)

Based on information available in the patient's chart, i.e. "blood product slip" and donor's blood type.

The number of units administered is based on the following equivalence:

Product	Volume or # administered	Number of "Study" units
O negative blood transfusion	1 unit	01
Uncrossmatched blood	1 unit	01

Matched red blood cells	1 unit	01
Fresh frozen plasma	1 unit	01
Platelet "pack"	6 units	01
Cryoprecipiate	10 units	01

9.2.3.2 Reason code for transfusion/treatment

Bleeding and coagulopathy is not an outcome of this study.
For this reason, the definition of active bleeding or abnormal laboratory results is not specified. The reason for the transfusion should correspond to the reason of the medical team.
Procedures include but are not restricted to:

- Intravascular access
- Bronchoscopy, gastroscopy, etc.
- Biopsy
- Cardiac pacing
- Paracentesis or other (i.e. pericardiocentesis)
- Chest tube insertion (includes pig-tail catheter)
- Lumbar puncture
- External ventricular drain insertion
- Intracranial pressure device insertion

9.2.4 Daily Volume Status Form 7.1

9.2.4.1 Additional fluid therapy (Q1)

Indicate only fluid therapy that was given in addition to maintenance fluid.
Do not include fluids running strictly for the purposes of medication administration.

9.2.5 Daily Sedation & Analgesia Form 8.1

Sedation and analgesia administered in the operating room should not be recorded on this form. Drugs given as a bolus, routine doses or infusions should be reported.

9.2.5.1 Final administration

If drug(s) was/were administered by an infusion, please consider the time of infusion cessation as the final administration.
If more than one drug was administered record the final administration of the last agent administered.
If final administration occurred at time of organ recovery, please enter the date and time of organ recovery.

9.2.5.2 Reversal agents given prior to death declaration (Q5)

This question is to be answered for all **DND** patients.
If patient is **DCD** check 'NA – DCD'.

9.2.6 Daily Antiarrhythmics & Antihypertensives Form 9.1

Antiarrhythmics and antihypertensives administered in the operating room should not be recorded on this form.
Agents may be administered as a bolus or infusion. NG antihypertensives include monocor,

amlodipine, clonidine.
If antiarrhythmic is administered for the treatment of heart rate less than 50 beats per minute (bpm) or more than 150 bpm, please fill the Arrhythmia Form 23.1.
If vasopressor or inotropes are administered for a mean arterial pressure (MAP) of <65 mmHg or is according to the Pediatric Advanced Life Support (PALS) guideline on Hypotension Form 23.1 for patients <10 years of age, please fill out the Hypotension Form 24.1.

9.2.6.1 Medications administered during a catecholamine storm (Q4)

This question is to be answered for all **DND** patients.
If patient is **DCD** check 'NA – DCD'.
A catecholamine storm is defined as any hemodynamic instability preceding a diagnosis of brain death.
Consult the ICU intensivist to determine whether antiarrhythmics and antihypertensives were administered during a catecholamine storm.

9.2.7 Daily Vasopressors & Inotropes Form 10.1

Vasopressors and inotropes administered in the operating room should not be recorded on this form.
Select ALL vasopressors administered by infusion only to the patient.
If any of the vasopressors or inotropes listed on this form were administered record the cumulative number of hours and maximum rate. For any of the vasopressors and inotropes listed, if they were not administered check 'NA'.

9.2.7.1 Cumulative hours

Cumulative hours of infusion should be rounded to the nearest hour. For example, if a potential donor was on norepinephrine infusion for 12 hours and 31 minutes the cumulative hours should be entered as 13 hours.
If patient was on infusion for less any period less than one hour, record as 01 hours.

9.2.7.2 Maximum Rate

The maximum rate of infusion within the last 24 hours could be established with the chart available in this document (see Appendix C).
Make sure to check off the appropriate units.
If necessary, round the rate so two decimal places.

9.2.8 Daily 'Other' Medications Form 11.1

This form is complementary to Forms 8.1 – 10.1, 12.1 & 13.1. Accordingly, the 'other' option (Q28-29) excludes inotropes, vasopressors, antihypertensive agents, antiarrhythmics, hyper osmolar therapy, sedatives, analgesics, and hormone therapy. The 'other' should be used to capture medications that are known to affect organ function (i.e neuromuscular blockers etc.) or are used primarily for organ donors.
Electrolyte repletion is not necessary to capture however a solution such as GIK (glucose-insulin-potassium) which is prepared by the pharmacists for organ donors, should be captured.
If the patient is on no medications listed on this form, or no medications that should be listed as 'other' check off 'none'.

9.2.8.1 Insulin (Q6)

Indicate whether insulin was administered as continuous infusion, as IV bolus or subcutaneously.

9.2.9 Bloodwork Forms 14.1 – 20.1

Bloodwork forms are to be completed for each day of study.
They are structured as a once only form where each study day is recorded on a different row. This section of forms includes hematology, acid-base, electrolyte, renal/liver, troponin and hormone bloodwork results.
Make sure when entering bloodwork to record results according to the units listed, convert if necessary.
Fill in any bloodwork values that correspond to what is listed. If there are no values for an entire row of data check NA.
For any test where a result is not available enter that value as missing in iDATAFAX. If only one value is available for an entire row of data, enter that value and mark the rest of the values as missing.

9.2.9.1 Highest, lowest, worst

'*Highest*': Refers to the highest value on the specified study day. If only a single value is available for a given study day, enter that value accordingly.
'*Lowest*': Refers to the lowest value on the specified study day. If only a single value is available for a given study day, enter that value accordingly.
'*Worst*': Instructions will vary depending on the analyte. Refer to the instructions on the **CRFs** (could be hypo or hyper depending on the analyte listed).

9.2.9.2 Prior to hospital, ER, C values, final

While some data may appear repetitive, this data must be collected at different time points because it could influence the assessment of the viability of organs.
'*Prior to hospital*': If available, record the most recent value (within the last year) prior to the current admission.
'*ER*': Applies only to when the patient is treated in the emergency room.
'*C-1, C, C+1…*': Refers to the corresponding study day, specifically while in a critical care area. If patient is in ER and a critical area in the same day, record the appropriate values under each category, even if they are the same.
'*Final value*: Refers to the last value available before the potential donor goes to the operating room for organ recovery. This value may be the same as the value in the **ICU**.

9.2.9.3 Hematology Bloodwork Form 14.1

WBC refers to white blood cells.
Hgb refers to hemoglobin.
INR refers to promthrombin time.
PTT refers to partial thromboplastin time.

9.2.9.4 Acid Base Bloodwork Form 15.1

Please record arterial blood gas (ABG) values at lowest pH. Enter the lowest pH value that corresponds with the ABG values.
Do not include ABG values that were part of an apnea test or recruitment maneuvers.

9.2.9.5 Electrolyte Bloodwork Form 16.1 & 16.2

If both occur in one day, hypernatremia is worse than hyponatremia in regards to sodium values.
For potassium, hyperphosphatemia is worse than hypophosphatemia.

9.2.9.6 Renal/Liver Bloodwork Form 17.1 & 17.2

AST refers to aspartate aminotransferase.
ALT refers to alanine aminotransferase.

9.2.9.7 Troponin Bloodwork Form 18.1

The type of troponin test available may vary according to your hospital standard procedures. For any test which you do not have a value for, mark the field as missing.
For high sensitivity troponin indicate whether the value corresponds to Trop T or Trop I by checking the appropriate box.

9.2.9.8 Hormone Bloodwork Form 19.1

Hormone bloodwork is not typically performed more than once a day. If there is more than one result for the tests listed here, record the highest value for each.
TSH refers to thyroid stimulating hormone.

9.2.9.9 Glycemic Bloodwork Form 20.1

RCs should record the maximum random glucose level with the last 24 hours (not fasting glucose).
The number of hours and minutes (estimated) that the patient's random glucose was above 8 mmol/L should be recorded along with the number of hours and minutes the patient's glucose was below 4 mmol/L.
If the patient's glucose was never above 8 mmol/L or below 4 mmol/L, enter 00:00.

9.2.10 Donor Physiology Forms 21.1 – 21.8

Donor physiology forms are to be completed for each day of study. They are structured as a once only form where each study day is recorded on a different row.
Donor's physiology data play a crucial role in the transplant assessment of organs. To this end, a number of data are collected. On Form 21.1 record the day and time of consent.
After time of consent, record all physiological data available every 4 hours.
If more than one set of physiological is data available **within the 4-hour window**, record the data that falls closest to the times recorded. For example, if consent occurs at 11:30, and vitals are available at 11:31, 13:31 and 15:29. The values for 11:31 should be entered at C, and the values for 15:29 should be entered for C+4. If, however only 13:31 was available, this data should be entered under C+4 because it is closer to C+4 than C.
If no data is available for any given time point check 'NA'.
If some data are available but not others, fill in the available data and mark the remaining fields as missing.
Physiological data collection is recorded until **DND** donors are leaving the ICU for organ recovery.
Do NOT record data after withdrawal of life support for **DCD** on this form (this is captured on Form 31.6).

9.2.10.1 Date and Time of Consent

Record the date and time of formal written consent for organ donation. This field corresponds with Q6 on Patient Registration Form 1.1.

9.2.10.2 Core temperature

Check off whether the core body temperature is measured in degrees Celsius or Fahrenheit. Stay consistent as to which unit is chosen.

9.2.10.3 Additional forms required

If physiology data is available past C+12 hrs, check the box at the bottom of the page indicating additional forms are required. Do this for every subsequent page until you reach the hour that corresponds with the last data available for the final day of data collection.

9.3 Event Based CRFs

For arrhythmia, hypotension, acute desaturation, apnea tests, and motor response events it is possible that more than one event may happen per day. In this case it is important to use sequentially numbered forms as described in Section 8.2.3.2.
Episodes of arrhythmia, hypotension and acute desaturation do not need to be captured after the time of withdrawal of life support.

9.3.1 Arrhythmia Forms 22.1 – 22.8

Please complete this form whenever potential donors have heart rate <50 bpm or >150 bpm where medical intervention is required (pharmacological agents, defibrillation or cardioversion, pacing or cardiopulmonary resuscitation).
Include episodes of arrhythmia that occur during apnea testing.
More than one form may need to be completed per day because of a:

- New episode of the same arrhythmia
- New episode of another type of arrhythmia or,
- Modification in the medical intervention for the same arrhythmia

NOTE: Occasional premature ventricular contractions (PVCs) for multiple hours, and a heart rate between 50 – 150 bpm is NOT considered an episode of arrhythmia.

9.3.1.1 Arrhythmia ongoing from previous day (Q3)

If the same arrhythmia continues overnight, it is considered to be ongoing from the previous day.

9.3.1.2 Type of arrhythmia (Q4)

If more than one type of arrhythmia is present within a single event, check the first rhythm that was noted.

9.3.1.3 Treatment (Q6)

If no defibrillation/cardioversion or pacemaker treatment was performed make sure to check 'NA' appropriately.

9.3.1.4 Whether the process of organ donation continued or not (Q9)

If the process of organ donation did not continue after the event of arrhythmia this indicates the final day of data collection. On Daily Data Form 4.1 indicate this discontinuation by checking off that the patient suffered a complication that excluded them from organ donation (Section 9.2.1.1).

9.3.1.5 Additional arrhythmia events in the same study day

If more than one episode of arrhythmia occurs within the same study day check the box at the bottom of the form. The next episode of arrhythmia should be recorded on the next sequentially numbered form (refer to Section 8.2.3.2).
Start back at Arrhythmia Form 22.1 for arrhythmias that occur on a different study day.

9.3.2 Hypotension Forms 23.1 – 23.8

Please complete this form when the patient has a mean arterial pressure (MAP) of <65 mmHg

requiring medical intervention.
More than one form may need to be completed per day for the following reasons:

- New episode of hypotension
- New episode of hypotension following the complete resolution of a previous episode
- Refractor hypotension requiring modification in treatment

9.3.2.1 CVP (Q2)

Record the CVP at the start of the event.
If this data is unavailable, record the most recent CVP to the time of the event.
If the most recent CVP is unavailable, mark the field as missing.

9.3.2.2 Vasopressors & Inotropes (Q6.2&6.3)

For any vasopressors or inotropes initiated at the time of hypotension record not only the end time but the end date. This will allow you to capture medications that were continued to the next study day due to the episode of hypotension.

9.3.2.3 Additional hypotension events in the same study day

If more than one episode of hypotension occurs within the same study day check the box at the bottom of the form. The next episode of hypotension should be recorded on the next sequentially numbered form (refer to Section 8.2.3.2).
Start back at Hypotension Form 23.1 for episodes of hypotension that occur on a different study day.

9.3.3 Acute Desaturation Forms 24.1 – 24.8

An episode of acute desaturation is defined as a patient having more than ten minutes of saturation < 90%.

9.3.3.1 Additional hypotension events in the same study day

If more than one episode of acute desaturation occurs within the same study day check the box at the bottom of the form. The next episode of acute desaturation should be recorded on the next sequentially numbered form (refer to Section 8.2.3.2).
Start back at Acute Desaturation Form 24.1 for episodes of acute desaturation that occur on a different study day.

9.3.4 Apnea Test Prior to C-1 Forms 25.1 – 25.10

This form is to be completed for all donors who underwent an apnea test prior to the day before consent.
Instructions for filling out this form are the same as Section 9.3.5 below.
Be aware that the numbering is different on the two forms due to the additional Q1 on this form not present on the Apnea Test Forms (26.1 – 26.10). Q1 refers to the date the apnea test was performed prior to C-1.

9.3.5 Apnea Test Forms 26.1 – 26.10

9.3.5.1 Confirmation of neurologic death (Q1)

If neurologic death is confirmed by the apnea test, make sure to enter the time of death (Q2) and the estimated delay from perceived time of death (Q3).
If neurologic death is not confirmed by apnea, enter 'no' and skip Q2-3 and go straight to Q4.

9.3.5.2 Time of death declaration by neurologic criteria (Q2)

Refers to the time reported on the OPO forms of neurologic death declaration. In case of two separated declarations (i.e. pediatric cases), record the time of the second declaration.

9.3.5.3 Did a motor response occur during or after death declaration? (Q10)

This question refers to spinal reflex from the time of neurological death declaration up to the time of organ recovery.
In case this situation is reported by health care providers, OPO coordinators or is noticed by **RCs**, fill out Form 27.1 – 27.2.

9.3.5.4 Physicians confirming neurologic death (Q11)

You may check more than one specialty per physician however you may only select one role for each physician.

9.3.5.5 Additional apnea tests in the same study day

If more than one apnea test occurs within the same study day check the box at the bottom of the form. The next apnea test should be recorded on the next sequentially numbered form (refer to Section 8.2.3.2).

9.3.6 Motor Responses After or During Neurological Death Declaration 28.1 - 28.2

This form is completed only for **DND** donors if a motor response is witnessed by healthcare providers, OPO coordinators or **RC**s beginning at the time of neurological death declaration.
If two different movements occurred simultaneously one form (2 pages each) must be completed for each movement.

9.3.6.1 Typical spinal reflex (Q1.1)

Typical spinal reflexes could be, but are not restricted to, one of the following:

- Plantar flexion response (ankle flexion or withdrawal response unilateral or bilateral)
- Abdominal reflex (contraction of the abdominal muscles resulting in deviation of the umbilicus)
- Triple flexion response (thigh flexes toward the pelvis, the calf toward the thigh and the foot toward the calf)
- Extension and pronation of the arm
- Undulating toe (slow flexion/extension movements of toes, spontaneous)
- Unusual facial movement
- Head turning

9.3.6.2 Lazarus sign (Q1.2)

Lazaraus sign is described as:

- One or both arms flexed at elbows with hands brought to chin or face and then returned to the bed beside the body

9.3.6.3 Atypical movement (Q1.3)

Atypical movement can be complex.

Here is a list of movements that could be considered as atypical:

- Extensor posturing (back arching to left or right spontaneously)
- Facial myokymia (intermittent repetitive undulating muscle contractions of left cheek)
- Spinal myoclonus (multifocal myoclonus involving lower limbs and abdominal muscles)
- Respiratory like movement (both shoulders adduct and slow cough like movements)
- Hugging-like movements
- Limb elevation with neck flexion (rapid jerk raising all four limbs off the bed with passive neck flexion)

9.3.6.4 Judged not to be neurologically dead on the basis of movement (Q6)

If the patient is judged NOT to be neurologically dead on the basis of this movement, the expected donor type may change from **DND** to **DCD** (indicate this on the Daily Data Form 4.1 Q2).

9.3.6.5 Additional motor movements in the same study day

If more than one motor movement occurs within the same study day check the box at the bottom of the form. The next motor movement should be recorded on the next sequentially numbered form (refer to Section 8.2.3.2).

9.3.7 Ancillary Tests of Neurological Death Forms 28.1 & 28.2

Ancillary tests are used to confirm death by neurologic criteria when there are potential confounders that could not be corrected. For example, it is possible that the apnea test results are uncertain or that an apnea test could not be performed (i.e. when on CO_2 retainer).

9.3.7.1 Reasons for ancillary tests (Q1-5)

Typically, there are four categories for indications of ancillary tests,

i) confounders,
ii) inability to complete one or more aspects of the neurological exam,
iii) inability to complete the apnea test and iv) primary brainstem injury.

If none of these reasons apply, check 'other' and specify the reason for ancillary testing. If more than reason applies, check all. Reasons for ancillary testing can be elucidated from discussion with the ICU team or diagnostic imaging requisitions.

9.3.7.2 Flow

Any indication of flow should be checked as flow (i.e. high flow, poor flow, minimal flow).

9.3.7.3 Complications during ancillary testing (Q11)

Record if arrhythmia, hypotension, desaturation or any other type of complication occurs during ancillary testing. If arrhythmia, hypotension, or desaturation occur make sure to fill out the associated event forms (Forms 22 – 24).

9.3.7.4 Date and time of death (Q12)

If ancillary tests confirm neurologic death make sure to record the date and time of death. If neurologic death cannot be confirmed check 'NA – neurologic death not confirmed'.

9.3.8 Withdrawal of Life Support Forms 31.1 – 31.6

If possible, **RCs** should collect data at the time of withdrawal of life support.
If necessary, consult with ICU staff to gather necessary data.

9.3.8.1 Withdrawal of Life Support (WLS)

Withdrawal of life support is defined by at least one of the following interventions:

- Cessation of mechanical ventilation or non-invasive ventilation
- Endotracheal extubation
- Endotracheal cuff leak
- Cessation of vasopressor therapy
- Cessation of inotropes

9.3.8.2 Family presence during WLS (Q4)

Family presence during DCD assessment refers to the presence of at least one relative in the physical location from the time of withdrawal of life support up to and including the second confirmation of death by cardiocirculatory criteria.

9.3.8.3 Discontinuation of vasopressors, ECMO/ECCOR, IABP, LVAD/RVAD (Q13-16)

If the patient was not any of the above therapies make sure to check NA in regards to discontinuation.

9.3.8.4 Analgesia & Sedation (Q18&19)

Only include on this form changes to pain medication in the 4-hour period prior to WLS and before organ recovery surgery.
If the level of any drug changed more than once during the 4-hour period (i.e. was increased and then decreased) record the NET effect (i.e. overall decrease).

9.3.8.5 Premature determination of cardiocirculatory death (Q20)

In rare instances it is possible that there may be a delayed unassisted return of spontaneous circulation after cessation of cardiopulmonary resuscitation (also known as Lazarus autoresuscitation phenomena). If this occurs, please record the details of the premature determination of cardiocirculatory death and the confirmatory diagnosis of death.
If this does not occur, check 'no' and proceed to Q21.

9.3.8.6 Bleeding intraoperatively during organ retrieval (Q23)

If patient did not die within timeframe for organ donation or was excluded from organ donation for any other reason, indicate `NA – patient did not go for organ recovery`.

9.3.8.7 Physiology data after WLS

This data is not often charted by ICU staff. When possible, make sure to be present at the WLS to be able to collect this time sensitive data.
If possible please provide the bedside nurse with a form to record the vital signs every 15 minutes during WLS (see Appendix D).
If there is no data for a given time point check 'NA'. Data that was unable to be obtained should be marked as missing.
If the patient did not die in the time frame for organ donation, make sure to note this on the Daily Data Form 4.1 Q1 as 'all organs were declined today'.

9.3.9 Eligible Patient Withdrawn Form 45.1

This form will only need to be filled out in the rare occurrence that a patient withdraws from the study. For each withdrawal make sure to provide details in regards to justification of the withdrawal. Given that this is a pilot study, data collected on this form are vital in the assessment of feasibility.

9.4 Once Only CRFs (Near End of Data Collection)

These forms are to be completed once only during the donor management period. We suggest they should be completed as data becomes available, however they must be completed by the time of organ recovery. Data collected should reflect the management from the day prior to consent (C-1) up to and including the day of organ recovery.

9.4.1 Hormone Replacement Therapy Form 12.1

For both thyroid hormone and corticosteroids, record the date and time of first dose and the dosage.
If only one dose, check 'one dose'.
If regular dose, indicate how often and at what dosage.
If first dose is different from regular dosage check both 'one dose' and 'regular dosing' and indicate the dosage of each as described.

9.4.1.1 Thyroxine (Q1.3)

Thyroxine (T4) may also be charted as levothyroxine.

9.4.2 Specific Organ Donation Medications Form 13.1

This form captures administration of medication ordered specifically for organ donation, vasopressin and DDAVP (or desmopressin), administered anytime from consent to the time of organ recovery or organ decline.
If either medication was not administered, please indicate this by checking 'NA'.

9.4.3 Temperature Control After Neurologic Death Declaration Form 29.1

This form should only be completed for **DND** donors.
If no physician order was placed for temperature management make sure to indicate 'no' for Q1. In this case no further questions require answers.
In the event that there was a physician order for temperature management, it is important to answer all questions on the remainder of the form.

9.4.4 Diagnostic Imaging & Procedures Forms 30.1 & 30.2

On this form when entering the number of images or procedures, make sure to enter 00 if none were performed.

9.4.4.1 Organ Biopsy (Q8)

To determine whether a biopsy was performed consult the operating room notes or the operation report.
If no pre- or intra- operative biopsies were performed make sure to check NA.

9.4.4.2 Complications during biopsy (Q11)

Record if arrhythmia, hypotension, desaturation or any other type of complication occurs during biopsy or transport to biopsy.
If arrhythmia, hypotension, or desaturation occur make sure to fill out the associated event forms (Forms 22 – 24).
Check 'NA – no complications' if no complications occurred.

9.4.5 Infections During Study Period Forms 32.1 & 32.2

This form must be completed for each episode of infection irrespective of antibiotic administration.
The clinical suspicion for each infection should be based on the most responsible physician's opinion (often the intensivist).
Infections should be recorded if they led to organ decline or changed treatment of antibiotics. Any infection that was acquired prior to being admitted to the ICU should be recorded if the infection is still being treated while in ICU.
Antibiotics or antimicrobials administered for suspected or confirmed infection should also be documented.
For the 'Pneumonia' and 'Other Infections' sections, if there is no clinical suspicion of infection, skip Q2 and go straight to Q3.

9.4.5.1 Gram stains (Q3)

Whether there was a suspicion of infection or not, make sure to note whether samples were sent for gram staining.

9.4.5.2 Cultures (Q4)

Indicate if culture was not sent, positive, or negative.
If positive, record the type of organism.

9.4.5.3 Antibiotics ordered empirically (Q5)

Antibiotics ordered without confirmation of infection that are not being ordered for prophylactic use should be marked as being ordered empirically.

9.4.6 Antibiotic/Antimicrobial Form 33.1 (Appendix E)

Antibiotic agents administered from the day prior to consent (C-1) up to organ recovery must be reported. Refer to Appendix E for a list of the antibiotic codes.
If more than one page of antibiotics/antimicrobials is needed check the box at the bottom of the form.
Please use the generic name for antibiotics rather than brands.

9.4.7 Co-enrolment Form 34.1

Co-enrolment in other studies is not a contraindication for participating in DONATE.
Were organs ruled out for donation is a question that can be difficult to answer accurately. To this end, please refer to the organ donation and transplantation coordinator to obtain a definitive answer to this question.
Warm ischemia time is applicable to DCD donors only. It is defined as the time from the first death declaration by cardiocirculatory criteria up to the time of administration of preservation solution.
In the process of work up, organ(s) refers to the period beginning immediately after the consent to organ donation up to and including organ recovery. In this case, if there is a doubt on the timing the organ was declined, please ask organ donation and transplantation coordinators.
Reasons for decline could be answered by organ donation and transplantation coordinators or by members of surgical teams.

9.4.8 Donor Forms 35.1 – 39.1

It is important to understand what happens with each organ from every patient enrolled in the study. In the case that the fate of a pair of organs is different (i.e. right lung declined and left lung transplanted) make sure to indicate the result of each organ.
Ruled out before consent refers to absolute exclusion criteria established by OPO (i.e. 65 years old will not take heart). This refers to organs not considered for donation.
Reason for decline is usually based on the decision of the transplant program. Reason for decline may be different for different transplant programs and we want to collect all.
NOTE: This data may or may not have to be obtained from the relevant OPO depending on the study site.